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Mild cognitive impairment: Influencing factors and intervention effects

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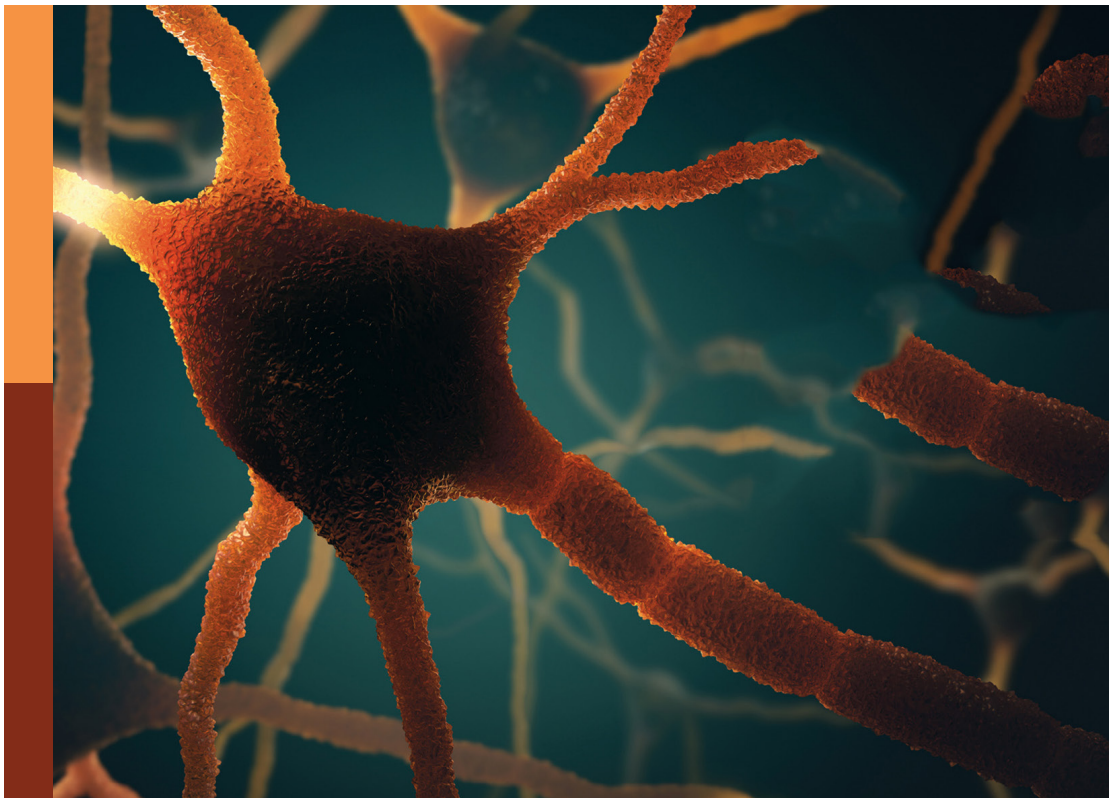

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Mild cognitive impairment: Influencing factors and intervention effects

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Waist-to-calf circumstance ratio and cognitive function among Chinese older adults: Mediating roles of physical performance and social activity

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Background: In light of the potentially detrimental effects of central fat and decreased muscle mass on cognitive function, it would be beneficial to learn more about the mediating mechanisms underpinning the association between the two. The purpose of this study is to determine the association between waist-to-calf circumstance ratio (WCR) and cognitive function, as well as to investigate whether physical performance and social activity mediate the relationship between WCR and cognitive function among older Chinese adults.

Methods: An analysis of 9,652 older Chinese adults was conducted during the 2018 wave of the Chinese Longitudinal Health Longevity Survey (CLHLS). The Mini-Mental State Examination (MMSE) and a self-reported scale were used to measure cognitive function, physical performance, and social activity, respectively. Multiple linear regression and mediation analyses were conducted.

Results: The findings suggest that a high WCR had a significant negative association with cognitive function ($B = -0.535$, 95% CI: −0.754, −0.317). Mediation analysis revealed that a high WCR influenced old adults' cognitive function in three ways: first, through the partial mediating effect of physical performance ($B = -0.270$; 95% CI: −0.340, −0.203); second, through the partial mediating effect of social activity ($B = -0.035$; 95% CI: −0.055, −0.017); and third, through the serial mediating effects of physical performance and social activity ($B = -0.021$, 95% CI: −0.029, −0.015).

Conclusion: The study results suggest the adverse impact of a high WCR on older adults' cognitive function, and the possible mechanisms of physical performance and social activity by which the association takes place. Multidimensional health and social interventions aimed at improving physical, social, and cognitive functioning among older adults with sarcopenic obesity are recommended.

KEYWORDS

waist-to-calf circumstance ratio, cognitive function, physical performance, social activity, sarcopenic obesity, mediation analysis

1. Introduction

Attention to variance in health, physical and cognitive function, and social embeddedness in a varied and aging community is critical to successful aging. According to the World Health Organization, ∼10 million people with cognitive impairments around the world develop dementia each year and more than 50 million people are diagnosed with it (Abdivalievna, 2022). A recent meta-analysis revealed that the global prevalence of mild cognitive impairment was 15.56% (95% CI: 13.24–18.03%) in community-dwelling adults aged 50 years and older (Atkins and Wannamathee, 2020). As the largest developing country, China is becoming an aging society. Almost one-fifth of China's population (18.70% in 2020) is over 60 years, and 13.50% is over 65 years. Mild cognitive impairment to severe dementia is common among older adults over 65 years old, accompanied by a high burden of limited life expectancy and healthcare utilization (Auyeung et al., 2013). According to a nationally representative survey in China, the prevalence of dementia was 6.0% and that of cognitive impairment was 15.5% among adults aged 60 years and older, representing 15.07 million people with dementia and 38.77 million people with cognitive impairment (Bai et al., 2022). Not only in China but also globally, large dementia and cognitive impairment population has become a significant health burden, necessitating stronger antidementia measures to combat this disease (Barnett et al., 2012). It is, therefore, imperative to identify and manage modifiable risk factors associated with cognitive impairment.

Previously known risk factors for cognitive impairments include age, sex, hypertension, diabetes mellitus, hyperlipidemia, stroke, congestive heart disease, chronic renal failure, homocysteinemia, and poor lifestyle (Batsis and Villareal, 2018). Meanwhile, obesity and sarcopenia, two important public health issues among older adults worldwide, are associated with a variety of risk factors that negatively affect long-term cognitive function (Berkman et al., 2000; Bennett et al., 2006; Batsis et al., 2021; Bilski et al., 2022). Whereas, sarcopenic obesity (SO) acts as a new category of obesity as well as a high-risk geriatric syndrome, and less is known about the effect of SO on cognitive performance in elderly individuals (Brewster et al., 2021). Although there is no consensus regarding the definition of SO (Brown et al., 2016), the coexistence of low muscle mass and strength as well as excess adiposity is this core connotation (Cauley, 2015; Buie et al., 2019). The prevalence of SO has risen in recent years due to the aging population crisis. Due to the lack of a uniform definition for SO and different study populations, its reported prevalence estimates range from 2.75% to 20% or more (Chang et al., 2015). According to some previous reports, the prevalence of SO in Chinese community-dwelling older adults was estimated at 6.0–25.0% (Chang et al., 2016; Chen et al., 2021; Cheng et al., 2022). SO is associated with poor health outcomes including frailty, disability (Choe et al., 2018), fractures, falls (Chou et al., 2022), cancer (Daviglus et al., 2010), cardiometabolic diseases (Donini et al., 2020), chronic kidney disease (Dye et al., 2017), and increased mortality (Espeland et al., 2022). Those who suffer from this geriatric syndrome are at risk of synergistic complications that can eventually result in long-term functional decline. Of importance, studies have shown associations between SO and impaired mental health (Etgen et al., 2011; Chen et al., 2021; Fan et al., 2021), including depression, dementia, and cognitive decline, as well as decreased psychological wellbeing. Considering these associations, researchers and policy experts are increasingly interested in identifying interventions that could improve health outcomes for older adults with SO.

Despite a few reports on the association between SO and cognition among old adults (Gao et al., 2015, 2020), sufficient attention has not been paid to cognitive changes in older adults with SO. In light of the potentially detrimental effects of SO on older adults' cognitive function, it is important to develop an understanding of the mediating mechanisms underlying this association. It would be helpful to identify these mechanisms to provide appropriate prevention and interventions to older adults who are confounded by SO. There is evidence that SO may have a synergistic effect on energy balance and muscular function/physical capacity (Gao et al., 2022). Based on some observations (Hayes, 2012; Hayes and Preacher, 2014; Henn et al., 2022), low levels of physical activity or physical fitness were observed in individuals with SO. Meanwhile, older persons with long-term functional impairments who engage with numerous barriers may have equal access to adequate social services (Hirani et al., 2017). Cognitive decline is less pronounced in socially active older adults in late life (Hirani et al., 2017). However, the underlying role of social activity in mediating the interaction of SO and cognitive function among elderly individuals with SO has not received full attention. Since SO has become a significant health concern among older adults and is greatly undertreated (Buie et al., 2019), exploring its influence on cognitive function and its potential social-psychological mediating factors is an appealing and potentially influential strategy to promote healthy aging. Mild cognitive impairment to severe dementia is common among elderly individuals over 65 years old, accompanied by a high burden of limited life expectancy and healthcare utilization (Auyeung et al., 2013). In light of the potentially detrimental effects of SO on mental health and cognition in older adults, a better understanding of the underlying mechanisms behind SO and cognitive decline is crucial. It would be helpful to identify these mechanisms to provide appropriate prevention and interventions to older adults facing age-related changes in body composition and physical dysfunction. Most importantly, studies have been rarely conducted in which both psychological and social pathways have been studied simultaneously to understand how SO affects cognitive function.

Therefore, to fill the abovementioned gaps, we chose the representative elderly subject from the Chinese Longitudinal Healthy Longevity Survey (CLHLS) database, since those included elderly population aged 65 years and older are reported to be susceptible to SO, as well as exhibiting an elevated level of cognitive impairment (Ida et al., 2018; Hong, 2020), with a diverse range of observed variables (Ji et al., 2022). In this study, we propose a higher adiposity-to-muscle ratio, that is high waist-to-calf circumstance ratio (WCR, see later), as an anthropometric measure of SO. As an index assessing the disproportion between abdominal fat and leg muscle mass, WCR has served as an alternative measure of SO in several studies (Jia et al., 2020, 2022; Jo et al., 2022). The first aim of this study was to examine the relationship between WCR and cognitive function among older Chinese adults based

on a database. A further objective of the study was to explore the role of physical performance and social activities in moderating the relationship between WCR and cognitive function. Specifically, we proposed the following hypotheses. First, there is a relationship between WCR and cognitive function among elderly individuals in China. Second, physical performance and social activities would mediate the association between WCR and cognitive function. Finally, physical performance and social activities would have a serial mediation effect between WCR and cognitive function (Supplementary Figure S1).

2. Methods

2.1. Study design and participants

We conducted a secondary analysis of the dataset derived from CLHLS-2018, a nationally representative prospective cohort study that recruited adults aged 65 years and older in major provinces of China. Details of the study participants and methods have been reported elsewhere (Kelly et al., 2017; Katayama et al., 2022). The CLHLS 2018 interviewed 15,874 older adults with a standard questionnaire using face-to-face interviews. Before the survey, each participant or proxy respondent signed an informed consent form. The research was approved by the Research Ethics Committee of Peking University (approval number: IRB00001052-13074). Those younger than 65 years of age (n = 95) were excluded from the current analysis. We restricted our final analysis to 9,652 older adults with completed information on the questions we are concerned about. Details of the screening procedure are described in Supplementary Figure S2. Based on existing research (Kohara et al., 2017; Kokkeler et al., 2019; Kim and Yoon, 2022), along with the design of the CLHLS questionnaire, a set of variables was selected for analysis (Supplementary Table S1).

2.2. Dependent variables

Cognitive function. Based on previous studies, this study used the Chinese version of a modified MMSE to measure cognitive function (Levine and Crimmins, 2012; Katayama et al., 2022), scoring ranging from 0 to 30, with a lower score indicating poorer cognitive performance. It includes 24 items regarding orientation, attention, registration, calculation, recall, and language. Cronbach's α coefficient of the MMSE for this study was 0.91. More details about this scale can be found in Supplementary Table S2.

2.3. Independent variables

High waist-to-calf circumstance ratio. Participants in CLHLS-2018 were instructed to relax their bodies before a measuring tape was used to measure their waist circumference (WC) and calf circumference (CC). WC was measured at the midpoint between the lower ribs and iliac crest at the end of expiration. CC was measured at the site of the largest circumference of the right calf of each participant while seated. WCR was the ratio of the two (Li et al., 2022). In this study, independent variables were created by assigning participants to tertiles of WCR. The highest tertile of WCR was classified as high WCR, while the lowest and middle tertiles of WCR were classified as low to intermediate WCR.

2.4. Mediators

Physical performance. According to a recent study (Kim and Yoon, 2022), muscle strength, walking ability, the strength of the lower extremities, and core strength were included in the present study. The relevant entries were collected in our study based on four questions (scoring range from 0 to 8), as described in Supplementary Table S3. A higher total score indicated poor physical performance. Cronbach's α coefficient of the score for this study was 0.87 (Kim and Yoon, 2022).

Social activity. In the context of the framework of Liu et al. (2022), playing cards/mahjong, participating in organized social activity, and visiting experiences were included in the present study, under the subdomain of social activity (Ma et al., 2022). According to previous studies, the relevant entries were collected in our study based on three questions (scoring range from 0 to 3), as described in Supplementary Table S4.

2.5. Covariates

As covariates, sociodemographic characteristics, lifestyles, and health status were classified as potentially related factors in previous studies (Levine and Crimmins, 2012; Kokkeler et al., 2019).

Sociodemographic characteristics. The sociodemographic characteristics included age (in years), sex (male or female), education (illiterate or literate), residence (rural or urban), marital status (married and living with a spouse or other statuses), living arrangement (living alone or living with someone else), occupation before age 60 (non-professional work or professional work), and financial support (insufficient or sufficient).

2.5.1. Lifestyle

As described in a recent study (Mendham et al., 2021), by adding the dietary pattern and daily habit scores, a combined lifestyle score was calculated between 10 and 50, as described in Supplementary Table S5. Since the missing proportion of the collected data in this domain was <5%, the average scores of each variable were utilized to replace the missing values. For analysis, the eight frequency options of food intake were measured, including staple foods, meat, fish, fresh fruits and vegetables, milk, sugar, and nuts (Mo et al., 2022). The dietary pattern score is determined as the total of all eight food category scores, ranging from 7 to 38, with higher scores reflecting better eating patterns, as indicated in prior research (Moreno-Franco et al., 2018; Mendham et al., 2021; Mo et al., 2022). Tobacco and alcohol consumption as well as the amount of outdoor exercise were also recalled by participants. The scores ranged from 1 to 4 for tobacco use and 1 to 3 for alcohol consumption. A higher score indicated fewer daily smoking or drinking sessions (Mendham et al., 2021). The participants were asked to rate how

often they performed outdoor activities, with a score ranging from 1 to 5 in ascending order according to the frequency of their participation. Across all daily life habits, the score ranged from 3 to 12 (Mendham et al., 2021).

2.5.2. Health status

This study evaluates health status primarily through body mass index (BMI, continuous variable), physical comorbidity of chronic diseases, and depressive symptoms. Physical comorbidity was measured by measuring 13 chronic conditions (e.g., hypertension, diabetes, stroke, cancers, Parkinson's disease) in the CLHLS (Panickar and Jewell, 2015; Ozkok et al., 2022). Physical comorbidities were defined as self-reported diseases or conditions that exceeded two of the 13 listed earlier (Panickar and Jewell, 2015; Ozkok et al., 2022). The 10-item Center for Epidemiologic Studies Depression (CES-D-10) was used to assess depressive symptoms, which was a self-reported scale for assessing the symptoms of depression in the past week (Peng et al., 2020). The CES-D-10 contains 10 items on somatic symptoms, depression impacts, and positive affect. In each item, a score is assigned between 0 and 3 ("rarely" to "almost always"), as described in Supplementary Table S6. The total score ranges from 0 to 30 with higher total scores indicating more severe depressive symptoms. A score of 10 or higher indicates possible depression. The CES-D-10 has been validated among older adults in China (Peng et al., 2020; Picca et al., 2022). Cronbach's α coefficient of the CES-D-10 for this study was 0.87.

2.6. Statistical analysis

For summary statistics, numerical variables are represented as the means and standard deviations, whereas categorical data are provided as frequencies. To assess differences between proportions and means, chi-square tests and t-tests were used. First, multivariate linear regression analysis was performed to explore the relationships between high WCR and cognitive function. Then, as determined by B-coefficients with 95% confidence intervals (CIs) from the initial analyses, significance for the next interaction analyses was set at $P < 0.10$. Finally, the PROCESS macro for SPSS was adopted to examine the mediation model (Pindus et al., 2021). In the Hayes PROCESS, the coefficients of the conditional indirect effects and conditional mediator tests are estimated along with the bias-corrected bootstrap confidence intervals. The regression-based, path-analytic framework we used in our analysis to determine if there was a serial mediation effect of physical performance and social activity between high WCR and cognitive function in older adults, relevant methods can be found in previous studies (Polyzos and Margioris, 2018). The mediation's significance was determined by computing bias-corrected 95% confidence intervals (CIs) with bootstrapping (5,000 resamples) (Preacher et al., 2007). In those models, covariates included age, sex, education level, residence, marital status, living arrangement, occupation before age 60, financial support, lifestyle, BMI, physical comorbidities, and CES-D-10 score. All analyses were conducted in IBM SPSS 24.0.

3. Results

3.1. Sample characteristics

As shown in Table 1, we compared the sample characteristics stratified by WCR. Among the 9,652 participants (4,588 men, 5,064 women), 2,837 (29.39%) had a high WCR (upper WCR tertile). Participants with a high WCR had a lower average MMSE score than those with low to intermediate WCR (24.09 vs. 26.28, $P < 0.001$). Those with high WCR were generally older, female, with lower levels of education, living in a rural area, widows/separated/single, living alone, with non-professional work before retirement, with lower lifestyle score, with lower BMI, and having a higher average CES-D-10 score ($P < 0.05$ or $P < 0.001$). Compared to those with a low to intermediate WCR, those with high WCR had a higher average physical performance score (2.85 vs. 1.74, $P < 0.001$) as well as a lower average social activity score (0.80 vs. 1.06, $P < 0.001$). Neither group showed significant differences regarding financial support or physical comorbidities ($P > 0.05$).

3.2. The association between WCR and cognitive function

In Table 2, we examined the unadjusted association between WCR and cognitive function (Model 1). WCR and cognitive function exhibited a significant negative correlation ($B = -2.194$, 95% CI: −2.443, −1.946). After adjusting for sociodemographic characteristics, lifestyles, and health status (Model 2), this correlation remained present ($B = -0.533$, 95% CI: −0.752, −0.315). Age ($B = -0.216$, 95% CI: −0.227, −0.205), sex ($B = -0.805$, 95% CI: −1.028, −0.583), and CES-D-10 score ($B = -0.165$, 95% CI: −0.187, −0.143) were negatively correlated with cognitive function. However, the education level ($B = 1.051$, 95% CI: 0.829, 1.274), marital status ($B = 0.256$, 95% CI: 0.022, 0.490), professional work before retirement ($B = 0.480$, 95% CI: 0.149, 0.810), BMI ($B = 0.027$, 95% CI: 0.011, 0.043), and higher total lifestyle score ($B = 0.081$, 95% CI: 0.059, 0.103) showed significantly positive correlations with cognitive function. The direction or significance of the associations did not transform substantially from Model 1 to Model 2, which adjusted for covariates.

3.3. Mediating roles of physical performance and social activity in the association between WCR and cognitive function

We next sought to clarify the underlying mechanism mediating WCR and cognitive function through physical performance and social activity. The bootstrap results from the mediation analysis are presented in Table 3. Path coefficients and their statistical significance are shown in Figure 1. As shown in Figure 1A, the WCR was negatively correlated with cognitive function (Path c: $B = -0.535$; 95% CI: −0.754, −0.317). There was a positive relationship between the WCR and physical performance score

TABLE 1 Characteristics of the sample stratified by waist-to-calf circumstance ratio (WCR).

Characteristics	Total Mean ± SD or *N* (%)	Low to intermediate WCR Mean ± SD or *N* (%)	High WCR Mean ± SD or *N* (%)	χ^2 or *t* statistics	*P*-value
N	9,652	6,815	2,837	–	–
Age (years)	83.09 ± 10.95	81.59 ± 10.60	86.69 ± 10.94	−21.33	<0.001
Sex					
Male	4,588 (47.5)	3,629 (53.3)	959 (33.8)	303.76	<0.001
Female	5,064 (52.5)	3,186 (46.7)	1,878 (66.2)		
Education level					
Illiterate	4,928 (51.1)	3,128 (45.9)	1,800 (63.4)	246.86	<0.001
Literate	4,724 (48.9)	3,687 (54.1)	1,037 (36.6)		
Residence					
Rural	4,720 (70.8)	4,720 (69.3)	2,109 (74.3)	24.98	<0.001
Urban	2,095 (29.2)	2,095 (30.7)	728 (25.7)		
Marital status					
Married	4,566 (47.3)	3,564 (52.3)	1,002 (35.3)	231.62	<0.001
Other statuses	5,086 (52.7)	3,251 (47.7)	1,835 (64.7)		
Living arrangement					
Living alone	1,535 (15.90)	1,044 (15.3)	491 (17.3)	5.92	0.015
Living with someone else	8,117 (84.10)	5,771 (84.7)	2,346 (82.7)		
Occupation before age 60					
Non-professional work	8,564 (88.7)	5,951 (87.3)	2,613 (92.1)	45.80	<0.001
Professional work	1,088 (11.3)	864 (12.7)	224 (7.9)		
Financial support					
Insufficient	1,301 (13.5)	933 (13.7)	368 (13.0)	0.89	0.346
Sufficient	8,351 (86.5)	5,882 (869.3)	2,469 (87.0)		
Total lifestyle score	29.91 ± 4.76	30.04 ± 4.81	29.60 ± 4.62	4.19	<0.001
Body mass index (kg/m^2)	23.53 ± 7.02	23.97 ± 6.89	22.47 ± 7.20	9.61	<0.001
Physical comorbidities					
Yes	3,308 (34.3)	2,306 (33.8)	1,002 (35.3)	1.95	0.162
No	6,344 (65.7)	4,509 (66.2)	1,835 (64.7)		
CES-D-10 score	7.33 ± 4.43	7.20 ± 4.43	7.65 ± 4.40	−4.57	<0.001
Physical performance score	2.06 ± 2.38	1.74 ± 2.23	2.85 ± 2.55	−21.47	<0.001
Social activity	0.98 ± 0.83	1.06 ± 0.85	0.80 ± 0.77	14.61	<0.001
MMSE score	25.64 ± 5.76	26.28 ± 5.17	24.09 ± 6.74	17.30	<0.001

Comparison was performed using the t-test or Chi-square test. SD, standard deviation. CES-D-10, The 10-item Center for Epidemiologic Studies Depression. MMSE, mini-mental state examination.

[Path a1: $B = 0.365$; 95% CI: (0.281, 0.449)], that is, a higher WCR value indicates worse physical performance. WCR was negatively associated with cognitive function [Path a2: $B = -0.062$; 95% CI: (−0.096, −0.028)]. Physical performance score had a negative association with cognitive function (Path b1: $B = -0.741$, 95% CI: −0.792, 0.690). Social activity had a significant positive association with cognitive function (Path b2: $B = 0.556$; 95% CI: 0.434, 0.679). The physical performance score had a negative association with social activity (Path a3: $B = -0.107$, 95% CI: −0.115, −0.099). Furthermore, we found that the absolute value of the coefficient of WCR on cognitive function decreased when controlling for physical performance and social activity (Path *c*': $B = -0.209$, 95% CI: −0.417, −0.011) (Figure 1B).

As shown in Table 3, there was a significant correlation between WCR, physical performance, social activity, and cognitive function. WCR had a total effect of −0.535 on cognitive function. In addition, it directly affected SWB by −0.209, accounting for 39.01% of the total effect. The path coefficients of WCR on cognitive function

TABLE 2 The association between waist-to-calf circumstance ratio (WCR) and cognitive function.

	Model 1				Model 2			
	B	95% CI (lower)	95% CI (upper)	*P*-value	*B*	95% CI (lower)	95% CI (upper)	*P*-value
High WCR	−2.194	−2.443	−1.946	<0.001	−0.533	−0.752	−0.315	<0.001
Age					−0.216	−0.227	−0.205	<0.001
Sex					−0.805	−1.028	−0.583	<0.001
Education level					1.051	0.829	1.274	<0.001
Residence					−0.010	−0.384	0.138	0.306
Marital status					0.256	0.022	0.490	0.032
Living arrangement					−0.008	−0.045	0.035	0.322
Occupation before age 60					0.480	0.149	0.810	0.004
Financial support					−0.015	−0.132	0.228	0.083
Total lifestyle score					0.081	0.059	0.103	<0.001
Body mass index					0.027	0.011	0.043	0.001
Physical comorbidities					0.012	−0.224	0.164	0.162
CES-D-10 score					−0.165	−0.187	−0.143	<0.001

Model 1 investigated the association between WCR and cognitive function. Model 2 investigated the association between WCR and cognitive function adjusting for covariates. CES-D-10, The 10-item Center for Epidemiologic Studies Depression. MMSE, mini-mental state examination.

TABLE 3 The serial mediating effect of waist-to-calf circumstance ratio (WCR) and cognitive function.

Path	*B*	SE	95% CI (lower)	95% CI (upper)	*P*-value	Proportion of effect (%)
Total effect (c)	−0.535	0.111	−0.754	−0.317	<0.001	100.00
Direct effect (c')	−0.209	0.106	−0.417	−0.011	0.048	39.01
a1	0.365	0.043	0.281	0.449	<0.001	–
a2	−0.062	0.017	−0.096	−0.028	<0.001	–
a3	−0.107	0.004	−0.115	−0.099	<0.001	–
b1	−0.741	0.026	−0.792	−0.690	<0.001	–
b2	0.556	0.063	0.434	0.679	<0.001	–
Total indirect effect	−0.326	0.039	−0.402	−0.251	<0.001	60.93
Indirect effect 1 (a1 × b1)	−0.270	0.035	−0.340	−0.203	<0.001	50.47
Indirect effect 2 (a2 × b2)	−0.035	0.010	−0.055	−0.017	<0.001	6.54
Indirect effect 3 (a1 × a3 × b2)	−0.021	0.004	−0.029	−0.015	<0.001	3.92

Indirect effect 1, high WCR → physical performance → cognitive function; Indirect 2, high WCR → social activity → cognitive function; Indirect3, high WCR → physical performance→ social activity → cognitive function. B, standardized regression B-coefficient. SE, standard error. 95% CI, 95% bootstrap confidence interval.

demonstrated that physical performance and social activity had a substantial mediating influence when modeled as mediators (indirect effect 1: a1 × b1 = −0.270, 95% CI: −0.340, −0.203; indirect effect 2: a1 × b1 = −0.035, 95% CI: −0.055, −0.017). Moreover, we found that physical performance and social activity play a serial mediating role in the relationship between WCR and cognitive function (indirect effect 3: a1 × a3 × b2 = −0.021, 95% CI: −0.029, −0.015). As a result, the total mediating effect of physical performance and social activity on WCR and cognitive function was −0.326, accounting for 60.93% of the total effect and involving three types of mediating effects. Physical performance mediated the relationship between WCR and cognitive function by −0.270, which accounted for 50.47% of the total effect. Social activity mediated the relationship between WCR and cognitive function by −0.035, which accounted for 6.54% of the total effect. The serial mediating effect of physical performance and social activity on the association between WCR and cognitive function was −0.021, which accounted for 3.92% of the total effect.

4. Discussion

Sarcopenic obesity is a growing public health challenge because of aging populations; however, relevant studies are still in their infancy (Rezende et al., 2019). To the best of our knowledge, this is the first study to examine the relationship between changes

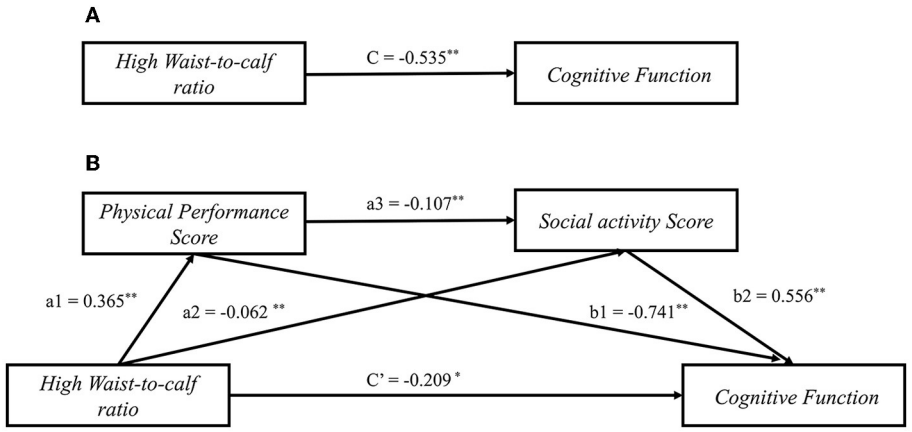

FIGURE 1
Mediation models of physical performance and social activity for waist-to-calf circumstance ratio on and cognitive function among Chinese older adults. **(A)** The total effect of waist-to-calf circumstance ratio on cognitive function; **(B)** The direct and indirect effects of waist-to-calf circumstance ratio on cognitive function through physical performance and social activity. a1, a2, a3, b1, b2, c', and c represent standardized regression B-coefficients of the path. *$P < 0.05$, **$P < 0.001$.

in body composition, including a shift toward higher fat mass and decreased lean muscle mass, and cognitive function, as well as the role of social factors, using the indicator of WCR in a sample of older adults aged 65 years or older in China, using a serial chain mediation model. The results showed that high WCR significantly positively predicted cognitive impairment, indicating that older adults with high WCR tended to have decreased levels of cognitive function. Furthermore, the findings confirm that physical performance and social activity partially mediate the relationship between WCR and cognitive function among older adults. Meanwhile, the results also suggest that physical performance and social activity had a significant serial mediation effect on WCR and cognitive function.

The current study confirmed that a high WCR is significantly associated with reduced cognitive function among elderly individuals, which is consistent with previous studies showing that SO or a higher adiposity-to-muscle ratio negatively impacts cognitive function in older adults (Gao et al., 2015, 2020; Ribeiro Santos et al., 2020; Brewster et al., 2021; Chen et al., 2021). This finding suggested that the combination of sarcopenia and obesity could generate a synergetic effect on cognitive impairment rather than a simple superposition, but the mechanism underlying this effect is unclear (Gao et al., 2020). Similarly, the mechanisms underlying obesity-related cognitive dysfunction are still incompletely resolved, although several pathways have been proposed, including sedentary behavior, inflammation, and endothelial function injury (Ryu et al., 2013; Rueger et al., 2016; Roh and Choi, 2020). An even more important predictor of decreased cognition might be sarcopenia or age-related loss of muscle mass and function. Sarcopenia has been linked with poor cognitive function either in epidemiological studies or in experimental *in vitro* and animal studies (Berkman et al., 2000; Bilski et al., 2022). According to a recent meta-analysis, independent of the research population, the definition of sarcopenia, or cognitive impairment, cognitive impairment is related to sarcopenia (Bilski et al., 2022). The role of sarcopenia in cognitive impairment was also confirmed by a neuroimaging study (Schoufour et al., 2021). Accumulated epidemiological, clinical, and basic research evidence indicates that inflammatory markers and the hormonal pathway (e.g., interleukin-6, C-reactive protein, myokine, and serum testosterone) are involved in the association between sarcopenia and cognitive impairment (Shi et al., 2015; Scott et al., 2017; Sharma et al., 2021; Seo et al., 2022). Based on these individual effects, this synergistic effect of sarcopenia obesity on cognition seemed even more apparent, which was supported by a cross-sectional analysis of NHANES data (Shim et al., 2021). Multiple suggested pathogeneses explain the sarcopenia–obesity–cognitive dysfunction link, including chronic inflammation, adipose tissue dysfunction, oxidative stress, insulin resistance, insulin resistance, and mitochondrial dysfunction, all of which are age-related (Snyder et al., 2016; Someya et al., 2022). Moreover, several new mediators have been proposed, such as the muscle–myokine–brain axis and gut–microbiota–brain axis (Spiteri et al., 2019).

Physical performance and social activity were also shown to have partial mediation effects on the relationship between WCR and cognitive function. This finding indicates that the coexistence of reduced lower limb muscle mass with abdominal obesity may impose an ill effect on physical performance and restrict opportunities for elderly individuals to engage in social activities. Recent data suggest that preserving muscular mass (with a larger calf circumference) and avoiding central obesity might help prevent functional impairment even in centenarians (Stern, 2002). Similar to sarcopenia, SO has been linked to frailty and osteoporosis (Fan et al., 2021; Chou et al., 2022). Moreover, individuals with SO are at greater risk of metabolic disorders and reduced physical performance, such as walking speed, than those with sarcopenia or obesity alone (Sun et al., 2021; Tan et al., 2022). It was proposed that individuals with SO tended to suffer from impairment of living functions and lower physical capabilities during aging (Hayes and Preacher, 2014; Jia et al., 2020; Tanaka et al., 2022). As a result of lower physical performance, older adults experience difficulties

communicating with others and engaging in daily activities (Tolea et al., 2018; Tanaka et al., 2022). Following the social support theoretical model (Wang H. et al., 2019), this finding suggests that appropriate late-life social activity may buffer the adverse effects of SO on older adults' cognitive function. Multiple studies have discussed the difficulties of participating in social activities for people with SO (Wang R. et al., 2019; Wang et al., 2021; Yang et al., 2022), which accounts for physical activity, oral function, and psychological and nutritional status. Reduced social activity and limited social interactions imply restricting social connections, which may result in the development of cognitive decline (Sun et al., 2021; Yang et al., 2021; Yin et al., 2021). In addition, we found that physical performance was a stronger mediator than social activity, which might not be adequately explored in previous research (Gao et al., 2020; Ribeiro Santos et al., 2020).

Our study's main result is that physical performance and social activity operate as a series of intermediaries in the link between WCR and cognitive function. Based on the theory of cognitive reserve (Yin et al., 2019), cognitive stimulation from social interactions may promote better cognitive aging (Yue et al., 2022). This result is consistent with previous studies and extends them by demonstrating the serial intermediating effect of physical performance and social activity in the association between SO and cognitive function among older adults (Brewster et al., 2021; Shim et al., 2021). The observed serial mediation role in the present study might be attributed to several behavioral mechanisms, all of which can increase the risk of cognitive impairment (Zeng, 2012). First, an increase in fat mass and a decrease in muscle mass are distinct factors that contribute to disability, incapacity, and mortality (Choe et al., 2018). Furthermore, it appears that SO has a synergistic effect on physical performance in older adults (Zeng et al., 2017). Second, the deterioration of the physical performance of elderly individuals increases their difficulty in participating in social activities. There was an independent association between physical frailty and all social activities (Zhong et al., 2016). Third, higher levels of social activity are associated with greater cognitive reserve, which results in the activation and strengthening of various neural circuits and behavioral pathways, improving the ability to compensate for adverse structural and functional brain consequences caused by hearing loss or other sensory impairments (Zhong et al., 2017; Kokkeler et al., 2019). In contrast, social isolation correlates with both restructuring and functional changes in the brain's social network and in brain regions that are related to mentalizing and social interaction, according to the social brain hypothesis (Zhuang et al., 2022). Given the positive effects of close social ties on health behavior, social interaction may influence cognitive outcomes (social control hypothesis) (Zovetti et al., 2021). Overall, maintaining physical function and participation in social activities may lessen the negative effects of high WCR on cognitive function in older adults.

Some limitations should be addressed in this study. First, the cross-sectional design renders causal inferences about the association between WCR, physical performance, social activity, and cognitive function, which could be explored in the future with a longitudinal design. Second, although geographically broad, the sample is not a random sample of the Chinese geriatric population. Third, self-report measures can be prone to bias and distortion. It is, therefore, essential to use multiple measures, such as an in-depth interview or observation of behavior. Finally, since we lacked muscle strength measurements, we used a surrogate marker for SO that only considers low muscle mass and obesity, not muscle function in this study. Although there is no consensus on the definition of SO, which varies considerably, we think this information should be taken into account in future research.

Despite the aforementioned limitations, there are some practical implications to our findings. Around the world, we must change the way we look at sarcopenic, obesity, and how SO impacts the physical, social, and cognitive functioning of older adults. From a practical view, given that high WCR can decrease the cognitive function of elderly individuals, families, caregivers, healthcare personnel, and institutions should pay more attention to old adults with SO or high-risk groups. First, prevention of SO rather than its treatment is more rational since attempting to reverse age-related diseases among the elderly is difficult due to their general disability, as well as their unwillingness to modify lifestyles and adhere to long-term medications. Unfortunately, SO among older adults has not received sufficient attention in all walks of life. In particular, age-related SO remains underdiagnosed and untreated, despite evidence suggesting that treatment (e.g., lifestyle intervention) can mitigate adverse outcomes (Snyder et al., 2016). Indeed, the patients themselves do not consider it a serious health matter either, treating SO as a normal aging phenomenon rather than a multifactorial disease. Although a cliché, early screening, diagnosis, and intervention should be performed. The identification of vulnerable individuals is essential to ensure that prevention and early intervention programs are targeted at them. In rehabilitative practice, broader consultations could specifically include discussing emotional aspects of social interaction with patients and how SO affects cognitive and physical functioning. This serial mediation model has the potential to facilitate earlier identification and increase motivation for SO diagnosis and treatment, as well as prevention. Overall, this model could be beneficial for older adults with SO, their families, and social circles, the healthcare system, and society as a whole. Currently, there is no approved pharmacological treatment for SO, regardless of novel drugs under investigation. As a result, the current management of SO focuses on weight loss and increased physical activity (Rezende et al., 2019). A growing body of evidence indicates that the addition of exercise to diet adjustment can increase myokine release from tissues into the blood and delay the onset and progression of SO, which has the potential to influence protein metabolism, mitochondrial quality control, inflammation, and other processes (Spiteri et al., 2019).

5. Conclusion

Overall, we discovered that physical performance and social activity serve as a series mediator in the relationship between WCR and cognitive function in a nationally representative sample of older Chinese adults. It might be worthwhile to recommend multidimensional health and social interventions aimed at improving physical and cognitive function as well as social inclusion among older adults with SO. Better levels of physical performance and social activity are connected with higher levels of cognitive function, with physical performance having a stronger

influence than social activity. The link between high WCR and cognitive impairment implies that more focused treatments should be implemented to improve cognitive and physical performance in older adults with SO. Furthermore, authorities should focus on physical performance recovery and encourage older persons with SO to engage in social activities according to their health status.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: https://opendata.pku.edu.cn/dataverse/CHADS.

Author contributions

XC and JZ conceived the concept and design of the study. XC and BY contributed to data cleaning and analysis. BY and JZ contributed to the writing assistance and proofreading of the article. All authors approved the final version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2023.1166341/full#supplementary-material

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Altered gut microbiota in older adults with mild cognitive impairment: a case-control study

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Introduction: The microbiota-gut-brain axis is implicated in Alzheimer's disease. Gut microbiota alterations in mild cognitive impairment (MCI) are inconsistent and remain to be understood. This study aims to investigate the gut microbial composition associated with MCI, cognitive functions, and structural brain differences.

Methods: A nested case-control study was conducted in a community-based prospective cohort where detailed cognitive functions and structural brain images were collected. Thirty-one individuals with MCI were matched to sixty-five cognitively normal controls by age strata, gender, and urban/rural area. Fecal samples were examined using 16S ribosomal RNA (rRNA) V3–V4 sequencing. Compositional differences between the two groups were identified and correlated with the cognitive functions and volumes/thickness of brain structures.

Results: There was no significant difference in alpha and beta diversity between MCIs and cognitively normal older adults. However, the abundance of the genus *Ruminococcus*, *Butyricimonas*, and *Oxalobacter* decreased in MCI patients, while an increased abundance of nine other genera, such as *Flavonifractor*, were found in MCIs. Altered genera discriminated MCI patients well from controls (AUC = 84.0%) and were associated with attention and executive function.

Conclusion: This study provides insights into the role of gut microbiota in the neurodegenerative process.

KEYWORDS

mild cognitive impairment, gut microbiota, 16S ribosomal RNA, cognitive functions, structural brain imaging

1. Introduction

Mild cognitive impairment (MCI) is a transitional and early-stage cognitive impairment on the continuum of Alzheimer's disease (AD) (Scheltens et al., 2021). Declines in cognitive performance can take place in various functions, including memory, executive function, attention, language, and visuospatial skills (Albert et al., 2011). Recent findings have suggested

that some MCI patients may revert to normal or near-normal cognition, though they are at higher risk of progressing to dementia (Petersen, 2004; Koepsell and Monsell, 2012; Shimada et al., 2019). In other words, MCI is an intermediate phase, and understanding biological changes in this stage may provide insight into mechanisms or intervention targets for delaying the onset of dementia.

The microbiota-gut-brain axis is a complex, bidirectional communication system between the gut and the brain, and several direct and indirect pathways are involved within the axis (Morais et al., 2020). Microbiota is the commensal, symbiotic, and pathogenic microbial communities (bacteria, archaea, fungi, etc.) residing in and on our bodies. Nowadays, the concept of microbiome encompasses microbiota and their "theater of activity," including structural elements, metabolites, and the surrounding environmental conditions (Berg et al., 2020). The microbiota-gut-brain axis has been implicated in the pathogenesis of AD, and the role of gut microbiota has been beginning to be understood in recent years (Bostanciklioğlu, 2019; Kowalski and Mulak, 2019). Studies in AD have demonstrated a microbial composition that deviates significantly from that of cognitively normal controls (Vogt et al., 2017; Zhuang et al., 2018; Liu et al., 2019; Saji et al., 2019a,b; Guo et al., 2021). There is also emerging data about gut microbiota change in MCI patients (Li et al., 2019; Liu et al., 2019; Saji et al., 2019a,b; Guo et al., 2021; Pan et al., 2021; Sheng et al., 2021, 2022; Zhang et al., 2021; Verhaar et al., 2022; Wanapaisan et al., 2022; Yıldırım et al., 2022). In general, similar gut microbiota changes as AD were found in MCI patients, such as decreased *Bacteroides* genus and increased *Staphylococcus* and *Escherichia* (Li et al., 2019; Nagpal et al., 2019). However, the alterations of gut microbes between studies are far from consistent. This inconsistency may be due to differences in study designs, the study population's ethnicity, dietary composition, and the criteria used to diagnose AD/MCI. Furthermore, it has been confirmed that there will be significant differences in identifying kinds of gut microbes among analytical pipelines and biobanks (Balvočiute and Huson, 2017; Prodan et al., 2020).

Therefore, we conducted a case-control study in a well-characterized cohort of community-dwelling older adults in Taiwan. We aim to investigate the differences in gut microbiota between older adults with MCI and normal cognition using a more recently-developed and accurate pipeline and biobank.

2. Materials and methods

2.1. Study design and participants

This case-control study was nested in a dynamic, community-based prospective cohort study, the Epidemiology of Mild Cognitive Impairment in Taiwan (EMCIT) (Chuang et al., 2021). Briefly, the EMCIT recruits independently living adults older than 60 years of age in a rural area and an urban area in North Taiwan with the aim of understanding the epidemiology of MCI. In this cohort, the diagnosis of MCI was adjudicated through the expert panel of a psychiatrist, a neurologist, and a clinical psychologist according to the NIA-AA criteria (Albert et al., 2011). In this study, thirty-one older adults with MCI were matched to sixty-five cognitively normal controls by six strata (age < 75, age >= 75, male, female, urban, and rural areas) between September 2019 to January 2021. The exact numbers of cases and controls in each stratum were presented in Supplementary Table S1. This study was approved by the Far Eastern Memorial Hospital Research Ethics Committee (108058-E) and the Institutional Review Board of the National Yang-Ming University (YM109137E). Informed consent was obtained from all participants.

2.2. Fecal sample collection, DNA extraction, and 16S rRNA amplicon sequencing

A fresh fecal sample was collected by participants at the same visit of neuropsychological testing for MCI diagnosis and mailed to Germark Biotechnology (Taichung, Taiwan). Bacterial DNA was extracted using QIAamp Fast DNA Stool Mini Kit (Qiagen, MD, United States). The amount and quality were then determined by NanoDrop ND-1000 spectrophotometer (Thermo Scientific, Wilmington, DE, United States). Extracted DNA was stored at −80°C before 16S rRNA sequencing. V3-V4 regions of bacterial 16S rRNA gene, which are hypervariable, were amplified by PCR using bar-coded primers 341F (forward primer; 5'-CCTACGGGNGGCWGCAG-3′) and 805R (reverse primer; 5'-GACTACHVGGGTATCTAATCC-3′) (Herlemann et al., 2011). Sequencing and library construction of amplicon DNA samples were entrusted to Germark Biotechnology (Taichung, Taiwan). Then, the 2 × 300 bp paired-end amplicon library with an insert size of 465 bp for each sample was prepared using the TruSeq Nano DNA Library Preparation kit (Illumina Inc., San Diego, CA, United States). At last, high-throughput sequencing was performed on an Illumina MiSeq 2000 sequencer with MiSeq Reagent Kit v3 (Illumina).

2.3. Microbiome bioinformatic analysis

The demultiplexed 16S rRNA gene sequences generated from the Miseq run were analyzed using the divisive amplicon denoising algorithm 2 (DADA2) pipeline (Callahan et al., 2016). Microbiome FASTQ files were first cleaned by the Cutadapt tool, which removed adapter and primer sequences (Martin, 2011). Subsequently, forward and reverse sequences were truncated at positions 230 and 210, and a maximum number of expected errors were set at 2 and 4, respectively. Error rates were later estimated and corrected by the DADA2 error model parameters. After merging forward and reverse reads to derive full denoised sequences, an amplicon sequence variant (ASV) table was established and disposed of unmatched pairs of reads. Finally, chimeric ASVs were detected and abandoned, and the latest SILVA reference 16S rRNA gene database 138.1 was used to assign taxonomies (Quast et al., 2013).

The resulting ASV table was imported into the Phyloseq package in R to analyze the overall structure of the microbiome, such as phylogenetic tree and biodiversity (McMurdie and Holmes, 2013). Alpha diversity indices, observed OTUs, Chao1 estimator, Shannon, Simpson, and InvSimpson, represented the mean diversity of species in a site within a local scale. The alpha diversity indices between MCIs and controls were compared using linear regression models adjusted for potential confounders. Beta diversity, the change in the diversity of species between the ecosystems, was measured by Jaccard, Bray–Curtis, unweighted UniFrac, and weighted UniFrac distance. The results of these different distance models were plotted by

principal coordinate analysis (PCoA). The difference in beta diversity between MCIs and controls would be evaluated by PERMANOVA (permutational multivariate analysis of variance) and Wd*-test (Anderson, 2017; Hamidi et al., 2019). The ASV table underwent a centered-log ratio (CLR) transformation, enabling us to conduct the following compositional analyses (Aitchison, 1982; Badri et al., 2018). To determine differences in genera of interest between MCIs and controls, we performed the linear discriminant analysis (LDA) effect size (LEfSe) method[1]. The LEfSe used Kruskal–Wallis (KW) sum-rank test to detect features with significant differential abundance and a set of unpaired Wilcoxon rank-sum tests to investigate subsequent biological significance among subclasses (Segata et al., 2011). A significant alpha value at 0.05 and an effect size threshold of 2.0 were used to discover genera of interest.

2.4. Cognitive assessments

A battery of neuropsychological tests in the Chinese version was used in the EMCIT to assess global cognition and cognitive domains of attention, memory, and executive functions (Chuang et al., 2021). Briefly, global cognition was evaluated by the Mini-Mental State Examination. Tests of attention included the Color Trails Test 1 (CTT 1), subtests of Digit Span (DS), Digit Symbol Substitute Test (DSST), Symbol Search (SS) in the Wechsler Adult Intelligence Scale-III (WAIS-III), and the immediate recall of the Logical Memory subset (LM I) of Wechsler Memory Scale. The delayed recall of the Logical Memory subset (LM II) was used to assess the memory domain. The executive function domain encompassed the Color Trails Test 2 (CTT 2), Semantic Verbal Fluency (VF), and the Stroop Color and Word Test (SCWT). Test scores were all z-transformed, and averaging *z*-scores of tests within each domain generated scores of each cognitive domain.

2.5. Brain structure analysis

Every participant was scanned on a 3 T scanner (MAGNETOM Skyra, Siemens Healthcare, Erlangen, Germany) with a 16-channel head coil. The detailed protocol was described elsewhere (Chiu et al., 2019). High-resolution T1-weighted images were acquired using the magnetization-prepared rapid-acquisition gradient echo (MPRAGE) and analyzed using Freesurfer version 7.1.1[2]. Preprocessing, including the skull stripping and reconstruction of the cortical surface, was followed by automated labeling, cortical parcellation, and subcortical segmentation (aparc+aseg). Five MCIs were excluded due to poor image quality, and one normal control was excluded because of brain lesions. Volume data of total brain, ventricles, gray and white matter, and the region of interest (ROIs) that play an important role in AD/MCI, e.g., hippocampus and entorhinal cortex, were obtained. Besides, estimated total intracranial volume (eTIV) would be used to adjust the individual differences in cranial volume.

Furthermore, the average cortical thickness of Alzheimer's signature MRI biomarkers (Dickerson et al., 2011) was calculated. The Alzheimer-signature brain regions include the medial temporal, temporal pole, inferior temporal, inferior parietal, supramarginal gyrus, superior parietal, precuneus, cauda middle frontal, and superior frontal. The volume of each brain region was obtained by multiplying each region's thickness by its surface area. Then an AD thickness score was generated by dividing the total volume of the Alzheimer-signature brain regions by the total surface area, representing the mean thickness of Alzheimer-signature brain regions.

2.6. Statistical analysis

To examine differences in demographic characteristics, the Pearson chi-square test was applied for categorical variables between groups, while *t*-test was used for continuous variables. Based on results from LEfSe, a group of genera of interest was used to generate a receiver operating characteristic (ROC) curve by pROC R package alone or in combination (Robin et al., 2011). The genera harbored by more than 60% of participants were used further for correlation with cognitive domains and brain structures. Partial correlations between these genera of interest, cognitive domains, and brain structure were adjusted for age, gender, and education years. Correlations were presented in heatmaps by heat function in R. Statistical analyses were done in R version 4.1.2 and Stata 16, and $p < 0.05$ in all tests was considered significant.

3. Results

3.1. Characteristics of participants

The characteristics of participants between individuals with MCI and cognitively normal controls are presented in Table 1. There were no significant differences in age, gender, and community, the strata of which were used to match the two groups. Participants with MCI had poorer education (6.3 vs. 9.0 years), a higher percentage of hypertension (61 vs. 37%), and a lower frequency of coffee consumption. A total of 8,370,548 non-chimeric high-quality reads were yielded by thirty-one MCIs and sixty-five controls, with an average of 87193.2 reads per sample. On average, these reads for subsequent analysis accounted for 66.8% of raw reads. MCI patients had a slightly lower percentage (65.5 vs. 67.4%) (Supplementary Table S2). A total of 4,925 ASVs were identified.

3.2. Biodiversities: alpha and beta diversity

Figure 1 shows the biodiversity comparisons in MCIs and controls. Alpha diversity and richness were both similar between the two groups, representing similar biodiversity within each sample. After adjusting for age, gender, rural/urban area, education, and hypertension, the indices of the MCI group remained lower than those of controls, although not statistically significant (Supplementary Table S3). The beta diversity presented by PCoA was also similar, which means that similarities and dissimilarities between samples were indistinguishable. Only unweighted Unifrac distance indicated that there was a differential clustering pattern by PERMANOVA and Wd* test (p-value < 0.05) (Supplementary Table S4). In summary, the alpha and beta diversity analyses did not show significant differences between individuals with MCI and cognitively normal controls.

1 https://huttenhower.sph.harvard.edu/galaxy/

2 http://surfer.nmr.mgh.harvard.edu/

TABLE 1 Characteristics of the study population.

Characteristics	MCI patients $n=31$	Healthy controls $n=65$	p-value
Age, years, mean ± SD	73.9 ± 6.7	74.2 ± 6.1	0.83
Gender, male/female	16/15	31/34	0.72
Urban area, *N*(%)	20 (65)	43 (66)	0.87
Education years, mean ± SD	6.3 ± 3.7	9.0 ± 4.4	0.005
Smoking never, *N*(%)	23 (74)	42 (65)	0.35
Drinking never, *N*(%)	20 (65)	41 (63)	0.89
BMI, mean ± SD	24.8 ± 3.1	24.4 ± 3.1	0.48
Diabetes mellitus, *N*(%)	11 (35)	13 (20)	0.10
Hypertension, *N*(%)	19 (61)	24 (37)	0.025
Vegetarian, *N*(%)*			
Vegetarian	2 (6)	5 (8)	0.81
Flexitarian	3 (10)	9 (14)	
Non-vegetarian	26 (84)	51 (78)	
Tea consumption, *N*(%)†			
Never	12 (39)	24 (37)	0.29
Sometimes	9 (29)	11 (17)	
Frequently	10 (32)	30 (46)	
Coffee consumption, *N*(%)†			
Never	27 (87)	33 (51)	0.002
Sometimes	3 (10)	11 (17)	
Frequently	1 (3)	21 (32)	
Neuropsychological test score, mean ± SD			
MMSE	24.6 ± 3.1	27.5 ± 2.1	<0.001
LMII	5.4 ± 5.1	14.7 ± 7.9	<0.001
LMI	15.1 ± 6.4	27.9 ± 11.1	<0.001
DS	13.8 ± 4.2	17.1 ± 4.1	<0.001
DSST	31.1 ± 17.2	47.9 ± 19.5	<0.001
SS	14.0 ± 7.1	23.8 ± 8.5	<0.001
CTT1 (sec)	115.1 ± 78.4	67.0 ± 36.9	<0.001
VF	30.0 ± 8.2	36.6 ± 8.4	<0.001
CTT2 (sec)	228.1 ± 111.0	142.2 ± 69.9	<0.001
SCWT-color	55.3 ± 12.1	72.6 ± 18.8	<0.001
SCWT-word	65.0 ± 17.2	86.0 ± 21.1	<0.001
SCWT-colored word	28.3 ± 10.7	41.7 ± 15.6	<0.001
SCWT-interference	−1.9 ± 8.6	2.6 ± 11.6	0.11
Memory	−0.8 ± 0.6	0.3 ± 0.9	<0.001
Attention	−0.6 ± 0.7	0.3 ± 0.7	<0.001
Executive functions	−0.5 ± 0.7	0.2 ± 0.6	<0.001

BMI, body max index; MMSE, Mini-Mental State Examination; LM, Logical Memory Test; DS, Digit Span; DSST, Digit Symbol Substitute Test; SS, Symbol Search; CTT, Color Trails Test; VF, Semantic Verbal Fluency; SCWT, Stroop Color and Word Test. *Vegetarian, a person who does not eat meat or meat products; Flexitarian, a person who follows a vegetarian diet but occasionally eats meat or fish; Non-vegetarian, a person who eats meat. †Never, less than 1 time per week; Sometimes, more than 1 but less than 5 times per week; Frequently, more than 5 times per week.

3.3. The compositional differences between MCIs and controls

The compositional analysis identified taxa of interest that differed between individuals with MCI and normal controls (LDA score > 2, $p < 0.05$, Figure 2). The LDA barplot and cladogram indicated the differentially abundant microbiota between the two groups. At the order level, two bacterial orders, including *Negativicutes* and *Flavobacteriales*, were significantly abundant in individuals with MCI. We also found that at the family level, *Gemellaceae* and *Saccharimonadaceae* had increased in the MCI group, while *Oxalobacteraceae* were more abundant in controls. Twelve genera of interest varied between the two groups. Nine genera: *Phocea*, *Gemella*, *Anaeroglobus*, *Cloacibacillus*, *Lactococcus*, *Flavonifractor*, *Lactiplantibacillus*, *Cetobacterium*, *Eubacterium fissicatena group* had increased in MCI, termed as MCI-abundant genera in the subsequent analysis. Three genera, *Ruminococcus*, *Butyricimonas*, and *Oxalobacter*, had increased in controls and were called control-abundant genera. Finally, as shown in Figure 2, several species were found to be different between the two groups; however, species identification is more prone to inaccuracy in 16S rRNA analysis. CLR transformed relative abundances of twelve genera different between MCIs and controls were shown in Supplementary Figure S1.

Figure 3 shows the ROC curves using the centered-log ratio transformed value of twelve genera of interest alone and all together. The blue-dashed and red-solid curves represented control-abundant and MCI-abundant genera, respectively. The black curve was fitted by logistic regression incorporating all twelve genera of interest as predictors. The twelve genera altogether showed a good performance in discriminating MCI from control [area under the ROC curve (AUC): 84.0%], demonstrating the potential of gut microbiota as a classification model.

3.4. Correlations between genera of interest and cognitive domains and brain structures

Among twelve genera of interest, some were present in very few individuals, and it's inappropriate to correlate their abundance with other clinical features because of scarcity. As a result, only genera harbored by more than 60% of participants were included in correlation analysis, including *Flavonifractor*, *Butyricimos*, and *Ruminococcus*. Figure 4 demonstrates the partial correlations between the abundance of the genera above and the cognitive functions and volumes/thickness of brain structures. The MCI-abundant genus, *Flavonifractor*, was associated with poorer performance in Color Trails Test 2 ($r = -0.22$, p-value = 0.04). Moreover, these nine MCI-abundant genera collectively had a significant negative association with executive function ($r = -0.22$, p-value = 0.03) and Color Trails Test 1 ($r = -0.24$, p-value = 0.02) and 2 ($r = -0.29$, p-value = 0.005). In contrast, control-abundant genera altogether were associated with better performance in Digit Symbol Substitute Test ($r = 0.26$, p-value = 0.01). *Ruminococcus* was positively correlated with Color Trails Test 2 ($r = 0.21$, p-value = 0.047).

The volumes/thickness of brain structures between the groups is shown in Supplementary Table S5. Cognitively normal adults have

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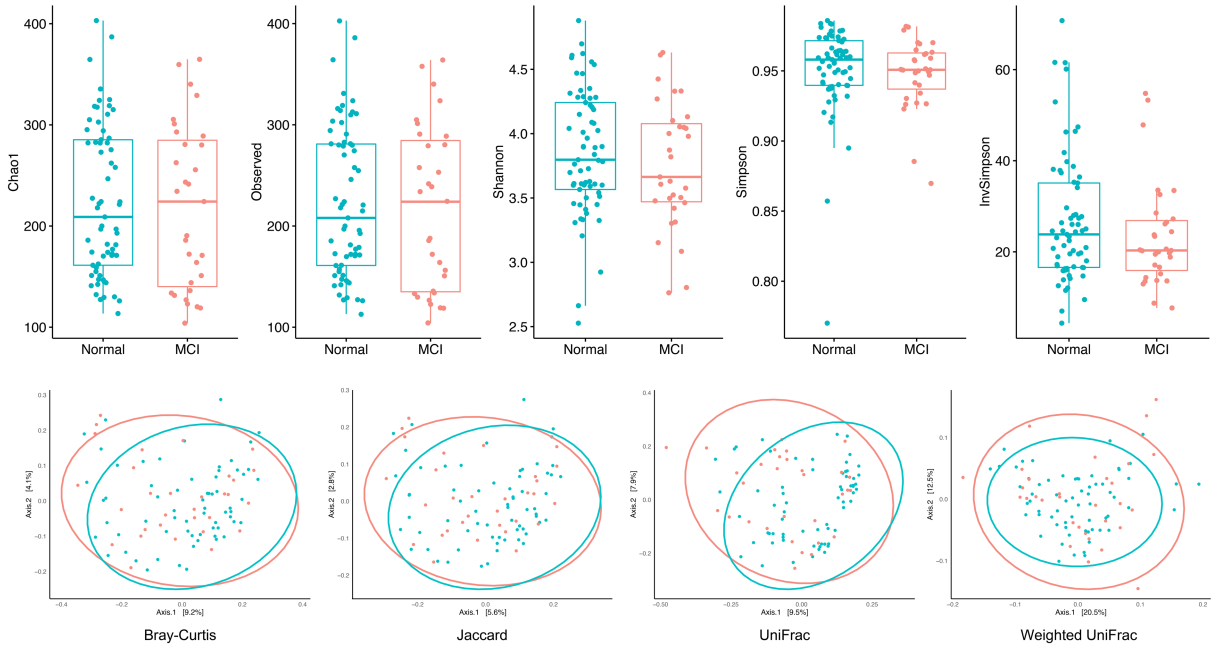

FIGURE 1
Alpha and beta diversity in MCI patients and healthy controls. Alpha diversity and richness indices (observed OTUs, Chao1 estimator, Shannon, Simpson, and InvSimpson) were both similar between the two groups, representing similar biodiversity within each sample. The beta diversity presented by PCoA (measured by Jaccard, Bray–Curtis, unweighted UniFrac, and weighted UniFrac distance) was also similar, which means that similarities and dissimilarities between samples were indistinguishable.

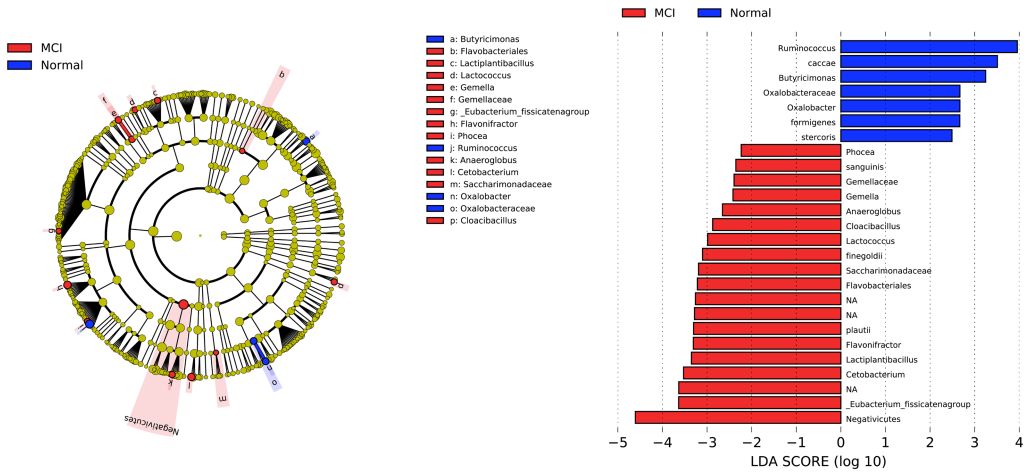

FIGURE 2
Differential bacterial taxonomies in LEfSe. The LDA barplot and cladogram indicated the differentially abundant microbiota between MCIs and controls (LDA score>2, $p<0.05$). At the order level, two bacterial orders, including *Negativicutes* and *Flavobacteriales*, were significantly abundant in individuals with MCI. We also found that at the family level, *Gemellaceae* and *Saccharimonadaceae* had increased in the MCI group, while *Oxalobacteraceae* were more abundant in controls. Twelve genera of interest varied between the two groups. Nine genera: *Phocea*, *Gemella*, *Anaeroglobus*, *Cloacibacillus*, *Lactococcus*, *Flavonifractor*, *Lactiplantibacillus*, *Cetobacterium*, *Eubacterium fissicatena group* had increased in MCI, while three genera, *Ruminococcus*, *Butyricimonas*, and *Oxalobacter*, had increased in controls.

generally larger total brain and gray/white matter volume, as well as the hippocampus, entorhinal, and amygdala, though not significantly different. AD-score thickness is identical between groups. The genera of interest did not show significant associations with the volumes/thickness of brain structures (Figure 4B).

4. Discussion

In this case-control study nested in a well-characterized community-based cohort, altered gut microbiota was found in individuals with MCI. Twelve genera of gut microbiota had a good

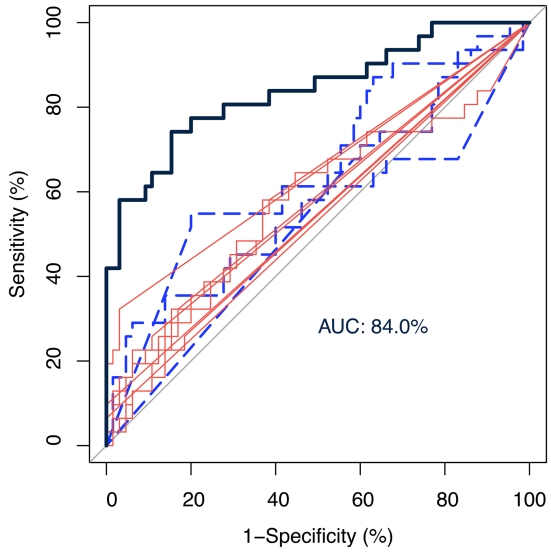

FIGURE 3
Receiver operating characteristic (ROC) curves of genera as biomarkers. The ROC curves were fitted by the centered-log ratio transformed value of twelve genera of interest alone and all together. The blue-dashed and red-solid curves represented control-abundant and MCI-abundant genera, respectively. The black curve was fitted by logistic regression incorporating all twelve genera of interest as predictors. The twelve genera altogether showed a good performance in discriminating MCI from control [area under the ROC curve (AUC): 84.0%], demonstrating the potential of gut microbiota as a classification model.

performance differentiating MCI from cognitively normal controls. MCI-abundant genera such as *Flavonifractor* were associated with poorer executive functions, whereas genera more abundant in controls, especially *Ruminococcus*, were linked to better performance.

The finding that no differences in biodiversity of gut microbiota were observed between individuals with MCI and normal cognition is consistent with previous studies (Li et al., 2019; Liu et al., 2019, 2021; Nagpal et al., 2019; Zhang et al., 2021; Hung et al., 2022). On the contrary, the reported microbial compositional differences between MCI patients and healthy controls varied considerably (Liu et al., 2019, 2021; Saji et al., 2019a; Guo et al., 2021; Pan et al., 2021; Zhang et al., 2021). We also revealed other families or genera of gut microbiota associated with MCI. Discrepancies may come from methodological differences, including the source of participants (memory clinic or community), the criteria used to diagnose MCI, and pipelines used to analyze gut microbiota. Most studies published before 2022 (Li et al., 2019; Liu et al., 2019, 2021; Guo et al., 2021; Pan et al., 2021; Sheng et al., 2021; Zhang et al., 2021) relied on OTU-or ZOTU-picking strategies and annotations in QIIME, which is more error-prone than DADA2-denoised ASV tables (Prodan et al., 2020). Therefore, different analytical pipelines coupled with various databases (SILVA or Greengene) used in each study made the results hardly comparable. Furthermore, since microbiota could be heavily dependent on the living environment and dietary styles, our study results are more likely to be comparable to studies conducted in Asia, including China, Japan, and Thailand instead of those in the Netherlands and Turkey.

We found that the genus *Ruminococcus*, *Butyricimonas*, and *Oxalobacter* decreased in participants with MCI, and the abundance of the genera was associated with better attention and executive function. *Ruminococcus* spp., one of humans' most abundant flora, plays a crucial role in deconstructing, fermenting, and utilizing a wide range of dietary plant polysaccharides into various nutrients and finally affects human health status (la Reau and Suen, 2018). Polysaccharides have long been seen as a modulator in the gut-brain axis. One of the significant components of dietary polysaccharides reaching the gut is insoluble plant fibers, or called dietary fibers, such as inulin, fructooligosaccharides, and pectin (Sun et al., 2023). These non-starch polysaccharides (NSPs) are rich in high-fiber diets, e.g., traditional rural African diets (De Filippo et al., 2010; Ho Do et al., 2021). Moreover, an animal study discovered that *Ruminococcus gnauvus* monocolonized mice performed better on a spatial working memory test and were associated with metabolites such as tryptamine, indolacetate, and TMAO (trimethylamine N-oxide). Tryptamine induces serotonin release through enterochromaffin cells, while indole-derived metabolites regulate the increase of the hippocampus's neural progenitor cells, some showing anti-inflammatory effects on the brain. Furthermore, TMAO has protective effects on BBB integrity (Hoyles et al., 2021; Coletto et al., 2022). The genus *Butyricimonas* produce butyrate, one of the short-chain fatty acids shown to exert crucial cognitive-protecting effects on the central nervous system. Butyrate prevents cognitive decline by improving barrier function and acting as an assumed negative regulator of amyloidosis and neuroinflammation (Marizzoni et al., 2020). In addition, *Butyricimonas* are grouped into taxa that increase with age yet deplete in unhealthy aging (Ghosh et al., 2022). Finally, *Oxalobacteraceae*, *Oxalobacter*, and *Oxalobacter formigenes* found in this study are less discussed in gut-brain communications. Some research highlighted the pathogenic role of oxalate distribution in the entorhinal cortex; nevertheless, the potential effect of oxalate on cognitive decline remains unclear (Heller et al., 2020).

In our study, several taxa found to increase in MCI patients were reported to increase in the AD patients. These taxa include the genus *Anaeroglobus*, the family *Gemellaceae*, and the genus *Gemella*. In addition, the genus *Flavonifractor* (Coello et al., 2019; Ogita et al., 2020) and the *Eubacterium fissicatena group* (Heo et al., 2016; Xiao et al., 2021) enriched in MCI in our study may involve an escalation of inflammation, oxidative stress, and proinflammatory response. *Flavonifractor* was further correlated with poor performance in the executive function test in our study. Derailed systemic immune system via circulating cytokines and increased gut inflammation is one of the proposed pathways linking the gut microbiota and the brain (Cattaneo et al., 2017). Intriguingly, *Lactococcus* and *Lactiplantibacillus*, both lactate-producing and commonly used as probiotics, produce several metabolites in the nervous system, such as serotonin, acetylcholine, histamine, and dopamine (Alkasir et al., 2017), which were increased in MCI patients. The increased amount of these two genera in MCI patients may imply the compensatory response toward the overrepresentation of inflammation-producing gut microbiota.

Some studies examined the cross-sectional relationship between gut microbiota and brain imaging. *Akkermansia*, *Lachnospiraceae* NK4A136 group spp., and *Anaerostipes* spp. were found to be correlated with medial temporal atrophy or global cortical atrophy (Li et al., 2019; Verhaar et al., 2022). MCI patients with more *Bacteroides* are more likely to present brain atrophy patterns compatible with AD (Saji et al., 2019a). Regarding regional brain volume, Wanapaisan et al. have discovered associations of left and right-hippocampus and right amygdala volumes with groups of bacteria identified in their study (Wanapaisan et al., 2022). However,

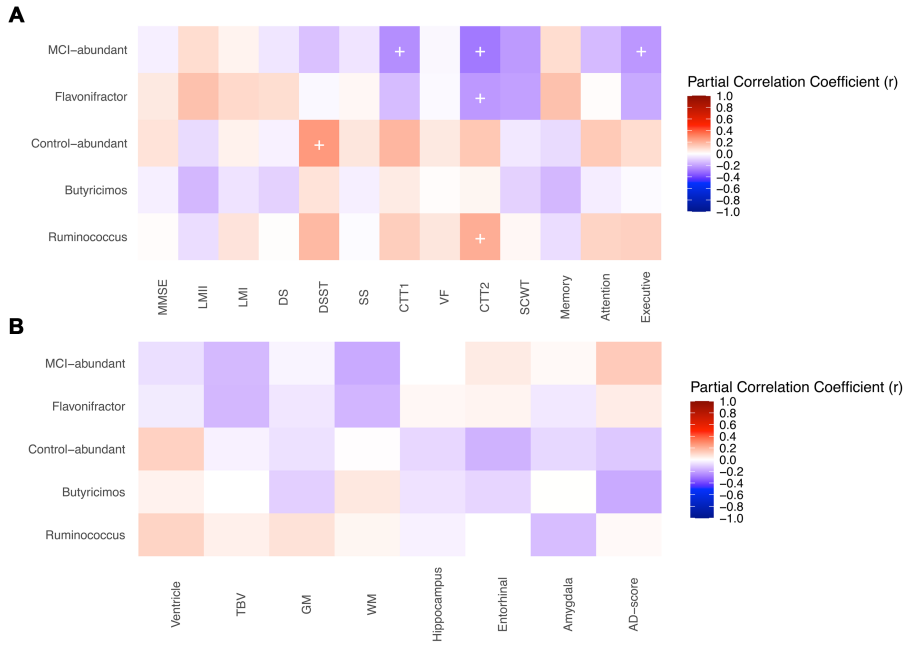

FIGURE 4
Correlations between genera of interest and **(A)** cognitive tests **(B)** brain structure. MMSE, Mini-Mental State Examination; LM, Logical Memory Test; DS, Digit Span; DSST, Digit Symbol Substitute Test; SS, Symbol Search; CTT, Color Trails Test; VF, Semantic Verbal Fluency; SCWT, Stroop Color and Word Test interference score; TBV, Total Brain Volume; GM, Gray Matter Volume; WM, White Matter Volume. + p-value<0.05. Partial correlations between the genera of interest and the cognitive functions and volumes/thickness of brain structures were shown. **(A)** Partial correlations of genera of interest and neuropsychological tests' scores were adjusted for age, gender, and year of education. Outcomes of color trails test 1 and 2 were added a minus sign to make the colors of correlations indicate the same direction. The MCI-abundant genus, *Flavonifractor*, was associated with poorer performance in Color Trails Test 2. Moreover, these nine MCI-abundant genera collectively had a significant negative association with executive function and Color Trails Test 1 and 2. In contrast, control-abundant genera altogether were associated with better performance in Digit Symbol Substitute Test. *Ruminococcus* was positively correlated with Color Trails Test 2. **(B)** Partial correlations genera of interest and brain volume indicators (cm^3) were adjusted for age, gender, and estimated intracranial volume (eTIV). Correlations of genera and AD-score, a cortical thickness indicator (cm), were only adjusted for age and gender. Ventricle included lateral ventricle, lateral inferior ventricle, and 3rd, 4th, 5th ventricles. The genera of interest did not show significant associations with the volumes/thickness of brain structures.

they also enrolled AD patients and mainly compared brain volumes in controls with AD/MCI. The insignificant correlations between brain volumes/thickness and the relative abundance of microbiota in our study may be explained by the early stage of cognitive impairment and less brain volume change in the individuals with MCI from the community.

Our research had several strengths. First, the study population was derived from a well-characterized community-based cohort, which better represents older adults' lifestyles and characteristics in the community than those from clinics. In addition, the diagnosis of MCI was rigorously made through a panel of experts. Second, we used the state-of-the-art pipeline with the best sensitivity and accuracy among all the 16S rRNA pipelines. The database was also the latest updated version. Third, we corroborated the results of identified bacteria by examining the relationship with other outcome assessments, cognitive functions, and brain volumes/thickness. This study is not without limitations. First, a single fecal sample was collected from each participant, rendering temporality hard to infer because microbial composition possibly fluctuates within a person over time. More importantly, 16S rRNA sequencing gives us a picture of bacterial composition; nevertheless, it fails to pinpoint species precisely with a complete view of microbiota. Moreover, we did not assess metabolites, pro-inflammatory markers, and BBB integrity. Hence, we could only postulate mechanisms but not construct robust associations. Second, although covariates were carefully measured and used for adjustment in analysis, unmeasured and residual confounding may still exist. For example, adjusting for levels of educational attainment in the analysis of cognitive functions may not fully account for confounding effects of factors closely related to the education level, such as healthy lifestyles diet, or socioeconomic resources. These factors could directly impact the gut microbiome or indirectly by modulating other behaviors (Herd et al., 2018). To what extent these factors confound the relationship between gut microbiota and cognitive function should be addressed in future research. Finally, although our sample size for gut microbiota analysis is comparable with other studies, it could still be insufficient to detect the relationship between the identified genera with subtle differences in brain volume/thickness. Future research with a larger sample size is needed to elucidate the brain structural differences associated with gut microbiota.

In conclusion, MCI was associated with altered gut microbiota, which further correlated with the performance of attention and executive functions. This altered gut microbiota collectively can differentiate MCI from cognitively normal adults. The findings supported the role of gut microbiota in the pathogenesis of cognitive impairment. Further longitudinal follow-up results from this cohort study are needed to elucidate the mechanism underlying how gut microbiota influences the aging brain and contributes to the development of cognitive impairment.

Data availability statement

The original contributions presented in the study are publicly available. This data can be found at: https://www.ncbi.nlm.nih.gov/sra/, PRJNA937331.

Ethics statement

The studies involving human participants were reviewed and approved by Far Eastern Memorial Hospital Research Ethics Committee, Institutional Review Board of the National Yang-Ming University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

YFC and YLC conceived and designed the study. YFC and YCL acquired the data. YPC and YJL assisted in MRI data collection and analysis. KCF and CCL analyzed the gut microbiota data. KCF and YFC interpreted the data and drafted the manuscript. All authors contributed to the manuscript revision and approved the final submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2023.1162057/full#supplementary-material

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Associations among multidomain lifestyles, chronic diseases, and dementia in older adults: a cross-sectional analysis of a cohort study

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Background: Unhealthy lifestyles and chronic diseases are commonly seen and treatable factors in older adults and are both associated with dementia. However, the synergistic effect of the interaction of lifestyles and chronic diseases on dementia is unknown.

Methods: We determined independent associations of multidomain lifestyles and chronic diseases (cerebrovascular disease, diabetes, and hypertension) with dementia and examined their synergistic impact on dementia among older adults. The data were drawn from the Hubei Memory and Aging Cohort Study. We created a summary score of six factors for multidomain lifestyles. Dementia was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders IV. Logistic regression and multiple correspondence analyses were used to explore the relationships among multidomain lifestyles, chronic diseases, and dementia. A sensitivity analysis was performed to minimize the interference of reverse causality and potential confounders.

Results: Independent associations with dementia were found in unhealthy (OR = 1.90, 95% CI: 1.38–2.61) and intermediate healthy lifestyles (OR, 3.29, 2.32–4.68), hypertension (OR, 1.21, 1.01–1.46), diabetes (OR, 1.30, 1.04–1.63), and cerebrovascular disease (OR, 1.39, 1.12–1.72). Interactions of diabetes (p = 0.004), hypertension (p = 0.004), and lifestyles were significant, suggesting a combined impact on dementia. Sensitivity analysis supported the strong association among multidomain lifestyles, chronic diseases, and dementia prevalence.

Conclusion: An unhealthy lifestyle was associated with a higher prevalence of dementia, regardless of whether the participants had chronic diseases; however, this association was stronger in individuals with chronic diseases. Multidomain lifestyles and chronic diseases may have an enhanced impact on dementia.

KEYWORDS

dementia, chronic disease, community-dwelling older adults, synergistic effect, lifestyle

1. Introduction

With an aging population and dramatic changes in lifestyles, the rising incidence of dementia has become an urgent public health problem (Chan et al., 2013). Dementia affects > 57 million people globally, which is set to increase to 152 million by 2050 (GBD 2019 Dementia Forecasting Collaborators, 2022). Studies have shown that altering 12 modifiable risk factors could delay or prevent the onset of 40% of dementia cases worldwide (Livingston et al., 2020). However, these studies have more often revealed individual or a couple of life behaviors (Baumgart et al., 2015; Smith and Blumenthal, 2016); hence, interventions targeting several risk factors have been trialed in older participants (Ngandu et al., 2015, 2021). Few researchers have investigated the combined effects of multidomain lifestyles on the prevalence of dementia, particularly in people with chronic diseases. Considering that dementia has complex pathogenesis and causes, some lifestyle factors may not be sufficient to individually influence dementia-related brain changes, and complex interactions between these factors may exert enhanced effects (Weuve et al., 2018).

The global increase in the prevalence of type 2 diabetes (Gregg et al., 2016), hypertension (Sun et al., 2022), and cerebrovascular diseases (Hao et al., 2021) has been well documented. Adults with type 2 diabetes, hypertension, and cerebrovascular disease are at increased risk of developing dementia (Biessels et al., 2008). These chronic diseases are significantly associated with multidomain lifestyles (Boehme et al., 2017; Altobelli et al., 2020; Ozemek et al., 2020; Hoshide et al., 2023; Zyriax and Windler, 2023) and an increased risk of dementia in the same direction (Janson et al., 2004; Brands et al., 2005; Biessels et al., 2006; Yang et al., 2017; Ou et al., 2020). Recent studies have shown that a more active life can mitigate the deleterious impact of chronic diseases on dementia (Marseglia et al., 2020; Wang et al., 2020). Therefore, it is crucial to understand complicated relationships among multidomain lifestyles, chronic diseases, and dementia in the context of the new era and to develop intensive prevention strategies that are in line with the current reality of social life.

In response to the urgent need to clarify the relationship among multidomain lifestyles, chronic diseases, and dementia, this study investigated the independent associations of multidomain lifestyles and chronic diseases with dementia and examined whether these factors interact with each other creating greater risks of dementia in older adults.

2. Materials and methods

2.1. Study participants

We used baseline data from the Hubei Memory and Aging Cohort Study (ChiCTR1800019164), a longitudinal cohort study characterized by the collection of multidimensional risk factors and cognitive aging trajectories in a large community-based old population. Detailed information about the cohort was described previously (Li et al., 2022). The sample included in the study comprised participants aged 65 years and older. We excluded persons with dementia diagnosed by a physician, serious physical illness, psychiatric illness, severe visual and hearing impairment, severely impaired ability to perform activities of daily living (ADL), and missing information. A total of 8,221 residents were included in this study. All procedures were performed in accordance with the basic principles of the Declaration of Helsinki and were approved by the Ethics Committee of the Medical School of Wuhan University of Science and Technology. All participants provided written informed consent.

2.2. Assessment of multidomain lifestyle

Lifestyle data were obtained from the participants' self-reports of their past experiences. In the main analysis, lifestyle was determined by summing the scores for six factors: smoking, alcohol consumption, dietary pattern, physical activity, cognitive activity, and waist circumference. Healthy status received a score of 1, whereas the opposite received a score of 0. Healthy smoking status was defined as never smoking; healthy drinking status was defined as moderate (and never) drinking (no more than 28 g of alcohol per day for men and no more than 14 g of alcohol per day for women) (Lloyd-Jones et al., 2010); healthy eating pattern was defined as eating a balanced diet that includes nutrient-rich foods, such as vegetables, fruits, whole grains, lean proteins, and healthy fats (Bojang and Manchana, 2023); regular physical activity was defined as at least 150 min of moderate to vigorous activity per week (U.S. Department of Health and Human Services and U.S. Department of Agriculture, 2015); regular cognitive activity was defined as at least one cognitive activity per day (reading books, reading newspapers, playing chess, playing cards, playing games, speculating on stocks, etc.); and healthy waist circumference was defined as <80 cm for women and <85 cm for men. Lifestyle scores ranged from 0 to 6, with higher scores representing healthier lifestyles, and were divided into three groups: unhealthy (0–2), intermediate healthy (3–4), and healthy (5–6).

2.3. Cognition evaluation and diagnoses

This study used a standardized cognitive assessment battery to test the cognitive status of the participants. These tests included (1) the Mini-Mental State Examination (MMSE) (Creavin et al., 2016) and the Montreal Cognitive Assessment-Basic (MoCA-BC) (Cao et al., 2012) to assess global cognition; (2) the auditory verbal learning test (An et al., 2018), shape trail tests A and B, forward and backward conditions of the digit span test, Boston naming test (Miebach et al., 2019) and animal fluency test, and clock-drawing test with 5 scales to assess memory, executive ability, attention, language ability, and visuospatial function, respectively.

Two neuropsychologists with expertise in dementia confirmed the diagnosis of MCI and dementia based on Petersen's MCI judgment criteria and the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V) criteria. The diagnostic criteria for MCI were as follows: (1) the presence of cognitive impairment reported or found by the patient, informant, and/or clinician; (2) the presence of objective evidence of impairment in at least one domain of cognitive functioning not limited to memory; (3) retention of independent functional abilities, though instrumental abilities might have been slightly impaired

[assessed by clinical dementia rating and ADL scales]; and (4) no diagnosis of dementia (assessed by DSM-V) (Petersen, 2004). The diagnostic criteria for dementia were as follows: (1) previous normal cognition, (2) acquired cognitive decline or abnormal mental behavior, (3) affected work ability or daily life, and (4) cannot be explained by delirium or other mental illness (American Psychiatric Association [APA], 2000).

2.4. Other measures

Other measures included sociodemographic characteristics, past medical history, family history, personal life history, physical examination, and laboratory tests. The Geriatric Depression Scale was used to assess depression in older adults over the past 6 months (Shin et al., 2019), and ADL and instrumental ADL scales were used to assess the participants' ability and disability in daily living (Lawton and Brody, 1969).

2.5. Statistical analysis

Continuous variables were found to be non-normally distributed using the Kolmogorov-Smirnov test; therefore, data for this component were expressed as median (interquartile range). Categorical variables were expressed as numbers (percentages). The differences between participants with and without dementia were analyzed using the Mann-Whitney U test and chi-square test. Univariate logistic regression was used to assess the strength of the association between the correlates and dementia. Multivariate adjusted models were used to explore the relationship between univariate lifestyle factors and dementia. In adjusted model, we adjusted for residence area, age, sex, education level, hypertension, diabetes, and cerebrovascular disease. We then used logistic regression models to assess the association among lifestyle classification, chronic diseases, and dementia separately. We performed partial correlation analysis to analyze the relationships among multidomain lifestyles, chronic diseases, and dementia. Subgroup analyses were performed to explore whether the association between lifestyles and dementia differed based on health status. Multiple correspondence analyses was performed to further explore the multiple relationships among multidomain lifestyles, chronic diseases, and dementia.

Finally, seven sensitivity analyses were conducted to minimize confounding by reverse causality and potential confounders: (1) conducted Spearman's correlation analysis to analyze the linear relationship between lifestyle scores and cognitive function scores; (2) excluded participants who showed significant loss of life skills based on ADL scores to rule out the effect of loss of life skills on lifestyle changes; (3) replaced moderate alcohol consumption with never drinking, as the effect of alcohol consumption on dementia is controversial; (4) redefined healthy diet as a balanced diet (balanced meat and vegetables), as some participants with diabetes reported concerns about exacerbating their condition by consuming fruits; (5) included good sleep status, i.e., defined as no insomnia; (6) further analyzed the relationship between lifestyle classification and dementia only in MCI and dementia participants; and (7) performed multiple correspondence analysis to analyze the multiple relationship between lifestyles, chronic diseases, and cognitive status. All p-values were bilateral, and the results were considered statistically significant at $p < 0.05$. SPSS version 26.0 was used for all statistical analyses.

3. Results

3.1. Sociodemographic characteristics

Table 1 demonstrates the characteristics of the participants with respect to sociodemographics, chronic diseases, and lifestyle factors. A total of 8,221 eligible participants aged 65 years and older, including 3,772 men and 4,449 women, were included. They were 3,164 rural and 5,057 urban participants. The proportions of participants aged 65–69, 70–74, 75–79, and ≥80 years were 41.9, 29.8, 15.7, and 12.6%, respectively. Further, 595 (7.2%) participants were diagnosed with dementia, and the prevalence of hypertension, diabetes mellitus, and cerebrovascular disease was 66.2, 16.6, and 17.5%, respectively. Participants with dementia were more likely to be rural ($p < 0.001$), older ($p < 0.001$), female ($p < 0.001$), and less educated ($p < 0.001$). Participants with dementia had higher rates of hypertension ($p = 0.036$) and cerebrovascular disease ($p = 0.006$) than those without dementia. Although some risk factors related to an unhealthy lifestyle were equally present in both participants with and without dementia, those without dementia were more inclined to have a healthy lifestyle ($p < 0.001$), which included a healthy diet pattern ($p < 0.001$), physical activity ($p < 0.001$), and cognitive activity ($p < 0.001$). No significant differences were noted in other factors between the groups.

3.2. Correlations among multidomain lifestyle, chronic diseases, and dementia

First, we assessed the strength of the individual association of six lifestyle factors, i.e., smoking, moderate alcohol consumption, dietary patterns, physical activity, cognitive activity, and waist circumference with dementia using univariate logistic regression (Table 2). Then, we built the multivariate adjusted models and found that having a healthy diet (OR = 0.50, 95% CI: 0.38–0.67, $p < 0.001$), regular physical activity (OR = 0.53, 95% CI: 0.44–0.63, $p < 0.001$), and cognitive activity (OR = 0.40, 95% CI: 0.32–0.48, $p < 0.001$) were significantly associated with a lower prevalence of dementia.

Second, we evaluated the strength of the association of individual health conditions with dementia (Table 3) and found that participants with diabetes had a 30% increased risk of dementia compared to that of those without diabetes (OR = 1.30, 95% CI: 1.04–1.63, $p < 0.05$). Moreover, cerebrovascular disease was positively associated with dementia (OR = 1.39, 95% CI: 1.12–1.72, $p < 0.01$). We further assessed the association of multidomain lifestyles with dementia and found that participants with an intermediate healthy lifestyle (OR = 1.90, 95% CI: 1.38–2.61, $p < 0.001$) were less associated with dementia than those with an unhealthy lifestyle (OR = 3.29, 95% CI: 2.32–4.68, $p < 0.001$).

Third, our partial correlation analysis for multidomain lifestyles, chronic diseases, and dementia showed that both cerebrovascular disease ($r = 0.030$, $p = 0.007$) and unhealthy

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TABLE 1 Sociodemographic characteristics, chronic diseases, and lifestyle factors of the participants.

Characteristics	Total, *n* (%)	Non-dementia, *n* (%)	Dementia, *n* (%)	*p*-value
Number of participants	8221	7626 (92.8)	595 (7.2)	
Sex (female)	4449 (54.1)	4082 (53.5)	367 (61.7)	<0.001**
Age (years), median (IQR)	71 (67, 75)	70 (67, 75)	76 (71, 81)	<0.001**
Age groups, in years				<0.001**
65–69	3441 (41.9)	3327 (43.6)	114 (19.2)	
70–74	2448 (29.8)	2282 (29.9)	166 (27.9)	
75–79	1292 (15.7)	1168 (15.3)	124 (20.8)	
≥80	1040 (12.6)	849 (11.1)	191 (32.1)	
Education (years), median (IQR)	9 (3, 12)	9 (3, 12)	2 (0, 8)	<0.001**
Education level				<0.001**
Primary school or below	3425 (41.7)	3043 (39.9)	382 (64.2)	
Junior high school	1955 (23.8)	1850 (24.3)	105 (17.6)	
Senior high school	1483 (18.0)	1426 (18.7)	57 (9.6)	
University or above	1358 (16.5)	1307 (17.1)	51 (8.6)	
Residential area (rural)	3164 (38.5)	2791 (36.3)	373 (62.7)	<0.001**
Diabetes	1367 (16.6)	1257 (16.5)	110 (18.5)	0.206
Hypertension	5440 (66.2)	5023 (65.9)	417 (70.1)	0.036*
Cerebrovascular disease	1440 (17.5)	1311 (17.2)	129 (21.7)	0.006**
Never smoking	6215 (75.6)	5743 (75.3)	472 (79.3)	0.028*
Moderate drinking	6546 (79.6)	6077 (79.7)	469 (78.8)	0.614
Healthy diet	2340 (28.5)	2271 (29.8)	69 (11.6)	<0.001**
Physical activity	6653 (80.9)	6282 (82.4)	371 (62.4)	<0.001**
Cognitive activity	4914 (59.8)	4734 (62.1)	180 (30.3)	<0.001**
Healthy waist circumference	2405 (29.3)	2232 (29.3)	173 (29.1)	0.921
Lifestyle category				<0.001**
Healthy	1799 (21.9)	1750 (22.9)	49 (8.2)	
Intermediate	4784 (58.2)	4447 (58.3)	337 (56.6)	
Unhealthy	1638 (19.9)	1429 (18.7)	209 (35.1)	

*$p < 0.05$; **$p < 0.01$.

lifestyle ($r = 0.085$, $p < 0.001$) were independently associated with dementia. Additionally, hypertension ($r = 0.061$, $p < 0.001$) and diabetes ($r = 0.037$, $p = 0.001$) were positively associated with unhealthy lifestyle. Among the three chronic diseases, the associations between hypertension, diabetes, and cerebrovascular disease were statistically significant ($r_{Hypertension-Diabetes} = 0.086$, $p < 0.001$; $r_{Hypertension-Cerebrovasculardisease} = 0.068$, $p < 0.001$; $r_{Diabetes-Cerebrovasculardisease} = 0.042$, $p < 0.001$) (Figure 1).

Fourth, to determine the possible interaction effect of lifestyles and chronic diseases on dementia prevalence, we conducted interaction tests and found interactions of hypertension ($p = 0.004$) and diabetes ($p = 0.010$) but not of cerebrovascular disease ($p = 0.817$) with lifestyles. We performed subgroup analyses using multifactorial logistic regression and found that among participants without diabetes, those with intermediate healthy (OR = 1.56, 95% CI: 1.11–2.19, $p = 0.010$) and unhealthy lifestyles (OR = 2.70, 95% CI: 1.86–3.93, $p < 0.001$) had a stronger association with dementia prevalence than those with a healthy lifestyle. A similar association was noted between lifestyle and the prevalence of dementia in participants with diabetes ($OR_{intermediate} = 7.14$, 95% CI: 2.18–23.34, $p = 0.001$; $OR_{unhealthy} = 12.25$, 95% CI: 3.56–42.14, $p < 0.001$). The model that included all participants demonstrated that a healthy lifestyle was associated with a lower prevalence of dementia, regardless of whether the participants had diabetes (Table 4). As for participants with hypertension and cerebrovascular disease, both intermediate healthy and unhealthy lifestyles were found to be positively associated with the prevalence of dementia, unlike healthy lifestyle (Supplementary Table 1). To more clearly and intuitively determine the complex relationship among different lifestyles, the prevalence of three chronic diseases, and different cognitive states, we conducted a multiple correspondence analysis and found that participants with an unhealthy lifestyle were more likely to have chronic diseases and dementia (Figure 2).

Finally, in the sensitivity analysis, we explored the correlation between lifestyle scores and the MMSE, MoCA, and ADL scores.

TABLE 2 Univariate analysis of lifestyle factors associated with dementia.

Characteristics	Unadjusted model			Adjusted model 1			Adjusted model 2		
	Odds ratio	95% CI	*p*-value	Odds ratio	95% CI	*p*-value	Odds ratio	95% CI	*p*-value
Never smoking	1.26	1.03, 1.55	0.028*	0.78	0.61, 1.01	0.055	0.78	0.61, 1.01	0.056
No	1 (Ref)			1 (Ref)			1 (Ref)		
Moderate drinking	0.95	0.77, 1.16	0.614	0.84	0.67, 1.06	0.141	0.83	0.66, 1.04	0.112
No	1 (Ref)			1 (Ref)			1 (Ref)		
Healthy diet	0.31	0.24, 0.40	<0.001**	0.51	0.39, 0.67	<0.001**	0.50	0.38, 0.67	<0.001**
No	1 (Ref)			1 (Ref)			1 (Ref)		
Physical activity	0.35	0.30, 0.42	<0.001**	0.52	0.43, 0.62	<0.001**	0.53	0.44, 0.63	<0.001**
No	1 (Ref)			1 (Ref)			1 (Ref)		
Cognitive activity	0.27	0.22, 0.32	<0.001**	0.39	0.32, 0.48	<0.001**	0.40	0.32, 0.48	<0.001**
No	1 (Ref)			1 (Ref)			1 (Ref)		
Healthy waist circumference	0.99	0.82, 1.19	0.921	1.11	0.92, 1.35	0.292	1.16	0.95, 1.41	0.146
No	1 (Ref)			1 (Ref)			1 (Ref)		

*$p < 0.05$; **$p < 0.01$.
Model 1 adjusted for area, age, sex, and education level.
Model 2 adjusted for area, age, sex, education level, hypertension, diabetes and cerebrovascular disease.

TABLE 3 Associations of dementia with lifestyle and chronic diseases.

Group	Unadjusted model			Adjusted model 1			Adjusted model 2		
	Odds ratio	95% CI	*p*-value	Odds ratio	95% CI	*p*-value	Odds ratio	95% CI	*p*-value
Lifestyle category									
Healthy	1 (Ref)			1 (Ref)			1 (Ref)		
Intermediate	2.71	2.00, 3.67	<0.001**	1.92	1.40, 2.64	<0.001**	1.90	1.38, 2.61	<0.001**
Unhealthy	5.22	3.80, 7.19	<0.001**	3.36	2.36, 4.77	<0.001**	3.29	2.32, 4.68	<0.001**
Diabetes	1.15	0.93, 1.43	0.206	1.33	1.06, 1.66	0.014*	1.30	1.04, 1.63	0.023*
No	1 (Ref)			1 (Ref)			1 (Ref)		
Hypertension	1.21	1.01, 1.46	0.036*	1.03	0.85, 1.24	0.789	0.99	0.81, 1.19	0.880
No	1 (Ref)			1 (Ref)			1 (Ref)		
Cerebrovascular disease	1.33	1.09, 1.64	0.006**	1.41	1.14, 1.74	0.002**	1.39	1.12, 1.72	0.003**
No	1 (Ref)			1 (Ref)			1 (Ref)		

*$p < 0.05$; **$p < 0.01$.
Model 1 adjusted for area, age, sex, and education level.
Model 2 adjusted for area, age, sex, education level, hypertension, diabetes and cerebrovascular disease.

We found a positive correlation between lifestyle and cognitive functioning scores, independently of chronic diseases. A significant negative correlation was observed between multidomain lifestyle and function ability scores, and this association was similar in participants with (rs = −0.19, $p < 0.001$) and without chronic diseases (rs = −0.20, $p < 0.001$) (**Supplementary Table 2**). We excluded participants with severely impaired function ability and analyzed the association between multidomain lifestyle classification and dementia prevalence and found no substantial change. An unhealthy lifestyle was significantly associated with a higher rate of dementia in both groups with (OR = 2.95, 95% CI: 1.86–4.69, $p = 0.001$) and without chronic diseases (OR = 3.02, 95% CI: 1.32–6.95, $p = 0.009$) (**Supplementary Table 3**).

After redefining moderate alcohol consumption as never drinking, reanalysis showed that the association of unhealthy (OR $_{\text{No chronic diseases}}$ = 3.48, 95% CI: 1.60–7.56, $p = 0.002$; OR $_{\text{Chronic diseases}}$ = 3.02, 95% CI: 2.04–4.49, $p < 0.001$) and intermediate healthy lifestyles (OR $_{\text{No chronic diseases}}$ = 2.34, 95% CI: 1.17–4.72, $p = 0.017$; OR $_{\text{Chronic diseases}}$ = 1.67, 95% CI: 1.16–2.40, $p = 0.005$) with higher dementia prevalence was statistically significant in different health conditions (**Supplementary Table 4**). The association in the results remained significant after removing the criterion of daily fruit consumption from the healthy diet (OR $_{\text{No chronic diseases}}$ = 3.64, 95% CI: 1.93–6.89, $p < 0.001$; OR $_{\text{Chronic diseases}}$ = 2.95, 95% CI: 2.09–4.18, $p < 0.001$; **Supplementary Table 5**). Furthermore, this association was statistically significant with the addition of

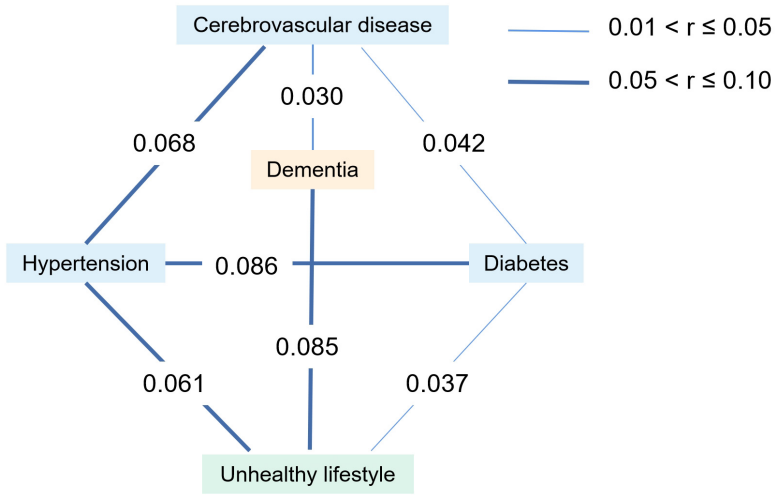

FIGURE 1
Correlation analyses between lifestyle categories, chronic diseases and dementia. The figure shows the statistically significant correlation coefficient (r) among unhealthy lifestyle, hypertension, diabetes, cerebrovascular disease and dementia. The thin correlation line indicates $0.01 < r \leq 0.05$, and the thick correlation line indicates $0.05 < r \leq 0.10$.

TABLE 4 Relationship between lifestyle and dementia in group with diabetes or not.

Diabetes		Unadjusted model			Adjusted model		
		Odds ratio	95% CI	*p*-value	Odds ratio	95% CI	*p*-value
In separate model							
No	Healthy	1 (Ref)			1 (Ref)		
	Intermediate	2.33	1.69, 3.20	<0.001**	1.56	1.11, 2.19	0.010*
	Unhealthy	4.67	3.34, 6.52	<0.001**	2.70	1.86, 3.93	<0.001**
Yes	Healthy	1 (Ref)			1 (Ref)		
	Intermediate	8.31	2.59, 26.59	<0.001**	7.14	2.18, 23.34	0.001**
	Unhealthy	13.70	4.16, 45.07	<0.001**	12.25	3.56, 42.14	<0.001**
In one model							
No	Healthy	1 (Ref)			1 (Ref)		
	Intermediate	2.33	1.69, 3.20	<0.001**	1.59	1.14, 2.22	0.007**
	Unhealthy	4.67	3.34, 6.52	<0.001**	2.77	1.92, 4.00	<0.001**
Yes	Healthy	0.36	0.11, 1.18	0.092	0.34	0.10, 1.10	0.071
	Intermediate	3.02	2.06, 4.42	<0.001**	2.24	1.51, 3.32	<0.001**
	Unhealthy	4.99	3.16, 7.88	<0.001**	3.83	2.35, 6.24	<0.001**

*$p < 0.05$; **$p < 0.01$.
Model adjusted for area, age, sex, education level, hypertension, diabetes, and cerebrovascular disease.

sleep status to lifestyle (OR $_{\text{No chronic diseases}}$ = 4.13, 95% CI: 2.18–7.80, $p < 0.001$; OR $_{\text{Chronic diseases}}$ = 3.19, 95% CI: 2.29–4.46, $p < 0.001$; Supplementary Table 6). When analysis of the sample included with MCI and dementia only, we found that an unhealthier lifestyle was continuously associated with a higher prevalence of dementia (OR $_{\text{No chronic diseases–Unhealthy}}$ = 4.97, 95% CI: 2.18–11.33, $p < 0.001$; OR $_{\text{Chronic diseases–Unhealthy}}$ = 2.89, 95% CI: 1.90–4.39, $p < 0.001$; Supplementary Table 7). Additionally, an intermediate lifestyle was associated with three chronic diseases and MCI. Finally, multiple correspondence analyses showed a strong association between unhealthy lifestyle and dementia and chronic diseases (Supplementary Figure 1).

4. Discussion

We determined independent associations of six lifestyle factors and three chronic diseases with dementia and demonstrated their enhanced combined impact on dementia among older adults. Although some individual lifestyle factors were not strongly associated with dementia prevalence, a comprehensive assessment of multidomain lifestyles showed a strong correlation with dementia prevalence; this correlation was stronger in patients with some chronic diseases. Our study suggests there may be a complex relationship among lifestyle, chronic diseases, and

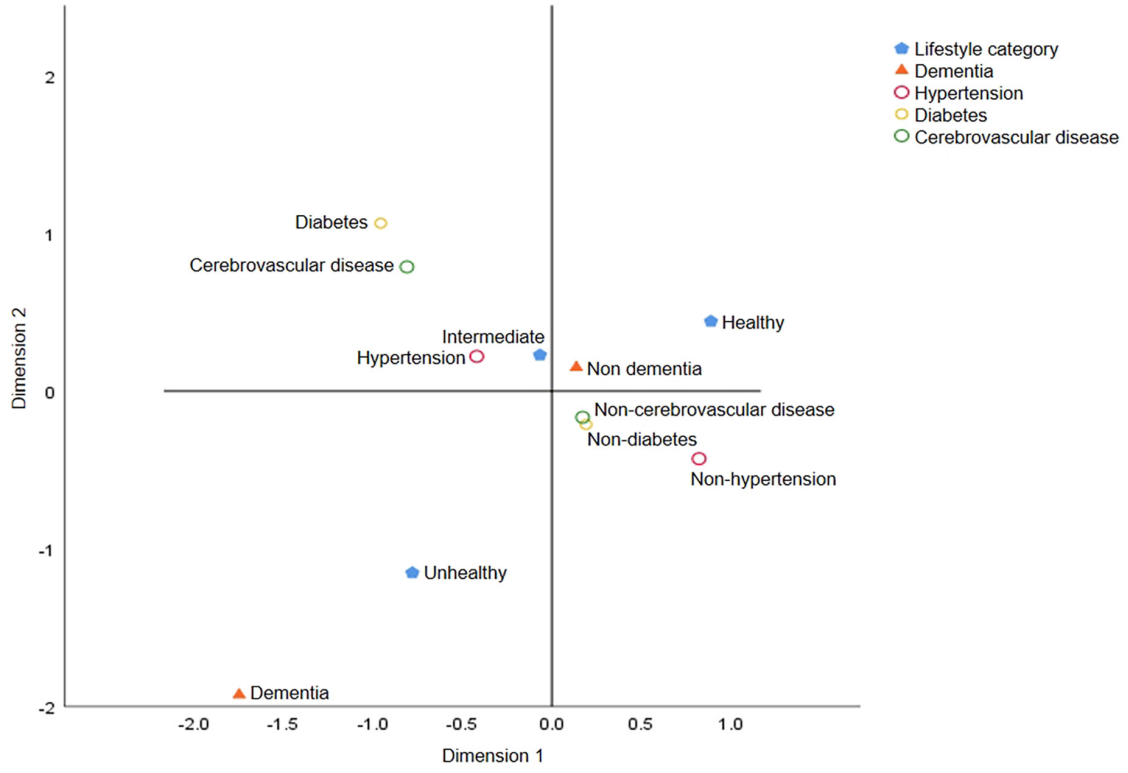

FIGURE 2
Multiple correspondence analysis charts for lifestyle categories, chronic diseases and dementia. The graph reflects the degree of association among lifestyle categories (healthy, intermediate, and unhealthy lifestyle), chronic diseases and dementia. The closer the category points are, the greater the correlation is. Unhealthy lifestyle and dementia are located in the same quadrant and far away from the center of the circle, indicating that these two points have distinct characteristics and are quite different from other points.

dementia. Although there are substantial evidences that healthy lifestyles may reduce the risk of cognitive decline and dementia (Lee et al., 2018; Amakye et al., 2019; Marseglia et al., 2019; Du Preez et al., 2021; Nabe-Nielsen et al., 2021), few trials have attempted to reveal the role of lifestyles in preventing dementia (Lee et al., 2014; Ngandu et al., 2015; Gregory et al., 2016; Andrieu et al., 2017). Our analysis found that some individual lifestyle variables were not significantly associated with dementia prevalence, whereas the combination of lifestyle factors had a reinforcing effect. In addition, most studies did not include patients with chronic diseases, a population at high risk of dementia. In this study, lifestyle was defined as a holistic concept to study the combined effect of multidomain lifestyle on dementia prevalence, with a specific focus on whether there was a similar association between individuals with and without chronic diseases. To minimize the impact of possible reverse causality of lifestyle changes due to dementia, all analyses were repeated after excluding participants with severely impaired life ability at baseline survey. The association between lifestyles and dementia prevalence among the participants was not altered, regardless of chronic diseases, suggesting that our findings are unlikely to be attributed to reverse causality.

Other lifestyle factors that were not included in the six comprehensive ones may also have an impact on the development of dementia. Therefore, we redefined some lifestyle factors, and our results showed a consistent association between lifestyle and dementia. In addition, we performed Spearman's correlation analysis to present the continuous correlation among lifestyle scores, cognitive function, and life ability scores. The results further showed that an unhealthier lifestyle was related to worse cognitive abilities.

Previous studies have confirmed that a healthy lifestyle is associated with a lower risk of cardiovascular disease and a healthier physical condition (Marmot, 2020; Zhang et al., 2021) as well as a lower risk of dementia (Anstey et al., 2009; Fletcher et al., 2013; Blondell et al., 2014; Mozaffarian, 2016). For example, never smokers and former smokers may have a healthier diet, such as eating more vegetables and fruits (Kawada, 2004), and a lower risk of cardiovascular disease (Dobson et al., 1991), both of which may be beneficial for delaying or reversing the pathological process of dementia (Sabia et al., 2008). Middle-aged and older men have a higher prevalence of cardiovascular disease and mortality, and thus the association between smoking, alcohol consumption, and dementia may be underestimated (Chêne et al., 2015; Du Preez et al., 2021). The mechanism of the relationship between lifestyle factors and dementia is not fully understood. Vascular, inflammation, oxidative stress, neurotoxicity, and psychosocial processes may play a role in the association between lifestyle related factors and pathological process of dementia (Dening et al., 2020), such as smoking (Dobson et al., 1991; Kawachi et al., 1993, 1994), drinking (Zahr et al., 2011). A healthy dietary pattern plays an important role in maintaining nerve membrane integrity and

upregulating neurotrophic factors (Coley et al., 2015). In addition, the gut-brain axis is beneficial for maintaining brain health and the progression of neurological diseases (Carabotti et al., 2015). There is evidence that physical activity can increase cognitive reserve, which is the brain's ability to resist in response to injury (Fratiglioni et al., 2004). Physical activity not only increases brain volume (Rovio et al., 2010; Ho et al., 2011) and levels of brain-derived neurotrophic factor (Komulainen et al., 2008), but also improves high blood pressure and elevated blood sugar levels, which are risk factors for dementia. This is beneficial to cardiovascular health and reduces metabolic risk (Ho et al., 2011). In addition, physical activity can also effectively relieve psychological stress (Fratiglioni et al., 2004). Cognitive activity can increase cognitive reserve and brain volume, which is similar to physical activity (Liu et al., 2012). Cardiovascular risk factors play a potential role in the association between waist circumference and cognitive function. Central obesity is associated with cardiovascular risk factors such as high blood pressure and high cholesterol (Tchernof and Després, 2013), and it is also an important risk factor for cardiovascular disease and T2D (Chang et al., 2012). These cardiovascular risk factors and cardiovascular disease are significantly associated with dementia (Whitmer et al., 2005; Kloppenborg et al., 2008). Moreover, other lifestyle factors and genetics may also play a role in their association. As a complex and multi-factorial disease, dementia may require multidomain comprehensive research on many related factors and disease mechanisms. Therefore, consideration of multidomain lifestyles can lead to a comprehensive and objective understanding of the correlation between lifestyle and dementia. One study has shown that the combination of modifiable risk factors is related to the risk of dementia (Peters et al., 2019); the healthy levels of many risk factors are controversial. Therefore, we reclassified the health criteria of some risk factors to explore the relationship among multidomain lifestyle, chronic diseases, and dementia under different criteria.

Previous studies have shown that the association between chronic diseases and dementia may be mediated by cardiovascular risk factors, education, socioeconomic status, and lifestyle factors (Twig et al., 2014), with equally complex interactions among these factors. Therefore, it is necessary to comprehensively examine the effects of multidomain lifestyles on cognitive function in patients with chronic diseases. Our study suggests that participants with diabetes and a healthy lifestyle were more strongly associated with a lower prevalence of dementia than those without diabetes. This indicates that the effect of healthy lifestyles does not seem to be affected by diabetes. Moreover, hypertension interacted with lifestyle in our study, suggesting that hypertension and diabetes have an interactive effect with lifestyle on the prevalence of dementia. The interaction effect between cerebrovascular disease and lifestyle was not significant; however, an unhealthy lifestyle was strongly associated with the prevalence of dementia, suggesting that lifestyle affects the prevalence of dementia through a pathway independent of cerebrovascular disease. Accelerated aging and age-related cerebrovascular diseases are associated with many pathophysiological processes. Regardless of the risk factors in previous studies, the complex vascular phenotype changes caused by aging make the brain prone to vascular cognitive impairment and dementia (Ungvari et al., 2010). Studies have shown that atherosclerosis, the main vascular lesion of vascular cognitive impairment disorders, may be associated with aging and persistent low-grade inflammation (Franceschi et al., 2000; Csiszar et al., 2008; Nilsson, 2015; O'Brien and Thomas, 2015). These inflammatory factors increase with age, independent of known risk factors (Bruunsgaard et al., 2000; Miles et al., 2008). This suggests that cerebrovascular disease and lifestyle-related risk factors may independently influence cognitive function. In the correspondence analysis, we found that people who endorsed healthier lifestyle was more likely to have better cognitive status and no chronic diseases, whereas those with an unhealthy lifestyle were more strongly associated with dementia than hypertension, diabetes, and cerebrovascular disease. Overall, our study suggests that people without chronic diseases should adapt to a healthy lifestyle to reduce their risk of developing dementia. Especially, people with chronic diseases were encouraged to reduce the likelihood of developing dementia in the future by re-establishing a healthy lifestyle. This is because people with chronic diseases can have more benefit in preventing dementia by having a healthy lifestyle than those without chronic diseases.

The present study has some limitations. First, although the response rate in this study was relatively high, we cannot exclude the possibility of selection bias among the participants. We excluded participants who were unable to participate in the survey for physical reasons; however, we could not confirm whether their physical conditions were associated with dementia. Second, the information on lifestyle included in our study was mainly through self-reports, which may have led to subjective cognitive errors. Although we validated these self-reports using health records from health centers, there may still be an impact on the true correlation. Third, the included indicators of lifestyle-related factors were limited and reflected only some aspects of lifestyle; other lifestyle factors may also affect dementia prevalence. The lifestyle scores in this study were derived from the sum of the scores of lifestyle-related factors. We assumed that these lifestyle factors have the same effect on physical status; however, this may have obscured the real interactions between lifestyle factors. Fourth, there may be potential confounding factors that interfere with our results, such as other physical conditions and socioeconomic status. Participants may have had serious medical conditions at baseline that were not covered in the survey, affecting their lifestyle behaviors and socioeconomic status. Fifth, since the present data were derived from an observational study, it was impossible to make clear causal inferences about the findings. Although our multivariate adjusted model analysis and sensitivity analysis produced results that were consistent with those of the main analysis, reverse causality and residual confounding may have existed.

5. Conclusion

Despite these limitations, based on a large size sample, sufficient amount of high-quality data, multivariate adjusted model analyses, and a series of sensitivity analyses, this study highlights the fact that an unhealthier multidomain lifestyle is associated with a higher prevalence of dementia, and this association is stronger in people with chronic diseases such as diabetes. Based on this, we suggest that people prioritize lifestyle modifications to prevent dementia. Particularly, people with chronic diseases who are at a high risk of dementia may gain greater preventive effects.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

All procedures involving human participants in this study were in accordance with the basic principles of the Declaration of Helsinki. The study was approved by the Ethics Committee of the Medical School of Wuhan University of Science and Technology (protocol code: 201845; approved on October 22, 2018).

Author contributions

J-jZ: conceptualization (supporting), formal analysis (lead), investigation (equal), methodology (supporting), software (lead), validation (equal), writing–original draft preparation (supporting), and writing–review and editing (supporting). Z-xW and WT: resources (lead). DL: supervision (equal) and validation (equal). G-rC: data curation (lead) and supervision (equal). LX: funding acquisition (equal). F-fH: investigation (equal). YZ: conceptualization (lead), funding acquisition (equal), methodology (lead), project administration (lead), supervision (equal), validation (equal), writing–original draft preparation (lead), and writing–review and editing (lead). All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2023.1200671/full#supplementary-material

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Impact of transcranial direct current stimulation on white matter microstructure integrity in mild cognitive impairment patients according to effect modifiers as risk factors for Alzheimer's disease

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Background: Little research exists on how individual risk factors for Alzheimer's disease (AD) affect the intermediate phenotype after transcranial direct current stimulation (tDCS), despite the importance of precision medicine-based therapeutic approaches.

Objective: To determine how an application of sequential tDCS (2 mA/day, left dorsolateral prefrontal cortex, 10 sessions) affects changes in white matter (WM) microstructure integrity in 63 mild cognitive impairment (MCI) patients with effect modifiers such as Aβ deposition, *APOE* ε4 carrier status, BDNF Val66Met polymorphism status, and sex.

Methods: We examined individual effect modifier-by-tDCS interactions and multiple effect modifiers-by-tDCS interactions for diffusion metrics. We also evaluated the association between baseline Aβ deposition and changes in WM microstructure integrity following tDCS.

Results: We found that *APOE* ε4 carrier status and sex had a significant interaction with tDCS, resulting in increased fractional anisotropy (FA) in the right uncinate fasciculus (UF) after stimulation. Additionally, we observed multiple effect modifiers-by-tDCS interactions on WM integrity of the right UF, leading to a more pronounced increase in FA values in *APOE* ε4 carriers and females with Val66 homozygotes. Finally, baseline Aβ deposition was positively associated with a difference in FA of the left cingulum in the hippocampal area, which showed a positive association with the changes in the score for delayed memory.

Conclusion: Our study shows the differential impact of individual AD risk factors on changes in the early intermediate phenotype after sequential tDCS in MCI patients. This research emphasizes the importance of precision medicine approaches in tDCS for the prodromal stages of AD.

KEYWORDS

transcranial direct current stimulation, amyloid-beta deposition, *APOE* ε4 allele, BDNF Val66Met polymorphism, sex

Introduction

Alzheimer's disease (AD) is a representative neurodegenerative disorder characterized by the deposition of amyloid beta (Aβ) and tau proteins, leading to impairment of cognitive function and the ability to perform daily activities (Scheltens et al., 2016). Mild cognitive impairment (MCI) is a prodromal stage of AD and approximately 10–15% of patients with MCI have been reported to convert to dementia each year (Gauthier et al., 2006). Despite the high risk of progression to dementia, treatment options for MCI are limited. Although several drugs have been investigated in clinical trials, their efficacy in delaying or preventing progression to dementia is modest and uncertain (Anderson et al., 2017). Therapeutic approaches such as cognitive intervention (Jean et al., 2010), physical exercise (Lautenschlager et al., 2010), and dietary modification have demonstrated some promising outcomes in terms of changes in cognitive function and biomarkers (Singh et al., 2014). However, further research is required to establish these interventions as effective strategies for preventing AD. Additionally, the complexity of these interventions can make them challenging for individuals with MCI to implement and maintain consistently (Coley et al., 2019), highlighting the need for a simple, fixed intervention that can be sustained over a specific period. In this regard, there is currently a need for alternative interventions that are accessible to individuals with MCI and can improve cognitive function and mitigate neurodegenerative changes. An interest in non-invasive brain stimulation treatment methods is also increasing, and in particular, transcranial direct current stimulation (tDCS), which is highly accessible in terms of cost and portability, is proposed as one of the appropriate treatment options for MCI (Liu et al., 2017). tDCS modulates the excitability of cortical neurons depending on the current flow direction and has synaptic after-effects through long-term potentiation (LTP), affecting neuroplasticity (Nitsche et al., 2003). It is also suggested to normalize brain function in patients with AD and facilitate the clearance of Aβ by modulating the integrity of the brain–blood barrier (Meinzer et al., 2015; Shin et al., 2020). Previous studies have shown that cognitive function can be improved through single or multi-session tDCS in patients with AD and MCI (Lu et al., 2019; Manenti et al., 2020). Moreover, long-term application of this technique is expected to modulate disease progression (Im et al., 2019; Yang et al., 2019).

Among intermediate phenotypes related to AD, changes in white matter microstructure have been demonstrated to occur earlier in dementia than changes in brain function, making it a useful early warning sign for the development of the disease (Zhang et al., 2009). Additionally, advanced imaging techniques, such as diffusion tensor imaging (DTI), can be used to quantify white matter assessment, allowing for more precise and objective measurement of changes over time (Le Bihan and Johansen-Berg, 2012). Patients with MCI have shown a reduced fractional anisotropy (FA) value, which reflects white matter integrity, in multiple posterior white matter regions, as well as in frontal, temporal, parietal, and occipital white matter and association fibers compared to normal subjects (Medina et al., 2006). Moreover, lower FA values of the splenium of corpus callosum and crus of fornix have accurately differentiated between amnestic MCI patients and control subjects (Medina et al., 2006). Furthermore, the deterioration of white matter microstructure has predicted a more rapid transition to MCI in cognitively intact older adults (Shafer et al., 2022). Additionally, prior research has indicated that the white matter microstructure changes in a non-linear manner as the clinical phenotype progresses and the extent of Aβ deposition increases (Dong et al., 2020; Pereira et al., 2021). In this regard, a connection to compensatory mechanisms has been proposed (Raghavan et al., 2021).

Despite the clinical evidence of white matter microstructure as an intermediate phenotype in the prodromal AD phase, few studies have examined changes in white matter microstructure after tDCS in MCI patients. In other vascular and neurodegenerative diseases, previous studies have shown that FA values increase in the frontal lobe after tDCS application in stroke patients with memory impairment (Hua et al., 2022). The white matter integrity of ventral language pathways has also predicted letter accuracy in primary progressive aphasia after tDCS application (Zhao et al., 2021).

Precision medicine, which involves personalized strategies based on an individual's genetic, biomarker, and clinical profile, has gained traction as a promising approach in the management of AD (Isaacson et al., 2018). It can help optimize tDCS treatment response and lead to more effective and efficient AD management by considering individual AD risk factors. Aβ deposition has been shown to affect the rate of cognitive decline and intermediate phenotype of brain structure and function, as well as the risk of transitioning to dementia in patients with MCI (Lukiw et al., 2020). In addition, *APOE* ε4 allele has been shown to affect the likelihood and severity of the Aβ pathophysiological cascade and is responsible for the greatest proportion of genetic risk factors for sporadic AD (Harrison et al., 2020). Brain-derived neurotrophic factor (BDNF) is a protein that impacts the growth and maintenance of neurons and has been known to play an important role in LTP-like neuroplasticity induced by tDCS (Chaieb et al., 2014). Previous studies have shown that its levels are decreased in AD (Ng et al., 2019). Moreover, research has suggested that BDNF Val66Met polymorphisms may modulate the risk of AD by affecting BDNF levels (Du et al., 2018). In regard to sex, research suggests that there are distinct differences in the clinical and intermediate phenotype patterns of males and females with AD (Ferretti et al., 2018). Specifically, studies have shown that females with MCI and dementia tend to experience a more rapid cognitive decline and brain atrophy after diagnosis (Ferretti et al., 2018). However, there have been few studies examining the impact of tDCS treatment based on individual AD risk factors, which would allow for more precise medical treatment strategies using tDCS in the prodromal stage of AD. In our previous pilot study in MCI patients, we have found that brain functional integration and segregation parameters differ after sequential tDCS to the left dorsolateral prefrontal cortex (DLPFC) depending on Aβ deposition and *APOE* ε4 carrier status (Kang et al., 2021). The BDNF Val66Met

polymorphism has been reported to have a duration-dependent effect on tDCS-induced motor cortex plasticity in older adults (Puri et al., 2015). However, other studies have exhibited inconsistent results on the impact of BDNF Val66Met polymorphism on cortical excitability (Antal et al., 2010; Teo et al., 2014). Regarding sex, previous research has reported a differential impact of tDCS on practice-related executive function in older adults, with higher current density observed in female older adults (Fehring et al., 2021). Therefore, it is worthwhile to investigate how the impact of tDCS on white matter microstructure integrity in the AD prodromal phase is modified by representative individual AD risk factors as effect modifiers.

In this context, we aimed to evaluate whether a 2-week application of sequential tDCS alters white matter microstructure integrity in patients with MCI and whether it depends on effect modifiers consisting of individual risk factors for AD. Furthermore, for white matter microstructure tracts that exhibit a significant association with baseline Aβ deposition, we assessed the correlation with the differences in cognitive function scores to elucidate the nature of the alteration.

Materials and methods

Participants

Participants were recruited through paper postings at the Brain Health Center, Yeoui-do St. Mary's Hospital, College of Medicine, the Catholic University of Korea, Republic of Korea. Inclusion criteria included the following: (1) participants who met Peterson's criteria for MCI (Petersen, 2004); (2) a Clinical Dementia Rating (CDR) score of 0.5. Potential participants were excluded for the following: (1) a history of alcoholism, drug abuse, head trauma, or psychiatric disorders; (2) taking any psychotropic medications (e.g., cholinesterase inhibitors, antidepressants, benzodiazepines, and antipsychotics); (3) contraindications to receiving tDCS or undergoing a MRI scan (ferromagnetic or coiled metal implants); (4) any skin disorder that compromised skin integrity over the scalp. The assessment process for inclusion and exclusion criteria was conducted by two geriatric psychiatrists. All potential participants consented to medical chart reviews. Additionally, all assessments were performed at the Brain Health Center, Yeoui-do St. Mary's Hospital, College of Medicine, the Catholic University of Korea, Republic of Korea. Study procedures were conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of the Catholic University of Korea (SC19DEST0012). Informed and written consent was obtained from all participants. This study is registered with the Clinical Research Information Service of Korea Disease Control and Prevention Agency (KCT0006020). The study was conducted from May 2020 to February 2022, and all on-site study procedures were performed at the Brain Health Center, Yeoui-do St. Mary's Hospital, College of Medicine, the Catholic University of Korea, Republic of Korea. The investigators have no ethical or financial conflict of interests with respect to the manufacturers of any of the equipment used in the study.

Study protocol

This study was conducted as a single-arm prospective trial, without the use of a sham condition. In this study, patients received 10 tDCS sessions at the patient's residence (five times per week for 2 weeks, totaling 10 sessions). We selected 10 sessions based on the results of previous clinical studies that used 10 sessions of tDCS to treat patients with AD and MCI (Cotelli et al., 2014; Khedr et al., 2014; Manenti et al., 2016; Roncero et al., 2017). We also considered the treatment adherence of older patients. The participants were assessed with a neuropsychological battery and underwent MRI scanning within 2 weeks before the first tDCS session and after the 10th session at the Brain Health Center of Yeouido St. Mary's Hospital. Subjects also underwent [^{18}F] flutemetamol (FMM) positron emission tomography–computed tomography (PET-CT), as well as *APOE*, and BDNF genotyping within 4 weeks before the first tDCS session. We have assessed side effects using the Udvalg for Kliniske Undersogelser side-effect rating scale at the end of each session (Lambert et al., 2003). In addition, participants and the psychologists who performed the neuropsychological battery were blinded to the results of amyloid-PET, *APOE*, and BDNF genotyping. Figure 1 displays a schematic diagram that illustrates the experimental procedures.

Transcranial direct current stimulation application

A constant direct current (2 mA, 20 min) was administered by an MRI-compatible stimulator (YDS-301 N, YBrain, Seoul, Republic of Korea). The anode was attached over the left DLPFC (F3 in the International 10/20 electroencephalogram system). The cathode was positioned over the right supraorbital region. The electrodes touched a saline-soaked sponge (disk type, radius = 3 cm) placed on the scalp. The staff skilled in the use of the device visited the patient's residence for each stimulus session to guide device application. To ensure that the electrodes were placed in the same location throughout the 10 stimulation sessions per participant, the staff used the international 10/20 electroencephalogram system, as well as electrode center locations relative to anatomical landmarks (nasion, inion, left and right preauricular points and vertex) identified on the participants' faces and heads. A vertex is defined as the intersection of the line connecting the nasion and inion and the line connecting both preauricular points. Position one end of a tape measure starting at one preauricular point and passing through the center of the electrode and note the intersection of that line with the line from the vertex to nasion. We also recorded the distance from the bilateral preauricular point to the center of the electrode and checked its position and distance to landmarks before the start of each session. Finally, to ensure the accuracy of the positioning, the staff double-checked the position of the electrodes 15 min after the start of the session. Additionally, the staff for each participant was kept unchanged throughout the 10 sessions.

Neuropsychological assessment

Cognitive function was assessed in all subjects using the Korean version of the Consortium to Establish a Registry for AD (CERAD-K; Lee et al., 2002). The measurements included assessments of the Korean version of the verbal fluency (VF) test, the 15-item Boston Naming Test, Mini-Mental State Examination (MMSE-K; Park, 1989), word list memory (WLM), word list recall (WLR), word list recognition (WLRc), constructional praxis, and constructional recall.

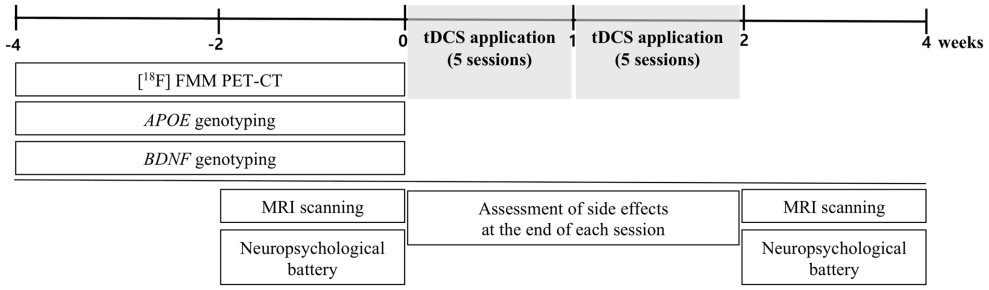

FIGURE 1
Schematic diagram showing timeline of experimental procedures. FMM, flutemetamol; BDNF, Brain-derived neurotrophic factor.

In addition, total memory (TM) scores were obtained by summing the respective scores from the WLM, WLR, and WLRc tests. The total CERAD-K scores were calculated by summing all subcategory scores, excluding the MMSE-K and constructional recall cores. Higher Trail Making Test B scores indicate lower executive function. Details regarding the use of specific tests and the reviewing process are described in the Supplementary Material.

Processing procedures of the DTI images

The procedures for magnetic resonance imaging acquisition are described in the Supplementary Material. The data was preprocessed using Statistical Parametric Mapping 12 (SPM12)[1] running on MATLAB version 2018b, the PANDA toolbox,[2] and the FMRIB software library v6.0.[3] The main procedure of PANDA includes (1) preprocessing; (2) producing diffusion metrics. The workflow of preprocessing includes five steps: (1) estimating the brain mask; (2) cropping the raw images; (3) correcting for the eddy-current effect; (4) averaging multiple acquisitions; and (5) calculating diffusion tensor (DT) metrics. We used FA, mean diffusivity (MD), and RD (radial diffusivity) as the DT metrics. Then, the images of the diffusion metrics were normalized to the MNI standard space for further analysis. For diffusion metrics images with voxel size of $1.0 \times 1.0 \times 1.0\,mm^3$ in the standard space, the regional averages were calculated according to prior white matter tract atlas (WM probtract atlas). This atlas comprises 20 regions, which are identified probabilistically by averaging the results of running deterministic tractography on 28 normal subjects (Hua et al., 2008). The WM probtract atlas includes the following WM tracts; (1) anterior thalamic radiation; (2) cingulum in the cingulate cortex area; (3) cingulum in the hippocampal area; (4) corticospinal tract; (5) forceps major; (6) forceps minor; (7) inferior fronto-occipital fasciculus; (8) superior longitudinal fasciculus (SLF); (9) the temporal projection of the SLF; (10) inferior longitudinal fasciculus; (11) uncinate fasciculus (UF). We obtained statistics result files for each WM tract in the left and right hemisphere (excluding forceps major and minor). These files contain several diffusion measures, including FA, MD, and RD. Each DT metric reflects a different aspect of white matter integrity (Mori and Zhang, 2006). (1) FA: This parameter represents the degree of anisotropy or directionality of water molecule diffusion within a voxel. Higher FA values usually signify greater directionality and are indicative of better white matter microstructure integrity; (2) MD: MD is a measure of the overall magnitude of water diffusion, irrespective of direction, within a voxel. Higher MD values typically indicate increased overall water movement, which can be suggestive of less dense white matter, potential injury, or degradation; (3) RD: RD is a measure of water diffusion perpendicular to the principal direction of diffusion. RD is often considered as a potential index of myelin integrity, with higher RD values interpreted as representing potential demyelination. Details regarding the main procedure of PANDA are described in the previous study (Cui et al., 2013).

APOE genotyping

The procedures for *APOE* genotyping are described in the Supplementary Material. Considering the protective effect of *APOE* ε2 allele (Li et al., 2020), we excluded participants with the *APOE* ε2 allele. If a participant had at least one *APOE* ε4 allele, they were categorized as an *APOE* ε4 carrier; if they had no *APOE* ε4 allele, they were categorized as an *APOE* ε4 non-carrier.

BDNF genotyping

The procedures for BDNF genotyping are described in the Supplementary Material. For BDNF Val66Met polymorphism (rs6265), the genotype groups were divided into Met66 allele carrier and Met66 allele non-carrier (Val66 homozygote) groups according to previous genetic studies on this genotype (Carballedo et al., 2012; Han et al., 2015). If a participant had at least one Met66 allele, they were categorized as a Met carrier; if they had no Met66 allele, they were categorized as a Met non-carrier.

SUVR calculation

Information on PET scanners and the procedures for [18F]-FMM PET image acquisition and processing are described in the

1 https://www.fil.ion.ucl.ac.uk/spm/software/spm12
2 https://www.nitrc.org/projects/panda/
3 https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSL

Supplementary Material. The semi-quantification of [^{18}F] FMM uptake on PET/CT scan was performed by obtaining the standardized uptake value ratios (SUVRs). The volumes of interest (VOIs) were restricted to gray matter, covering the frontal, superior parietal, lateral temporal, anterior, and posterior cingulate cortex/precuneus regions. These VOIs are known to be preferentially affected by Aβ deposition in the early stages of AD (Thal et al., 2002) and were also considered in a previous study (Thurfjell et al., 2014). The reference region for SUVR calculations was pons. The pons does not typically show significant Aβ deposits even in later stages of AD (Thal et al., 2002) and has been utilized as a reference area for SUVR measurements (Landau et al., 2014). The mean uptake counts of each VOIs and reference region were measured on the preprocessed image. A regional SUVR was calculated as the ratio of each cortical regional mean count to the pons mean count ($SUVR_{PONS}$). The global cortical average (composite SUVR) was calculated by averaging regional cortical SUVRs weighted for size. We used a cut-off of 0.62 for "positive" versus 'negative' neocortical SUVR, consistent with the cut-off values used in a previous [^{18}F] FMM PET study (Thurfjell et al., 2014). PET scans classified with negative Aβ accumulation also exhibited normal visual reading.

Statistical analysis

Statistical analyzes were performed using R software (version 2.15.3), jamovi (version 1.6.23),[4] and SPM 12. Assumptions of normality were tested for continuous variables using the Kolmogorov–Smirnov test in R software; all data demonstrated a normal distribution and were standardized by z-score transformation for the analysis.

Repeated-measures ANOVA was used to predict the impact of effect modifier-by-tDCS interaction (effect modifier*tDCS) for diffusion metrics (i.e., FA, MD, and RD), with tDCS (pre- and post-tDCS) as repeated-measures factor and *APOE* ε4 carrier status, BDNF Val66Met polymorphism status, and sex as the between-subject factor (effect modifier), with covariates of age, years of education, and global [^{18}F] FMM $SUVR_{PONS}$. Using four between-subject factors did not allow for a suitable repeated-measures ANOVA. To address this issue, we evaluated Aβ deposition using global [^{18}F] FMM $SUVR_{PONS}$, which provides a continuous variable for Aβ deposition. This allowed us to reduce the number of between-subject factors. We examined not only individual effect modifier*tDCS interaction, but also multiple effect modifiers*tDCS interaction (effect modifier1*effect modifier2*tDCS) for diffusion metrics. With respect to Aβ deposition, we evaluated global [^{18}F] FMM $SUVR_{PONS}$*tDCS interaction.

In addition, partial correlation analysis was performed to evaluate the association between baseline [^{18}F] FMM $SUVR_{PONS}$ and differences in diffusion metrics (i.e., FA, MD, and RD), adjusting for age, sex, education years, *APOE* ε4 carrier, and BDNF Val66Met polymorphism status. For the differences in diffusion metrics of WM probtract atlas displaying a significant association with [^{18}F] FMM $SUVR_{PONS}$, we evaluated a relationship with a difference in neuropsychological performances by partial correlation analysis, adjusting for age, sex, education years, Aβ deposition, *APOE* ε4 carrier, and BDNF Val66Met polymorphism status. Furthermore, we explored the association between baseline [^{18}F] FMM $SUVR_{PONS}$ and differences in diffusion metrics in each subgroup stratified by AD risk factors, adjusting for age, education years, and AD risk factors except for Aβ deposition, and the other AD risk factors we used to stratify subgroups. For the differences in diffusion metrics of WM probtract atlas displaying a significant association with [^{18}F] FMM $SUVR_{PONS}$ in each subgroup, we also examined an association with a difference in neuropsychological performances by partial correlation analysis, adjusting for age, education years, and AD risk factors except for the risk factors we used to stratify subgroups. All statistical analyzes used a two-tailed p-value <0.05 to define statistical significance. For the results of partial correlation analyzes in subgroups stratified by AD risk factors, a p-value <0.01 was considered statistically significant given the small sample size.

Results

Baseline demographic and clinical data

A total of 70 participants who met the inclusion and exclusion criteria were enrolled. Seven participants dropped out of the study due to refusal ($N = 6$) and a tDCS-related adverse event ($N = 1$, tingling under the electrode). Sixty-three subjects completed the study and were included in the analysis (Figure 2). Table 1 shows the baseline demographic data for the participants who completed the study.

Changes in white-matter microstructure integrity according to effect modifiers

We observed several important interactions in our study. First, a significant interaction was found between *APOE* ε4 carrier status and tDCS, manifesting as increased FA in the right UF (Rt. UF) of the *APOE* ε4 carriers ($p = 0.01$; Figure 3A). Moreover, a sex*tDCS interaction was also identified, which was shown by an increased FA in the Rt. UF of female participants ($p = 0.019$; Figure 3B). Interestingly, our study revealed a BDNF polymorphism*tDCS interaction. This was evidenced by decreased MD and RD in the left cingulum of the cingulate cortex and increased MD in the Rt. UF of the Met non-carriers (MD in Lt. cingulum of the cingulate cortex, $p = 0.024$; RD in Lt. cingulum of the cingulate cortex, $p = 0.027$; MD in Rt. UF, $p = 0.038$; Figure 3C).

Regarding multiple effect modifiers, our results showed a BDNF polymorphism**APOE* ε4 carrier status*tDCS interaction, this was seen as increased FA in Rt. UF of Met non-carriers with *APOE* ε4 carrier status ($p < 0.001$; Figure 3D). Furthermore, a BDNF polymorphism*Sex*tDCS interaction was found, contributing to increased FA in Rt. UF of female participants with Met non-carrier status ($p < 0.001$; Figure 3D).

Despite these significant findings, no interaction between Aβ deposition and tDCS was observed for any of the diffusion metrics of each WM tract. A table containing all statistical comparisons shown in Figure 3 can be found in the Supplementary Results.

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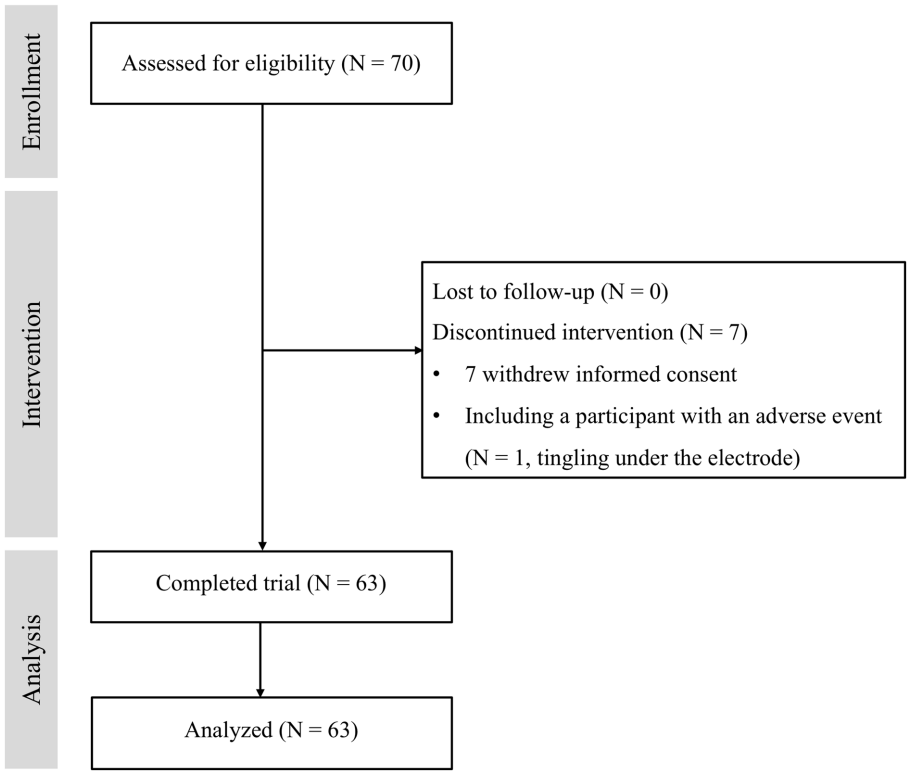

FIGURE 2
The flowchart of the study.

Association between baseline Aβ deposition and changes in white matter microstructure integrity

Concerning the relationship of difference in diffusion metrics with baseline Aβ deposition, there was a positive association in difference in FA of Lt. cingulum in the hippocampal area (Figure 4A; $r = 0.282$, $r^2 = 0.08$, $p = 0.034$), which showed a positive relationship with a difference in CERAD-K WLR (Figure 4B; $r = 0.28$, $r^2 = 0.08$, $p = 0.037$). Additionally, we found a positive association between Aβ deposition and the difference in FA of the left cingulum in the hippocampal area, which was observed not only in the overall group but also in *APOE* ε4 carriers ($r = 0.518$, $r^2 = 0.268$, $p = 0.007$). Table showing the association between Aβ deposition and changes in white matter microstructural integrity in *APOE* ε4 carrier is provided in the Supplementary Results. However, for the difference in FA of this track of interest, there was not a significant association with a difference in neuropsychological performances in the *APOE* ε4 carriers. In subgroups excluding *APOE* ε4 carriers, we could not identify a significant association between baseline Aβ deposition and differences in diffusion metrics.

Safety and tolerability

Among the enrolled 70 participants, one subject complained of tingling under the anode in the 4th session and withdrew informed consent (Figure 2). After dropping out, the subject reported improvement in tingling and recovered.

Discussion

The present study was designed to investigate how the effect of 2 weeks of tDCS on white matter microstructural integrity in MCI patients varies according to an effect modifier composed of individual factors of AD, including Aβ deposition, *APOE* ε4 carrier status, BDNF Val66Met polymorphism status, and sex.

This study found a significant interaction between AD risk factors and tDCS for white matter microstructural integrity in tracts at risk for AD. The interaction between *APOE* ε4 carrier status and tDCS was attributed to increased FA in Rt. UF of *APOE* ε4 carriers after sequential tDCS sessions. The UF is a white matter tract involved in cognitive functions such as episodic memory and language (Von Der Heide et al., 2013), and previous studies have shown that FA levels in the UF decrease with the progression of AD (Liu et al., 2011; Qin et al., 2021). *APOE* ε4 carrier status has been found to differentially affect the integrity of white matter microstructure depending on age and severity of AD (Kljajevic et al., 2014), inducing better integrity of the UF compared with *APOE* ε4 non-carrier without a family history of AD (Adluru et al., 2014). However, there is a paucity of research on the effects of tDCS on white matter integrity at any stage of AD, including MCI, and there is also a lack of research on potential interactions with effect modifiers such as *APOE* ε4 carrier status. Taken together, the increased white matter microstructural integrity of the UF observed in *APOE* ε4 carriers after 10 sessions of sequential tDCS may reflect a compensatory mechanism for AD progression. However, given that white matter integrity is an intermediate phenotype for AD progression, further work is needed to clarify that

TABLE 1 Baseline demographic and clinical characteristics of the study participants.

Demographic and clinical characteristics ($N = 63$)	
Age (years)	73.2 ± 7.9
Gender	
- Male	21 (33.3%)
- Female	42 (66.7%)
Years of education	12.0 ± 5.0
[^{18}F] Flutemetamol deposition (positivity, %)	26 (41.3%)
Global [^{18}F] Flutemetamol $SUVR_{PONS}$	0.62 ± 0.15
APOE ε4 carrier status (carrier. %)	30 (47.6%)
BDNF polymorphism (Val/Met or Met/Met, %)	52 (82.5%)
CERAD-K	
VF	12.1 ± 5.1
BNT	10.7 ± 3.1
MMSE	23.2 ± 5.0
WLM	14.6 ± 4.6
CP	10.1 ± 1.5
WLR	3.7 ± 2.6
WLRc	6.8 ± 2.8
CR	4.5 ± 3.4
TMT B (seconds)	224.1 ± 77.7
Stroop word-color	26.0 ± 14.2
Total memory	25.2 ± 8.8
Total CERAD-K	58.1 ± 15.2

Data are presented as the mean ± SD unless indicated otherwise. $SUVR_{PONS}$, standardized uptake value ratio of [^{18}F] Flutemetamol, using the pons as a reference region; CERAD-K, Korean version of Consortium to Establish a Registry for Alzheimer's Disease; VF, verbal fluency; BNT, Boston Naming Test; MMSE, the Korean version of the Mini-Mental Status Examination; WLM, Word List Memory; CP, Constructional Praxis; WLR, Word List Recall; WLRc, Word List Recognition; CR, constructional recall; TMT B, Trail Making Test B; Total memory, composite score summing scores of the WLM, WLR, and WLRc tests; Total CERAD-K, composite score summing scores of the CERAD-K VF, BNT, WLM, CP, WLR, and WLRc domains.

changes in this metric are compensatory for the cognitive and functional deterioration. Given that the transition from MCI to AD takes 4–5 years (Vermunt et al., 2019), it is important to assess the impact of long-term changes in white matter microstructural integrity on changes in cognitive function and the risk of transition from MCI to AD.

In the present study, sequential tDCS led to increased FA in the Rt. UF of female subjects due to the sex*tDCS interaction. This may be due to the fact that white matter microstructure deterioration in females begins later and progresses more gradually than in males (Toschi et al., 2020), and older females receive a higher intensity of tDCS current at the target site compared to males, which may be due to the age-dependent sex difference in tDCS current intensity resulting from cerebral atrophy (Bhattacharjee et al., 2022).

The BDNF Val66Met polymorphism status of participants in the research interacted with the tDCS application, resulting in increased MD in the Rt. UF and decreased MD and RD in the Lt. cingulum of the cingulate cortex of the Met non-carriers after sequential tDCS. The BDNF has been shown to affect white matter microstructure by modulating myelinogenesis (Du et al., 2003), but its impact varies depending on factors such as age and type of tract (Voineskos et al., 2011; Tost et al., 2013). A previous study found that the BDNF Val66Met polymorphism interacts with age to affect white matter microstructure, particularly in corticocortical association tracts and late-myelinating fiber tracts in the brain, suggesting that older Val66 homozygotes may be more susceptible to changes in white matter microstructure (Voineskos et al., 2011). However, in the present study, the Rt. UF and Lt. cingulum of the cingulate cortex showed differential changes after tDCS application in Val66 homozygotes, despite both being the latest-myelinated fibers. Furthermore, changes in the microstructural integrity of the Rt. UF were found to be different between *APOE* ε4 carriers and older Val66 homozygotes, although both groups are susceptible to AD. Relative to *APOE* ε4 carrier status, the BDNF Val66Met polymorphism has shown inconsistent effects on white matter integrity, with both increased and decreased FA and RD reported in different brain tracts (Soliman et al., 2010; Chiang et al., 2011; Tost et al., 2013). This highlights the complexity of the interaction between BDNF Val66Met polymorphisms, white matter integrity, and the response to tDCS. Further research is therefore needed into the factors that may contribute to this inconsistency.

This study also found that tDCS interacts with multiple factors to affect white matter integrity who were Val66 homozygotes and *APOE* ε4 carriers following sequential tDCS. Similarly, female with Val66 homozygosity showed a significant improvement in white matter integrity in the Rt. UF after tDCS sessions. Previous studies have shown accelerated Aβ deposition in *APOE* ε4 carriers with BDNF Met carriers (Stonnington et al., 2020; Riphagen et al., 2022), but there is limited investigation into the impact on the white matter integrity. Regarding the sex, although some studies suggest a sexually dimorphic effect of the BDNF Met66 allele on AD susceptibility (Fukumoto et al., 2010), others contradict this (Voineskos et al., 2011). In the prodromal phase of AD, Val66 homozygotes with a higher susceptibility to age-related decline in white matter integrity (Voineskos et al., 2011) are assumed to induce a greater increase in integrity in the AD susceptible tract in response to sequential tDCS in the presence of AD risk factors. In addition, the UF that shows an interaction between tDCS and AD risk factors in this study is a pathway that connects the anterior temporal lobe to the orbitofrontal cortex and is involved in cognitive functions such as episodic memory and language (Von Der Heide et al., 2013). It is therefore worth investigating how improved integrity in this pathway affects the clinical course of AD in the long term.

In this investigation, we observed a significant correlation between baseline Aβ deposition and enhanced FA in the left cingulum within the hippocampal region, following the administration of sequential tDCS. This aligns with prior research that reported diminished fiber connections in this specific area among patients in the early stages of AD and those with MCI (Zhou et al., 2008). Moreover, we identified a positive association between the increase in FA of the Lt. cingulum in the hippocampal region and improvements in delayed memory performance, corroborating earlier findings (Zhou et al., 2008). In subgroups stratified by AD risk factors, we also found a positive association between Aβ deposition and the difference in FA of the left cingulum in the hippocampal area in *APOE* ε4 carriers. However, regarding the FA of this tract, there was not significant relationship with the differences in neuropsychological performances. Taken together, these observations suggest a potential compensatory mechanism whereby Aβ deposition triggers alterations in the white

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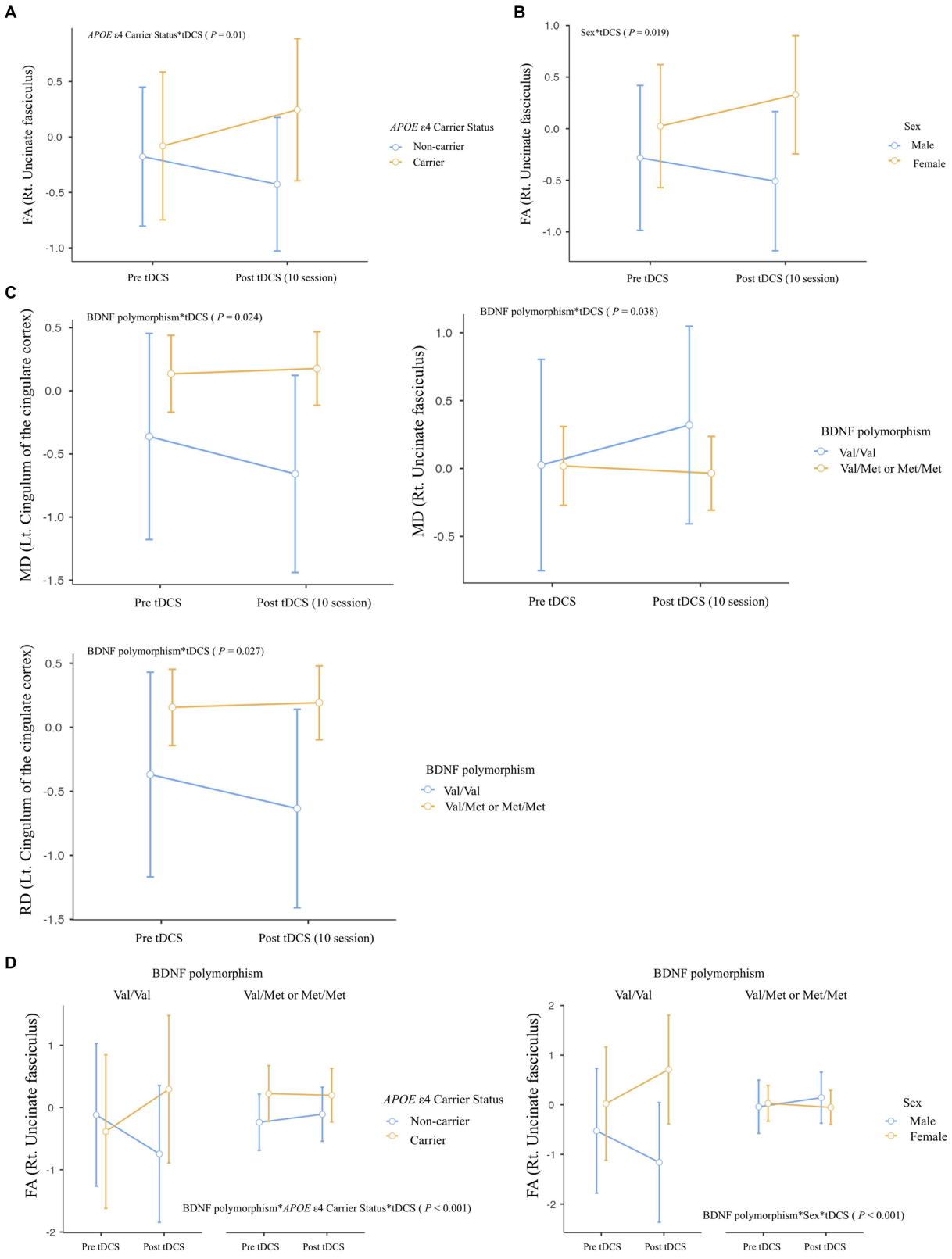

FIGURE 3
Differential impact of tDCS on white matter microstructural integrity according to effect modifiers: **(A)** *APOE* ε4 carrier status, **(B)** Sex, **(C)** BDNF polymorphism, and **(D)** Multiple effect modifiers. Repeated-measures ANOVA was used to predict the impact of effect modifier-by-tDCS interaction (effect modifier*tDCS) for white matter microstructural integrity (Between-subject factors: *APOE* ε4 carrier status, BDNF polymorphism, and sex), with covariates of age, years of education, and global [^{18}F] FMM $SUVR_{PONS}$. FA, fractional anisotropy; MD, mean diffusivity; RD, radial diffusivity.

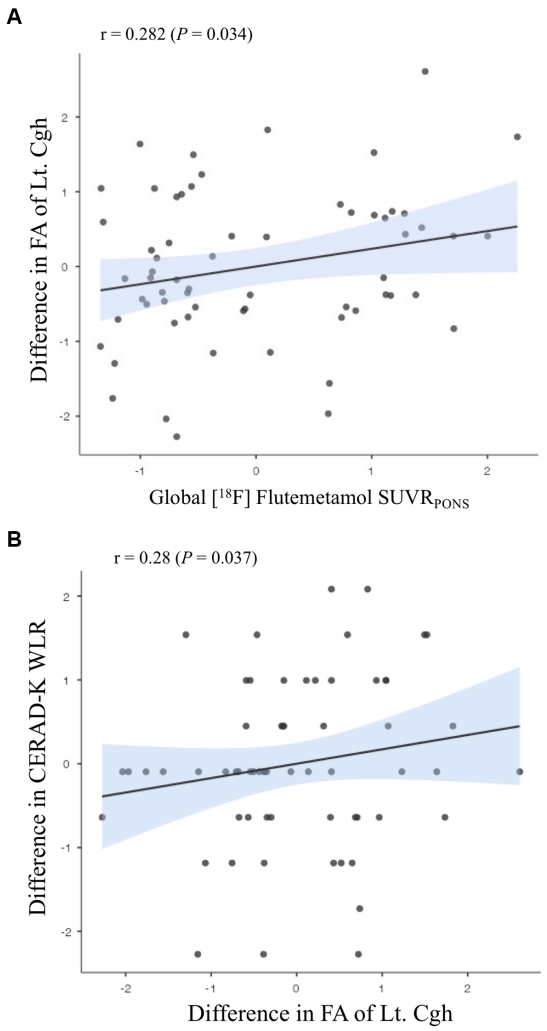

FIGURE 4
Associations **(A)** between amyloid-beta deposition and changes in white matter microstructural integrity; **(B)** between the differences in white matter microstructural integrity and those in neuropsychological performances. Partial correlation analysis adjusting for **(A)** age, sex, education years, *APOE* ε4 carrier status, and BDNF polymorphism; **(B)** age, sex, education years, Aβ deposition, *APOE* ε4 carrier status, and BDNF polymorphism. WLR, Word List Recall; FA, fractional anisotropy; Cgh, cingulum in the hippocampal area.

matter integrity of the Lt. cingulum in the hippocampal area, especially in the *APOE* ε4 carriers. This change could be catalyzed by the application of sequential tDCS during the prodromal phase of AD. Nonetheless, further research with larger sample size is warranted to substantiate these preliminary insights.

A limitation of this study is the duration of sequential tDCS. As this study only involved a 10-session application of tDCS, conducting a long-term study would offer a more comprehensive understanding of the clinical implications of the compensatory changes in white matter microstructure integrity that were inferred from this study. Furthermore, conducting a study that includes a sham stimulation group would enhance our understanding of the role and clinical implications of the effect modifiers identified in the present study with MCI patients.

The purpose of this research was to assess the impact of a 2-week application of sequential tDCS on changes in white-matter microstructure integrity of MCI patients, taking into account individual factors for AD. Additionally, we examined the association between baseline Aβ deposition and changes in white matter microstructure integrity, as well as the relationship between changes in cognitive function and those in white matter integrity. The study revealed a significant effect of the effect modifiers*tDCS interaction on the white matter microstructure integrity of the AD vulnerable tract. Furthermore, there was a positive association between Aβ deposits and changes in the integrity of the white matter tract which reflects the AD progression. Finally, the changes in the tract of interest also exhibited a positive relationship with the differences in the memory performance in the prodromal stage of AD. AD is a multi-faceted neurodegenerative disease that elicits various responses to treatments among patients diagnosed with MCI. Therefore, it is essential to apply a precision medicine therapeutic approach that takes into account individual AD-related factors, especially regarding non-invasive brain stimulation. In this regard, this study provides a cornerstone for the clinical importance of precision medicine approaches in tDCS and in the field of non-invasive brain stimulation therapy for patients on the AD trajectory. Additionally, conducting additional research to address the limitations of the current study would provide an opportunity to reassess the therapeutic potential of tDCS in the prodromal AD phase, which has limited treatment options available.

Data availability statement

The datasets presented in this article are not readily available because the datasets generated or analyzed during the current study are not publicly available due to the Patient Data Management Protocol of Yeouido Saint Mary's Hospital but are available from the corresponding author upon reasonable request. Requests to access the datasets should be directed to DWK, kato7@hanmail.net.

Ethics statement

The studies involving humans were approved by Institutional Review Board of the Catholic University of Korea. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

DWK: conceptualization, methodology, data curation, writing–original draft, visualization, formal analysis, and funding acquisition. S-MW: methodology, data curation, and writing–review and editing. YU: software and investigation. SK: methodology and data curation. TK: methodology and data curation. DK: methodology and data curation. CL: conceptualization and supervision. HL: conceptualization, methodology, writing–review and editing, supervision, and project administration. All authors contributed to the article and approved the submitted version.

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Conflict of interest

HL, TK, and DK were employed by NEUROPHET Inc.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. The data processing services provided by NEUROPHET Inc. were utilized to enhance the quality and analysis of the brain imaging data collected during the study. Authors declare that the research outcomes and conclusions remain unbiased and are not influenced by any commercial interests associated with the NEUROPHET Inc.'s products or services.

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Health factors associated with cognitive frailty in older adults living in the community

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Introduction: This study aims to investigate the health factors associated with cognitive frailty in frail and pre-frail older adults living in the community.

Methods: A total of 233 older adults meeting Fried's criteria for pre-frailty or frailty were included. Cognitive status was evaluated using the Short Portable Mental Status Questionnaire. Health factors encompassed nutritional status (evaluated using the Mini Nutritional Assessment tool, body mass index, and waist, arm, and leg circumferences), physical function (assessed with the Short Physical Performance Battery), quality of life (measured with the total index of the EuroQoL 5-Dimension 5-Level questionnaire - EQoL-Index -, and the Visual-Analogue Scale - QoL-VAS - for today's health state), as well as sleep, physical activity, and inactivity estimated through wrist-worn accelerometers. Multivariable logistic regression analyses were conducted to identify potential predictors of cognitive frailty, considering age as a confounding factor.

Results: Cognitive frail participants exhibited advanced age, heightened self-reported exhaustion, diminished overall physical performance, reduced leg perimeter, decreased engagement in moderate-to-vigorous physical activity, and higher levels of inactivity (all $p<0.05$). However, after adjusting for age, only QoL-VAS emerged as a cognitive frailty risk factor (Odds ratio: 1.024), while the EQoL-Index, calf perimeter, and levels of moderate-to-vigorous physical activity were identified as protective factors (Odds ratios: 0.025, 0.929, and 0.973, respectively).

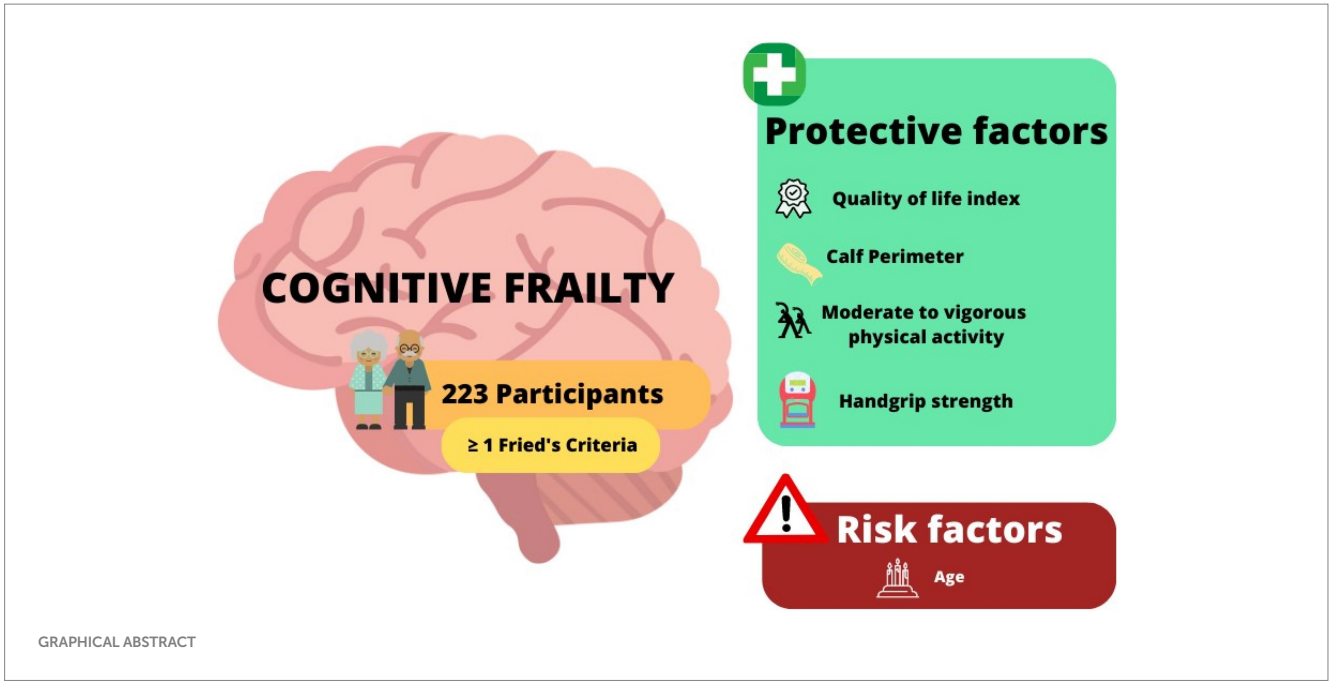
Discussion: This study highlights the complex relationship between non-modifiable factors such as age, and modifiable factors including quality of life, nutritional status, and physical activity in the development of cognitive frailty among older adults with a frailty phenotype living in the community.

KEYWORDS

physical activity, physical function, accelerometer, quality of life, malnutrition risk, cognitive impairment, aging, frail adults

1. Introduction

As the aging population continues to grow, frailty remains a prevalent geriatric syndrome among older adults living in the community, thus increasing awareness of its associated risk factors within this population (Clegg et al., 2013; Ofori-Asenso et al., 2019). Frailty is



GRAPHICAL ABSTRACT

characterized by its multifaceted origin (Pilotto et al., 2020). While a consensus on its precise definition remains elusive, it can be conceptualized as an age-related disruption in the harmonious interplay across various dimensions, including genetic, biological, functional, cognitive, psychological, and socio-economic aspects (Pilotto et al., 2020).

Given this complex nature, the establishment of a universally accepted standard instrument for frailty assessment is currently lacking (Roopsawang et al., 2022). However, the adoption of a multidimensional approach to frailty holds promise for both preventing its onset and ameliorating associated adverse health outcomes (Wleklik et al., 2020). Consequently, although one of the most commonly used frailty assessment tool is the one proposed by Fried et al. (2001), it primarily emphasizes physical frailty, thus highlighting the need for focused attention on the cognitive domain.

The operational definition of cognitive frailty pertains to the concurrent presence of physical frailty and mild cognitive impairment in older individuals, excluding Alzheimer's disease and various forms of dementia (Kelaiditi et al., 2013). Currently, cognitive frailty is classified into two subtypes: reversible and potentially reversible (Sugimoto et al., 2018). Reversible cognitive frailty involves the simultaneous existence of physical frailty or pre-frailty and subjective cognitive decline or pre-mild cognitive impairment, whereas potentially reversible cognitive frailty is characterized by the coexistence of physical frailty or pre-frailty and mild cognitive impairment (Sugimoto et al., 2018).

Cognitive frailty is associated with an elevated risk of adverse health outcomes, including depression, compromised quality of life, dementia, falls, hospitalization, dysfunction, and even premature mortality (Panza et al., 2018; Sugimoto et al., 2022; Zou et al., 2023). The domains of physical and cognitive frailty are thought to be interconnected (Tang et al., 2023). Notably, cognitive frailty is linked to a decline in executive function (Sugimoto et al., 2022) and limitations in instrumental activities of daily living (Shimada et al., 2016), positioning cognitive frailty as a contributor to the motoric cognitive risk syndrome.

This syndrome is characterized by the coexistence of subjective cognitive complaints and a slow gait, in the absence of concurrent dementia or mobility disability (Verghese et al., 2013; Sugimoto et al., 2018). Various investigations into cognitive frailty have emphasized motor deterioration and gait variables, highlighting the need for specific motor performance assessment within the context of cognitive frailty (Facal et al., 2019, 2021). In this regard, wearable sensors have been proposed to estimate daily levels of physical activity (Zhou et al., 2019; Razjouyan et al., 2020), and accelerometer-based measurements could also be of interest.

Despite recent advances in understanding cognitive frailty, there is still much to be explored. Limited evidence exists regarding the incfluence of health-related factors in older adults which are typically integrated into the comprehensive geriatric assessment, such as mobility, nutritional status, sleep behavior, and physical activity, on cognitive frailty (Pilotto et al., 2020). This knowledge gap underscores the necessity for further research to identify potentially modifiable risk factors and develop targeted interventions aimed at preventing or delaying the onset of cognitive frailty in older adults (Facal et al., 2021; Zhang et al., 2022).

For all of these reasons, this study aims to investigate the health factors associated with cognitive frailty in frail and pre-frail older adults residing in the community. The health factors under consideration include various sociodemographic characteristics, Fried's frailty components, physical function, quality of life, nutritional status, sleep beaviour, and daily levels of physical activity and inactivity.

2. Materials and methods

2.1. Design

The current cross-sectional study was carried out in the provinces of Cádiz and Málaga, located in Spain, during the period between March and December 2022. The Ethics Committee of Provincial Research of Málaga approved the study (reference code FRAGSALUD,

date 31/01/2019), and all actions adhered to the principles stated in the Declaration of Helsinki for human research. Individuals who indicated their willingness to participate in the study were provided with a document outlining all procedures and potential risks and an informed consent form. Before the commencement of the study, participants were required to affix their signatures on both documents.

A total of 233 older individuals from Spain were included in the study, with an average age of 74.8 ± 6.4 years. To meet the eligibility criteria for participation, participants had to fulfill the following requirements: (i) age 65 years or older, and (ii) presentation of at least one component of Fried's frailty phenotype. Individuals who were institutionalized or displayed symptoms of dementia were excluded from the study.

Upon inclusion in the study, participants were asked to provide socio-demographic details, including age, sex, marital status, housing conditions, educational attainment, daily medication usage, number of falls in the preceding year, use of walking aids, and approximate monthly income.

2.2. Cognitive frailty

The participant's frailty status was assessed using Fried's frailty phenotype (Fried et al., 2001), including five domains: (i) unintentional weight loss, (ii) self-reported exhaustion and fatigue, (iii) low weekly physical activity estimated through the short version of the Minnesota Leisure Time Activity Questionnaire (Ruiz Comellas et al., 2012), (iv) low gait speed measured by the 4.57-meter gait test, and (v) low handgrip strength assessed by dynamometer. Individuals meeting one or two of these criteria were classified as pre-frail, while those fulfilling three or more criteria were classified as frail (Fried et al., 2001).

The cognitive status of the participants was evaluated using the Short Portable Mental Status Questionnaire (Pfeiffer, 1975), which has demonstrated good validity and reliability in the Spanish population (Martínez de la Iglesiaa et al., 2001). This test is widely used due to its brevity and ease of administration, making it a rapid screening tool. Comprising 10 questions, it evaluates short-and long-term memory, orientation, and the capacity to perform serial mathematical tasks. A point was awarded for each question that a participant answered incorrectly. Accumulating three or more points (errors) indicates the manifestation of subjective cognitive decline, which could suggest the presence of cognitive impairment. An additional error is permitted in the scoring for individuals with a primary education or lower, while one less error is allowed for those with education beyond the high school level. Participants who met at least one Fried's frailty criteria and scored higher than three on the Short Portable Mental Status Questionnaire were categorized into the cognitive frailty group.

2.3. Nutritional status

The Mini Nutritional Assessment (MNA) was employed to identify participants at nutritional risk (Rubenstein et al., 2001). The MNA contains six items assessing weight loss, body mass index (BMI), illness or stress, mobility, depression or dementia, and loss of appetite. The MNA has been validated for use in populations aged over 65 (Salvà Casanovas, 2012). A MNA score of ≤11 indicates malnutrition or risk of malnutrition. The MNA demonstrated a sensitivity of 97.9%, specificity of 100%, and diagnostic accuracy of 98.7% in predicting malnutrition (Rubenstein et al., 2001).

Participant's body mass was measured using a digital scale (Omron Medizintechnik, Mannheim, Germany) after removing footwear, heavy clothing, and accessories. To determine body height, participants stood on the Frankfort plane and exhaled normally while using a stature-measuring instrument (SECA 225, Hamburg, Germany). The BMI was calculated by dividing weight (in kilograms) by the square of height (in meters). Waist, arm, and leg circumferences were measured using a non-extensible metallic tape (Lufkin W606PM, Washington, United States) at their narrowest (waist circumference) and longest (arm and leg circumferences) points.

2.4. Physical function

The Short Physical Performance Battery (SPPB) was utilized to assess the physical function of the participants, which is a valid and reliable tool for older individuals (Pavasini et al., 2016). The SPPB evaluates three physical domains: (i) balance, including three tests (side-by-side, semi-tandem, and tandem stands), (ii) gait speed over a 4-meter distance, and (iii) lower body performance assessed through the five-repetition sit-to-stand test. Participants' performance in each domain was compared to normative data and scored between 0 and 4 points. A score of 0 was assigned to participants unable to complete the test. The final score ranged from 0 (highly dependent) to 12 (totally independent).

2.5. Quality of life

The EuroQoL 5-Dimension 5-Level (EQ-5D-5L) questionnaire was used to evaluate the health-related quality of life of the participants (Herdman et al., 2011). The EQ-5D-5L is a widely utilized tool comprising five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Whitin each dimension, participants rate their health status on a Likert scale ranging from no problems (score of 1) to extreme problems (score of 5). The scores from these five dimensions are then combined into a five-digit number representing the participant's health state. A formula is applied to convert this health state into a single index score (EQoL-Index) that ranges from 0 to 1, with 1 indicating the best possible health status (Oppe et al., 2014). The Visual-Analogue Scale (QoL-VAS) ranges from 0 to 100 where participants rate their overall health status today, with 100 indicating the best possible health. The EQ-5D-5L has been validated in many countries, including Spain (Hernandez et al., 2018), and has shown excellent psychometric properties.

2.6. Sleep behavior, physical activity, and inactivity

The GENEActiv wrist-worn accelerometer was used to assess daily sleep behavior, physical activity, and inactivity. Participants were instructed to wear the accelerometer on their non-dominant wrist for a minimum of six consecutive days. Valid results were

considered for participants with a wear time of 16 h or more per day, across at least 4 days, including a minimum of three weekdays and one weekend day. The accelerometers were set to operate at a frequency of 60 Hz, and the GENEActiv software (version 3.3) was used to collect the unprocessed data. All unprocessed data files were stored on the University of Malaga servers and were analyzed using the open-source GGIR software (version 2.5-0) with R-package (R CoreTeam, Vienna, Austria). This R-package was applied to mitigate sensor calibration errors by automatically adjusting the data based on local gravity (van Hees et al., 2014) and calculating the Euclidean norm minus one (ENMO) for accelerations.

Sleep behavior was assessed as previously described by Valero-Cantero et al. (2021), involving the measurement of sustained inactivity periods (≤57 miliGravities, mG) with low z-angle variability (<5° over 5 min). A computer algorithm was then used to detect sleep onset and offset based on sustained inactivity periods (van Hees et al., 2018). Bedtime was defined as the estimated time participants went to bed, while sleep time was estimated as the difference between sleep onset and wake-up time. Wake after sleep onset (WASO) was defined as the total time spent awake between sleep onset and termination, while awakenings were defined as the number of times a person was awake for at least 5 min during the sleep period. Sleep efficiency was defined as the proportion of time spent sleeping from onset to termination, with a score of 100 indicating no waking occurred between sleep onset and termination.

To categorize physical activity and inactivity, pre-established ENMO thresholds for the wrist were utilized for older adults: (i) Inactivity: ENMO ≤57 mG, (ii) Light-intensity Physical Activity (LPA): ENMO >57 mG and <104 mG, and (iii) Moderate-to-Vigorous-intensity Physical Activity (MVPA): ENMO ≥104 mG (Sanders et al., 2019).

2.7. Statistical analyses

Categorical variables are presented as counts and percentages, while continuous variables are expressed as mean ± standard deviation (SD). The normality of continuous variables was assessed using the Kolmogorov–Smirnov test. The study sample was characterized through descriptive analyses. Additionally, the differences between physical frail and cognitive frail participants were assessed using Student's *t*-test and chi-square test. To control for the potential impact of age on these differences, an Analysis of Covariance (ANCOVA) was conducted, with age utilized as a covariate.

Logistic regression models were utilized to explore the relationship between cognitive frailty and health factors. The models examined the associations between cognitive frailty status and variables such as physical frailty status, nutritional status, physical function, quality of life, sleep, and physical activity. An unadjusted model was used to test the initial associations between the variables. Variables that displayed significant values in Table 1 were included in the multivariable logistic regression models to identify potential confounders. Age was identified as the only significant confounder and was included in the adjusted model. Finally, odds ratio (95% confidence interval) and *p*-values were reported in each model.

All analyses were performed by using the IBM SPSS Statistics 26 software (SPSS Inc., Chicago, IL, United States) and GraphPad Prism 9 (GraphPad Software, Boston, MA, United States), with a significance set at $p < 0.05$.

3. Results

The characteristics of the study sample are presented in Table 1, indicating that 23.61% of participants exhibited cognitive frailty. Cognitive frailty was significantly associated with advanced age, a higher occurrence of falls in the preceding year, and dependence on a mobility device for walking. Although all three variables were indicative of cognitive frailty, only age remained a statistically significant predictor when all three variables were incorporated into the same model.

Table 2 displays the outcomes concerning Fried's frailty phenotype and cognitive frailty, indicating that individuals with cognitive frailty were more likely to experience exhaustion during the week and demostrate poorer performance in both the 4.57-meter gait and handgrip tests, when compared to those without cognitive frailty. After adjusting for age, expressing exhaustion on any day of the week and experiencing fatigue for more than 3 days per week were idenfified as significant risk factors for cognitive frailty, while performance in the handgrip strength test remained as a protective factor.

Regarding nutritional status, participants with cognitive frailty had reduced values for leg perimeter (as depicted in Figure 1). Concerning physical function and quality of life, participants with cognitive frailty demonstrated poorer performance in the 4-meter gait and sit-to-stand tests and, although they obtained higher scores on the QoL-VAS, significantly lower EQoL-Index scores were observed (as shown in Figure 2). In terms of sleep behavior and daily levels of physical activity and inactivity, participants with cognitive frailty had higher inactivity time and lower levels of MVPA compared to their counterparts without cognitive frailty (as shown in Figure 3).

In logistic regression models, all of the aforementioned variables that showed significant differences between the groups were also significantly associated with the risk of cognitive frailty, except for the sit-to-stand test and inactivity time (as reported in Table 3). After adjusting for age, QoL-VAS was identified as a risk factor for cognitive frailty, whereas calf perimeter, EQoL-Index, and time spent in MVPA were identified as protective factors.

4. Discussion

In this multicentre cross-sectional study, we enrolled 233 community-dwelling older adults who met Fried's criteria for frailty phenotype. Our sample showed a cognitive frailty prevalence of 24%, which is comparable to findings in a prior study (Katayama et al., 2021). The influence of sex on the development of cognitive frailty remains an unresolved question. In our sample, consisting of a higher proportion of women (67%) than men (33%), there was no significant difference in the prevalence of cognitive frailty between sexes. Moreover, the logistic regression analyses did not identify sex as a risk factor for this condition.

These findings are in line with previous research that has not identified sex as an independent risk factor for cognitive frailty (Ruan et al., 2020). Furthermore, a systematic review and meta-analysis of

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TABLE 1 Participant characteristics by cognitive status.

	Total (n = 233)	Frailty (n = 178)	Cognitive frailty (n = 55)	p	Cognitive frailty OR (95% CI)	p
Sex, *n* (%)						
Men	77 (33.0)	64 (36.0)	13 (23.6)	0.090	Ref	0.092
Women	156 (67.0)	114 (64.0)	42 (76.4)		1.814 (0.907–3.628)	
Age (years)	74.82 ± 6.38	74.11 ± 6.08	77.13 ± 6.81	**0.002**	**1.077 (1.025–1.131)**	**0.003**
Marital status, *n* (%)						
Single	8 (3.4)	8 (4.5)	0 (0)	0.101	Ref	
Married	112 (48.1)	90 (50.6)	22 (40.0)		0.458 (0.048–4.420)	0.5
Widowed	79 (33.9)	54 (45.5)	25 (33.9)		1.426 (0.523–3.887)	0.488
Divorced	34 (14.6)	26 (14.5)	8 (14.6)		1.467 (0.524–4.105)	0.466
Housing, *n* (%)						
Not alone	144 (61.8)	114 (64.0)	30 (54.5)	0.419	Ref	
Alone	89 (38.2)	64 (36.0)	25 (45.5)		1.292 (0.693–2.410)	0.42
Education status, *n* (%)						
Less than primary school	47 (20.2)	32 (27.3)	15 (20.2)	0.073	2.585 (0.809–8.262)	0.109
Primary School	105 (45.1)	77 (50.9)	28 (45.1)		1.745 (0.607–5.019)	0.301
Secondary school	52 (22.3)	45 (12.7)	7 (22.3)		0.747 (0.214–2.606)	0.640
University and above	29 (12.4)	24 (9.1)	5 (12.4)		Ref	
Number of daily medications (number)	5.39 ± 3.85	5.20 ± 3.79	5.98 ± 4.00	0.195	1.053 (0.974–1.138)	0.195
Number of falls in the last year, *n* (%)						
None	152 (65.2)	124 (69.7)	28 (50.9)	**0.018**	Ref	
1–5	66 (28.3)	46 (25.8)	20 (36.4)		**2.111 (1.044–4.270)**	**0.038**
5–10	11 (4.7)	7 (3.9)	4 (7.3)		1.407 (0.141–14.062)	0.771
More than 10	4 (1.7)	1 (0.6)	3 (5.5)		**12.667 (1.268–126.557)**	**0.031**
Need for walking assistance, *n* (%)						
No	195 (83.7)	154 (74.5)	41 (74.5)	**0.042**	Ref	
Yes	38 (16.3)	24 (13.5)	14 (25.5)		**2.144 (1.017–4.521)**	**0.045**
Monthly income, *n* (%)						
Lower than 600 €	33 (23.7)	25 (23.8)	8 (23.5)	0.664	1.222 (0.433–3.445)	0.705
600–1,200 €	53 (38.1)	38 (36.2)	15 (44.1)		1.507 (0.617–3.682)	0.368
Higher than 1,200 €	53 (38.1)	42 (40.0)	11 (32.)		Ref	

Values are expressed as counts (percentages) or mean ± standard deviation, statistically significant values ($p < 0.05$) are bolded.

previous studies revealed a lack of association between sex and cognitive frailty (Zhang et al., 2022). Our findings add to this evidence and suggest that sex may not have a significant influence on the development of cognitive frailty in older adults with frailty phenotype.

Numerous sociodemographic variables have been associated with the development of cognitive frailty. Advancing age is a well-known risk factor for developing frailty and cognitive frailty, as supported by robust scientific evidence (Navarro-Pardo et al., 2020; Katayama et al., 2021). Consistent with these findings, our study identified age as a significant and independent risk factor for cognitive frailty in frail and pre-frail older adults living in the community.

Falls represent another condition commonly linked to cognitive frailty. Our study revealed that experiencing falls between 1 and 5 times, as well as more than 5 times within the last year, were identified as risk factors for cognitive frailty. This is in line with previous data that demonstrated that cognitively impaired adults are at higher risk of falling than those without cognitive impairment (Tsutsumimoto et al., 2018). The need for walking assistance was also identified as a sociodemographic variable that increases the risk of cognitive frailty, which is similar to previous studies demonstrating an association between cognitive frailty and disability (Panza et al., 2018).

However, after conducting a logistic regression analysis including all sociodemographic variables, age was the only variable that remained a significant risk factor. Given the fact that previous research has identified age as a primary risk factor for these conditions (Stewart Williams et al., 2015), these results suggest that in older people with frailty phenotype, age is the main variable contributing to the

TABLE 2 Fried's frailty characteristics by cognitive status and odds ratio for cognitive frailty.

	Total (*n* = 233)	Frailty (*n* = 178)	Cognitive frailty (*n* = 55)	*p*	Cognitive frailty OR (95% CI)	*p*	Adjusted Cognitive frailty OR (95% CI)	*p*
Unintended weight loss, *n* (%)								
Lost <5% of body mass	160 (68.7)	124 (69.7)	36 (68.7)	0.645	Ref	0.645	Ref	0.765
Lost >5% of body mass	73 (31.3)	54 (30.3)	19 (31.3)		1.163 (0.612–2.210)		1.107 (0.567–2.164)	
Self-reported exhaustion and fatigue, *n* (%)								
Did not meet the criteria	67 (28.8)	54 (30.3)	13 (23.6)	0.288	1.593 (0.757–3.350)	0.220	1.673 (0.783–3.575)	0.184
Met the criteria	166 (71.2)	124 (69.7)	42 (76.4)					
Exhaustion, *n* (%)								
Never	42 (18.0)	38 (21.3)	4 (7.3)	**0.041**	Ref		Ref	
1–2 days	42 (18.0)	31 (17.4)	11 (20.0)		**4.138 (1.041–16.444)**	**0.044**	**4.495 (1.109–18.224)**	**0.035**
3–4 days	69 (29.6)	53 (29.8)	16 (29.1)		**3.529 (1.001–13.093)**	**0.049**	**3.806 (1.008–14.370)**	**0.049**
5–7 days	80 (34.3)	56 (31.5)	24 (43.6)		**5.647 (1.580–20.185)**	**0.008**	**5.791 (1.594–21.033)**	**0.008**
Fatigue, *n* (%)								
Never	69 (29.6)	58 (32.6)	11 (20.0)	0.213	Ref		Ref	
1–2 days	60 (25.8)	46 (25.8)	14 (25.5)		1.702 (0.680–4.259)	0.255	1.981 (0.769–5.105)	0.157
3–4 days	49 (21.0)	35 (19.7)	14 (25.5)		2.234 (0.879–5.677)	0.091	**2.690 (1.021–7.085)**	**0.045**
5–7 days	55 (23.6)	39 (21.9)	16 (29.1)		2.316 (0.949–5.649)	0.065	**2.857 (1.130–7.229)**	**0.027**
Physical activity expenditure, *n* (%)								
Low	35 (15.0)	30 (16.9)	5 (9.1)	0.151	0.525 (0.189–1.496)	0.217	0.525 (1.189–1.461)	0.217
Normal	198 (85.0)	148 (83.1)	50 (90.9)					
Physical activity expenditure (kcal/week)	3031.62 ± 3173.28	3171.45 ± 3324.75	2584.18 ± 2607.46	0.232	1.000 (1.000–1.000)	0.29	1.000 (1.000–1.000)	0.502
Gait speed, *n* (%)								
Low	61 (26.2)	42 (23.6)	19 (26.2)	0.140	1.580 (0.810–3.085)	0.180	1.213 (0.598–2.461)	0.593
Normal	172 (73.8)	136 (65.5)	36 (73.8)					
4.57-meter Gait test (s)	6.02 ± 2.52	5.79 ± 2.41	6.73 ± 2.75	**0.016**	**1.131 (1.009–1.268)**	**0.034**	1.068 (0.945–1.208)	0.293
Handgrip strength, *n* (%)								
Low	143 (61.4)	105 (59.0)	38 (69.1)	0.095	1.824 (0.903–3.685)	0.094	1.526 (0.740–3.147)	0.252
Normal	90 (38.6)	73 (41.0)	17 (30.9)					
Handgrip strength (kg)	21.51 ± 9.45	22.31 ± 9.80	18.80 ± 7.64	**0.019**	**0.954 (0.919–0.991)**	**0.014**	**0.963 (0.927–0.999)**	**0.049**
Frailty status, *n* (%)								
Pre-frail	161 (69.1)	129 (58.2)	32 (69.1)	**0.033**	**1.928 (1.014–3.666)**	**0.045**	1.600 (0.819–3.127)	0.169
Frail	72 (30.9)	49 (41.8)	23 (30.9)					
Frail criteria	2.05 ± 0.97	1.99 ± 0.95	2.24 ± 1.01	0.098	**1.294 (0.950–1.763)**	**0.103**	1.187 (0.860–1.639)	0.297

Values are expressed as counts (percentages) or mean ± standard deviation. Statistically significant values ($p < 0.05$) are bolded. OR, Odd Ratio. Adjusted OR ratio included age as covariable.

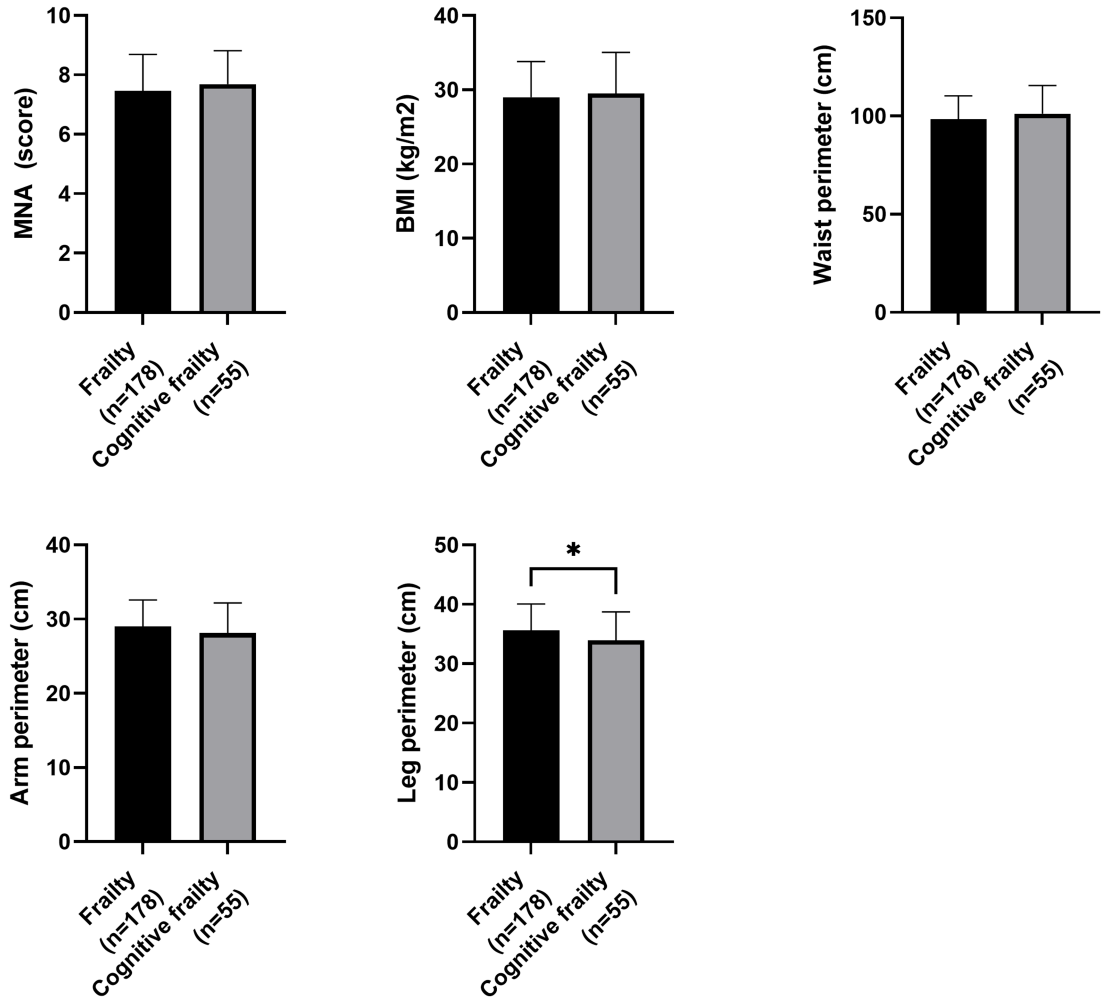

FIGURE 1
Differences in nutritional status between frail and cognitive frail participants. MNA, Mini Nutritional Assessment; BMI, Body Mass Index; *$p < 0.033$.

development of cognitive frailty, falls, and disability. Therefore, we included age as an adjusting variable in our analyses to account for its potential influence on the relationship between other health factors and cognitive frailty.

Our findings revealed that the proportion of older adults with cognitive frailty who reported exhaustion and fatigue was similar to those without cognitivefrailty (76.4% vs. 69.7%). However, reporting exhaustion for any day of the week and fatigue for more than 3 days per week were identified as significant risk factors for the development of cognitive frailty. These results emphasize the importance of considering psychological factors such as exhaustion and fatigue as mediators in the relationship between frailty and cognition (Robertson et al., 2013, 2014).

Thus, cognitive frailty has been consistently associated with a higher risk of poor quality of life (Arai et al., 2018). Interestingly, our study yielded contrasting results when evaluating the quality of life in our population. While the self-perceived quality of life, assessed using a QoL-VAS, emerged as a significant risk factor for cognitive frailty in both unadjusted and adjusted models, the EQoL-Index, which encompasses responses to various daily life activities, was found to be a protective factor. These findings suggest that using the complete version of the quality of life tool is essential.

Although utilizing only the QoL-VAS scale may appear convenient for a shorter evaluation time, it may not be appropriate for individuals with frailty or pre-frailty and cognitive impairment. Notably, our results indicate that participants with cognitive frailty tend to have a more favorable perception of their health status compared to those with frailty alone. These findings shed light on the complex relationship between cognitive frailty and quality of life, highlighting the importance of utilizing comprehensive measures to capture the multidimensional aspects of well-being.

Compelling evidence highlighting a significant interconnection between physical frailty and cognitive decline, specifically emphasizing executive dysfunction, has been reported (Amanzio et al., 2017; Bartoli et al., 2020). The findings underscore the intricate interplay between the physiological manifestations of physical frailty and the cognitive intricacies of neurodegenerative conditions, shedding light on potential shared mechanisms and pathways that contribute to the complex clinical landscape of these disorders. Although we excluded neurocognitive disorders in our study, our findings are in line with this relationship between physical and cognitive frailty.

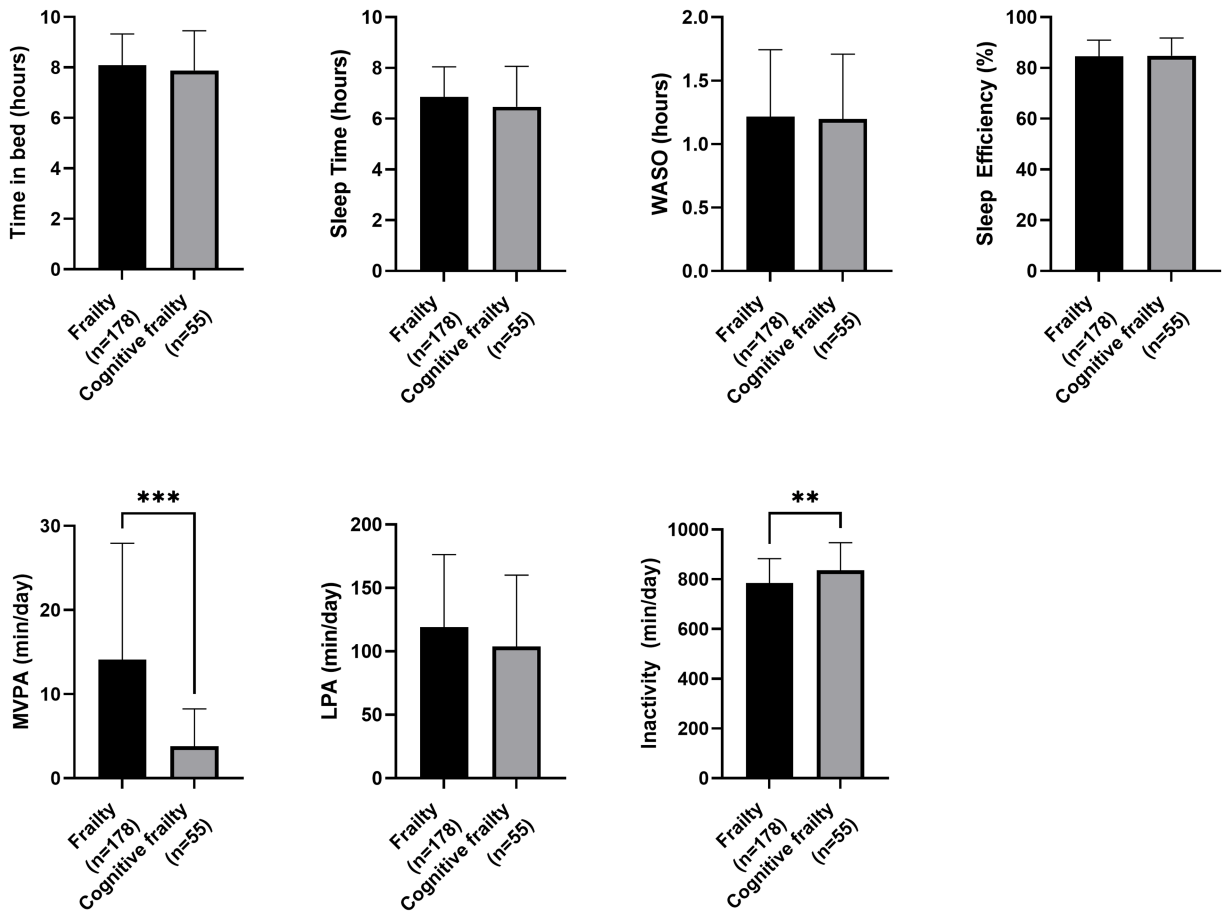

FIGURE 2
Differences in physical function and quality of life between frail and cognitive frail participants. STS, Sit-to-Stand test; SPPB, Short Physical Performance Battery; QoL, Quality of life; VAS, Visual-Analogue Scale; *$p < 0.033$.

Specifically, our results demonstrated that handgrip strength was a significant protective factor against cognitive frailty. These findings align with previous cross-sectional and prospective studies, providing strong evidence that physical health, as indicated by handgrip strength, is associated with cognitive function in older adults over time (Luo et al., 2022). Regarding gait speed, although the time spent in the 4.57-meter gait test was initially associated with cognitive frailty, this association became non-significant after adjusting for age. The same pattern occurs with the evaluation of the gait speed of the SPPB, which was the only variable of the battery that was associated with cognitive frailty. Thus, age might be a more influential factor for cognitive impairment than gait speed.

This finding partially contradicts previous studies that supports the motoric cognitive risk syndrome (Verghese et al., 2013) and that identified gait speed as a significant predictor of cognitive frailty (Armstrong et al., 2020). The motoric cognitive risk syndrome, which has several subtypes according to individual quantitative measures of cognitive impairment (Bortone et al., 2022), has been associated with sarcopenia, body fat indices and systemic inflammation in pre-frail older adults (Merchant et al., 2023). As a result, these observations prompt further investigation and exploration into the complex interplay of these factors in the context of cognitive frailty.

Prior research has demonstrated a connection between cognitive decline in older adults, particularly those experiencing motoric cognitive risk syndrome, and reduced levels of physical activity (Bortone et al., 2021). Aligning with these findings, our study revealed notable differences in the daily levels of MVPA and inactivity between participants with and witouth cognitive frailty. Cognitive frail individuals spent significantly less time engaged in MVPA and more time in inactive behaviors compared to their counterparts witouth cognitive frailty. Importantly, only MVPA was found to be significantly associated with a reduced risk of cognitive frailty.

These findings contribute to the growing body of evidence supporting the beneficial effects of physical activity, particularly at intensities higher than moderate, in the management of cognitive frailty. Similar positive effects of increasing MVPA levels on cognitive frailty have been observed in both shorter (12 weeks) (Kwan et al., 2020) and longer interventions (24 months) (Liu et al., 2018). These findings underscore the importance of incorporating progressively regular and sustained MVPA into the daily-life style of older adults with frailty with or without cognitive impairment at preventing and managing cognitive frailty in older adults.

Although participants with cognitive frailty demonstrated a longer time to complete 5 repetitions of the sit-to-stand test compared to those without cognitive frailty, this variable did not show a

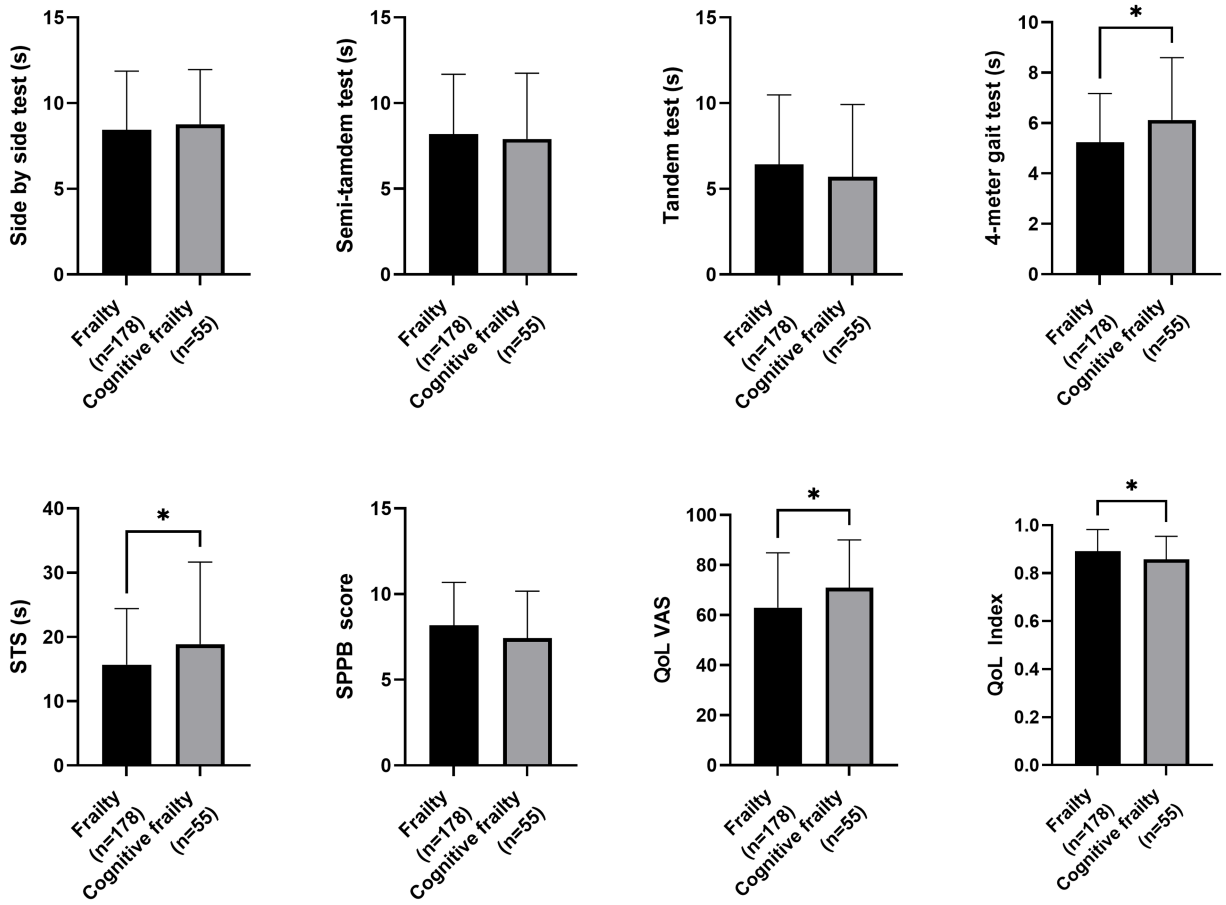

FIGURE 3
Differences in sleep behavior and physical activity between frail and cognitive frail participants. WASO, Wake After Sleep Onset; MVPA, Moderate-to-Vigorous-intensity Physical Activity; LPA, Light-intentisy Physical Activity; *$p < 0.033$; **$p < 0.002$.

significant association with this condition. These findings suggest that while the sit-to-stand test is commonly used to evaluate overall physical function (Yoon et al., 2018), the strength and function of the knee extensor/flexor muscles may not be a determining factor for cognitive impairment in older adults with frailty. This is in contrast with the observed utility of accelerometers in assessing daily levels of physical activity of frail or pre-frail older adults living in the community, where the significance of wearable sensors has been underscored (Zhou et al., 2019; Razjouyan et al., 2020).

Consistent with this, among the nutritional status variables investigated in our study, we identified calf circumference as a notable protective factor against the development of cognitive frailty. These findings align with previous research that has demonstrated an inverse association between calf circumference and disability, specifically highlighting the importance of leg circumference (Sun et al., 2017). This suggests that calf circumference, serving as a simple proxy for skeletal muscle mass and sarcopenia, may play a crucial role in the development of frailty and cognitive impairment. Reduced calf circumference is indicative of muscle mass atrophy, which has been identified as a significant factor in the pathogenesis of both frailty and cognitive impairment (Kim et al., 2018).

The significant association between calf circumference and cognitive frailty underscores the potential utility of measuring calf circumference as a means of monitoring cognitive frailty in older adults with frailty. This measurement could prove valuable in both clinical and research settings, providing a practical and accessible tool for assessing muscle mass and its implications for cognitive health. Further investigation is warranted to explore the underlying mechanisms linking calf circumference, skeletal muscle mass, and cognitive frailty, which may pave the way for targeted interventions aimed at preserving muscle mass and mitigating the risk of cognitive decline in older individuals with frailty.

The risk of malnutrition assessed using the MNA is a viable tool for monitoring changes in older adults (Casals et al., 2015). Previous research has shown that the MNA score in frail or pre-frail older adults is linked to physical function and independency and has been suggested as a predictor of frailty (Casals-Vázquez et al., 2017; Casals et al., 2018; Kiljunen et al., 2023). Nevertheless, this association was absent in our sample, thus, a further dietary assessment is encouraged in future studies.

It is important to acknowledge several limitations associated with our multicenter cross-sectional study conducted among community-dwelling frail and pre-frail older adults. The cross-sectional design restricts our ability to establish causal relationships or track changes in variables over time. The findings should be interpreted as associations rather than causation. Also, there may be a potential for selection bias, as our study only included individuals residing in the community, excluding those who are

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TABLE 3 Nutritional status, physical function, sleep, and physical activity odds ratios for cognitive frailty.

	Cognitive frailty OR (95% CI)	*p*	Adjusted cognitive frailty OR (95% CI)	*p*
Nutritional status				
MNA (score)	1.183 (0.916–1.527)	0.197	1.188 (0.913–1.546)	0.200
BMI (kg/m^2)	1.084 (0.960–1.084)	0.515	1.063 (0.993–1.137)	0.078
Waist perimeter (cm)	1.017 (0.993–1.041)	0.160	1.015 (0.991–1.040)	0.209
Arm perimeter (cm)	0.976 (0.903–1.055)	0.541	0.989 (0.911–1.072)	0.782
Calf perimeter (cm)	**0.914 (0.849–0.984)**	**0.017**	**0.929 (0.863–0.999)**	**0.049**
Physical function and quality of life				
Side-by-side test (s)	1.046 (0.945–1.159)	0.384	1.078 (0.970–1.197)	0.162
Semitandem test (s)	0.987 (0.906–1.075)	0.764	1.020 (0.932–1.116)	0.674
Tandem test (s)	0.954 (0.886–1.028)	0.220	0.983 (0.909–1.062)	0.660
Sit-to-stand test (s)	1.004 (0.988–1.021)	0.594	1.000 (0.983–1.017)	0.963
4-meter gait test (s)	**1.180 (1.025–1.358)**	**0.021**	1.132 (0.979–1.309)	0.094
SPPB score (score)	0.895 (0.794–1.008)	0.066	0.944 (0.831–1.072)	0.376
QoL-VAS (score)	**1.021 (1.003–1.039)**	**0.023**	**1.024 (1.004–1.044)**	**0.015**
EQoL-index (score)	**0.027 (0.001–0.775)**	**0.035**	**0.025 (0.001–0.771)**	**0.035**
Sleep and physical activity				
Time in bed (hours)	0.890 (0.699–1.132)	0.343	0.860 (0.674–1.098)	0.226
Sleep time (hours)	0.808 (0.629–1.038)	0.096	0.794 (0.614–1.022)	0.074
WASO (hours)	1.266 (0.837–1.915)	0.265	1.207 (0.791–1.840)	0.383
Sleep efficiency (%)	2.072 (0.023–187.101)	0.751	4.938 (0.054–455.780)	0.489
MVPA (min/day)	**0.969 (0.946–0.993)**	**0.012**	**0.973 (0.949–0.997)**	**0.029**
LPA (min/day)	1.004 (0.998–1.011)	0.189	1.005 (0.998–1.011)	0.181
Inactivity time (min/day)	1.000 (0.996–1.003)	0.843	1.000 (0.996–1.003)	0.794

Adjusted OR ratio included age as a covariable. Statistically significant values ($p < 0.05$) are bolded. OR, Odd Ratio; MNA, Mininutritional Assessment; BMI, Body Mass Index; SPPB, Short-Performance Physical Battery; QoL-VAS, Quality of life Visual-Analogue Scale; EQoL-Index, Quality of Life EuroQol Index; WASO, Wake After Sleep Onset; MVPA, Moderate-to-Vigorous-intensity Physical Activity; LPA, Light-intensity Physical Activity.

institutionalized or have more advanced health conditions, such as dementia or Alzheimer's disease. This may limit the generalizability of our results to broader populations. Additionally, the sample size of our study should be considered. While we made efforts to include an adequate number of participants, a larger sample size would enhance the statistical power and generalizability of the findings.

Furthermore, it is imperative to underscore that the cognitive status of the participants was exclusively evaluated using a screening test, a method that can be readily administered by nurses in clinical care settings. Notwithstanding this advantage, this approach may have limitations in fully capturing the participants' cognitive abilities. Hence, future studies incorporating a more comprehensive set of neuropsychological tests are warranted to provide a more thorough evaluation of these associations. Similarly, the assessment of the nutritional status encompassed easily accessible measures (BMI, body circumferences, and the MNA) to ensure its unfeasibility for routine clinical implementation. However, the omission of a more comprehensive analysis of dietary intake highlights the need for a more thorough evaluation of participants' eating habits.

Despite these limitations, our study provides valuable insights into the characteristics of frail and pre-frail older adults living in the community and their risk of cognitive frailty. By identifying these associations, we contribute to the existing body of knowledge and pave the way for future research in this field. It is crucial to consider these limitations when interpreting the findings and to further investigate these relationships in longitudinal studies with larger and more diverse populations.

5. Conclusion

In conclusion, our study highlights the complex interplay of both non-modifiable and modifiable factors in cognitive frailty among older adults with a frailty phenotype living in the community. Age remains a key non-modifiable factor associated with cognitive impairment in this population. However, our findings also shed light on several modifiable factors that can be targeted for intervention.

Nutritional status, quality of life, and physical activity are identified as important modifiable factors associated with cognitive frailty. Specifically, our results suggest that assessing calf circumference may provide valuable insights into cognitive risk factors in older adults with frailty, surpassing the utility of other commonly used

anthropometric measures. Furthermore, daily levels of moderate-to-vigorous physical activity (MVPA) emerge as a protective factor against cognitive frailty, emphasizing the importance of incorporating regular MVPA into preventive and management strategies.

Additionally, our findings highlight the relevance of considering psychological outcomes, such as self-reported exhaustion and fatigue, alongside physical frailty indicators like handgrip strength, as risk factors for cognitive frailty. Fried's criteria, without strict cut-off points, offer a comprehensive tool for evaluating both physical and psychological aspects of frailty.

In summary, this study underscores the need to address a range of modifiable factors in the prevention and management of cognitive frailty in older adults with a frailty phenotype. By targeting nutritional status, quality of life, and physical activity, and considering psychological factors, healthcare interventions can strive to mitigate the risk and impact of cognitive frailty on older individuals' overall well-being and independence.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethics Committee of Provincial Research of Málaga. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

CC and MV-S participated in the research concept and study design. JC-P and CC did the literature review. JC-P, CC, LÁ-C-d-V, AG-M, IM-Z, FV-E, RR-C, and MV-S contributed to the data collection. JC-P, CC, and MV-S did the data analysis, interpretation, and statistical analysis. JC-P wrote the manuscript. CC, LÁ-C-d-V, AG-M, IM-Z, FV-E, RR-C, and MV-S reviewed and edited the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Impact of a multidomain lifestyle intervention on white matter integrity: the SUPERBRAIN exploratory sub-study

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In the South Korean study to prevent cognitive impairment and protect BRAIN health through lifestyle intervention in at-risk elderly people (SUPERBRAIN), we evaluated the impact of a 24-week facility-based multidomain intervention (FMI) and home-based MI (HMI) on white matter integrity. Among 152 participants, aged 60–79 years without dementia but with ≥1 modifiable dementia risk factor, 19 FMI, 20 HMI, and 16 controls underwent brain MRI at baseline and 24 weeks. Between the intervention and control groups, we compared changes in fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) at regions-of-interest (ROI) including the cingulum cingulate gyrus (CgC), cingulum hippocampus (CgH), superior longitudinal fasciculus (SLF), as well as the uncinate fasciculus (UF). In addition, correlations between total and standard scores cognitive domains of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) or serum brain-derived neurotrophic factor (BDNF) and changes in brain image measures were evaluated at a statistical significance level of $p < 0.05$ (uncorrected for multiple corrections). The FA, MD, AD, and RD at each ROI at the baseline were not different among groups after Bonferroni correction. In the statistical analysis using two-way repeated measures ANOVA, any significant difference in longitudinal changes in the FA, MD, AD, and RD was not revealed. The statistical analysis, among the significant regions in paired *t*-test of the intervention group, compared with the control group, the FMI, HMI, and intervention group yielded significantly more beneficial effects on the AD of the CgC. In addition, longitudinal AD changes of the left CgC correlated with the BDNF changes ($r = 0.280$, $p = 0.048$). In this study, enhanced cognitive reserve after the multidomain lifestyle intervention could be revealed by changes in brain imaging for white matter integrity.

KEYWORDS

white matter integrity, cingulum cingulate gyrus, dementia, prevention, lifestyle, intervention, cognition, SUPERBRAIN

1. Introduction

Recent research suggests that multidomain lifestyle interventions, which encompass dietary counseling, physical exercise, cognitive training, and vascular/metabolic risk monitoring, can confer cognitive benefits to individuals at risk of developing cognitive decline. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) (Ngandu et al., 2015), exploratory subgroup analyses in the French Multidomain Alzheimer Preventive Trial (MAPT) (Andrieu et al., 2017; Chhetri et al., 2018), the Dutch Prevention of Dementia by Intensive Vascular Care (PreDIVA) (Moll van Charante et al., 2016) studies, or the South Korean study to prevent cognitive impairment and protect BRAIN health through lifestyle intervention in at-risk older adults (SUPERBRAIN) (Moon et al., 2021) have reported the cognitive benefits of a multidomain lifestyle intervention in participants with increased risk of dementia. It is suggested that these interventions may enhance cognitive reserve and reduce inflammation and vascular/oxidative damage in the brain.

Cognitive reserve refers to the brain's efficiency in performing its functions and is determined by factors such as brain volume, cerebral metabolism, and neural network density. The efficacy of multidomain lifestyle interventions in enhancing cognitive reserve can be evaluated through changes in structural or functional brain imaging or neurotrophic factor levels, such as brain-derived neurotrophic factor (BDNF). A previous exploratory analysis of the SUPERBRAIN study showed that facility-based multidomain interventions (FMI) resulted in a significant increase in serum BDNF levels compared to the control group (Moon et al., 2021). However, the impact of multidomain lifestyle interventions on structural or functional brain imaging remains controversial. The findings from the SUPERBRAIN study indicate that a 24-week FMI can increase both global and regional cortical thickness (Moon et al., 2022a) and alter regional homogeneity in the resting-state functional brain magnetic resonance imaging (MRI) (Moon et al., 2022b). However, an exploratory MRI sub-study of the FINGER trial did not reveal any significant differences in regional brain volumes, cortical thickness, or white matter lesion volume between the intervention and control groups after 2 years in at-risk elderly individuals without substantial impairment (Stephen et al., 2019). The controversial results of the previous studies may have arisen due to the difference of their sample size and intervention durations. Trials with the smaller sample sizes ($N < 160$ participants) and shorter intervention durations (up to 24 weeks) are more likely to report intervention benefits on overall cognition, specific domains (e.g., spatial working memory, executive functioning), or biomarkers (Solomon et al., 2021). However, interestingly, another FINGER MRI sub-study that used diffusion tensor imaging (DTI) found that the intervention group had a greater decrease in fractional anisotropy (FA) than the control group, although no significant intergroup differences were observed in other diffusion parameters (Stephen et al., 2020).

In this study, we evaluated the impact of a 6-month multidomain lifestyle intervention on changes in white matter integrity of DTI using data from the SUPERBRAIN.

2. Methods

2.1. Study population

The SUPERBRAIN trial protocol (ClinicalTrials.gov: NCT03980392) (Park et al., 2020) and primary findings (Moon et al., 2021) have been described previously. Briefly, this study was a 24-week randomized controlled trial conducted at three hospitals and five public health centers across South Korea, with a three-parallel-arm design including the FMI, home-based multidomain intervention (HMI), and control groups. Participants were selected from people who visited outpatient clinics or public health centers for memory problems, and those recruited through advertising. The study included 152 participants aged 60–79 years who had no dementia but had one or more modifiable dementia risk factors such as hypertension, diabetes mellitus, dyslipidemia, smoking, obesity, abdominal obesity, metabolic syndrome, educational level of ≤9 years, social isolation, and physical inactivity. In addition, they had a Mini-Mental State Examination z score of ≥ -1.5 based on the means and standard deviations in the age- and education-matched normal elderly Korean population (Han et al., 2008), were able to perform independent activities of daily living and pass a literacy test, and had a reliable informant who can provide investigators with the requested information. The individuals with major psychiatric illness such as major depressive disorder, dementia, Parkinson's disease, malignancy within the previous 5 years, cardiac stent or revascularization within the previous 1 year, serious or unstable cardiovascular disease, other serious or unstable medical disease such as acute or severe asthma, active gastric ulcer, severe liver disease, or severe renal disease, as well as severe loss of vision, hearing, or communication disability were excluded. The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice Guidelines, and the institutional review boards of all institutions approved the protocol and consent forms before the start of the study. Written informed consent was obtained from all potential participants prior to enrollment. The SUPERBRAIN MRI exploratory sub-study included 63 participants from three trial sites (Ajou University Hospital, Ewha Womans University Medical Center, and Inha University Hospital) (Figure 1). Brain scans were conducted at baseline and 24-week visits. The present study included 55 participants with both baseline and repeat scans of good quality.

2.2. Randomization and intervention

The participants were randomly assigned to the FMI, HMI, and control groups at baseline at a 1:1:1 ratio. The FMI and HMI groups received interventions consisting of five components, including monitoring and management of metabolic and vascular risk factors, cognitive training and social activity, physical exercise (Lee et al., 2020), nutritional guidance, and motivational enhancement, as previously described in detail (Park et al., 2020; Moon et al., 2021).

Before the intervention, metabolic and vascular risk factors were assessed using blood tests and anthropometric measurements. These risk factors included hypertension, diabetes mellitus, dyslipidemia, obesity, abdominal obesity, smoking, and high alcohol consumption, which were monitored and managed. Study doctors met with each participant at baseline and week 12 to inform them of their risk factors and prescribe medications if necessary. Participants were educated

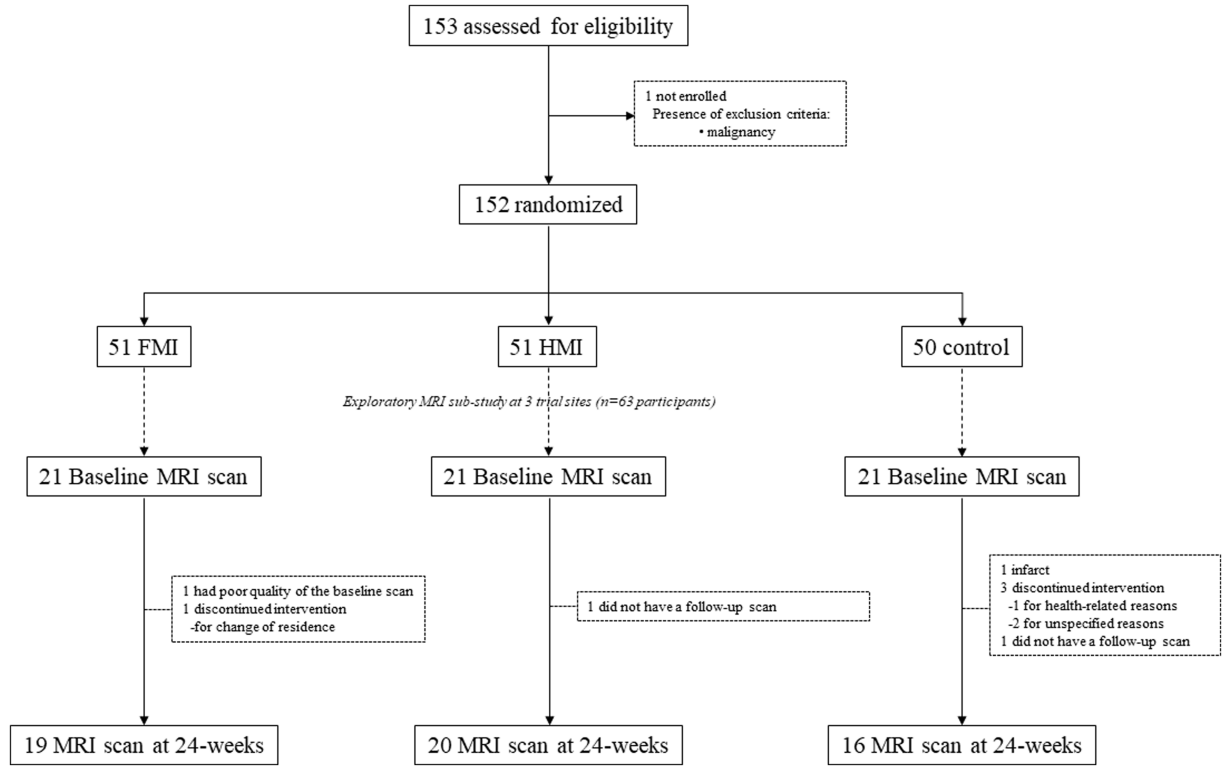

FIGURE 1
Diagram depicting the exploratory MRI analyses in the SUPERBRAIN trial. SUPERBRAIN, South Korean Study to Prevent Cognitive Impairment and Protect Brain Health Through Lifestyle Intervention; MRI, magnetic resonance imaging; FMI, facility-based multidomain intervention; HMI, home-based multidomain intervention.

about their risk factors and given lifestyle guidelines to prevent dementia by a study nurse at baseline. The nurse also met with participants every 4 weeks for measurements and monitoring of smoking and alcohol consumption. Measurements were recorded in the participants' SUPERBRAIN notebooks. If a participant's risk factors did not improve, they were re-educated by the nurse at week 12 using the booklets. The FMI group received facility-based interventions three times a week, while the HMI group received the same cognitive training and physical exercise programs as the FMI group but with a different schedule. In the first 2 months of the trial, the HMI group participated in one group-based cognitive training session (50 min) and one home-based cognitive training session (30–40 min) per week, and one group exercise session (60 min) and two home-based exercise sessions (60 min) per week. For the rest of the 6-month study, the HMI group attended one group cognitive training session and one group exercise session every 2 weeks. On weeks that included group sessions, the participants attended one cognitive training session and two exercise sessions individually at home each week. On weeks that did not include group sessions, participants attended two cognitive training sessions and three exercise sessions alone at home each week. The cognitive training focused on episodic memory, executive function, attention, working memory, calculation, and visuospatial function and was conducted using a tablet-based application or workbooks supervised by trained health professionals. The physical exercise program was designed to include aerobic exercise, exercises to enhance balance and flexibility, muscle-strengthening activities involving major muscle groups, and finger-and-toe movements. Trained exercise professionals guided the exercise programs during group sessions at a gym, using portable tools such as elastic bands, floor plates with numbers, and chairs. The exercise intensity increased every 2 months. During home-based exercise sessions, participants exercised by watching videos on a tablet PC or by following instructions in a poster or booklet. The nutritional intervention consisted of three individual counseling sessions (each lasting 30 min) and seven group sessions (each lasting 50 min) led by study nutritionists. The individual sessions involved tailoring the participant's daily diet and providing education on customized diets to manage individual vascular risk factors. The group sessions provided discussions, practical exercises, and cooking lessons on making meals with recommended ingredients. Motivational enhancement included four group counseling sessions (each lasting 50 min) led by a psychologist at 1, 2, 13, and 24 weeks. These sessions provided information and support to facilitate dementia prevention program activities and included discussions on the importance of change, ambivalence, and self-efficacy, as well as family education using video clips. The family-coach program involved a family member in reinforcing the motivation of a participant. Encouraging pop-up video messages made by participants' families and self-rated achievement pop-up messages were provided every week before the tablet-based cognitive intervention. Participants in workbook-type cognitive interventions were sent the encouraging pop-up video messages on their cell phones and performed self-rated achievement assessments on paper. The control group received regular health advice according to established guidelines.

2.3. Cognitive outcomes and serum BDNF

The study used the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) to evaluate cognitive function. The RBANS is a well-validated and reliable cognitive screening battery comprising 12 subtests that can be administered in 20–30 min with 4 alternate versions (A, B, C, and D) for reevaluation (Randolph et al., 1998). The subtests for each cognitive domain are as follows: digit span and coding for attention, picture naming and semantic fluency for language, figure copy and line orientation for visuospatial-construction, list learning and story memory for immediate memory, and list recall, list recognition, story recall and figure recall for delayed memory. Participants completed versions A and D at baseline and post-intervention, respectively, and a standard score was obtained for each cognitive domain based on same-aged peers. The total scale index score of cognitive functioning was calculated by combining these scores. Assessors received education on outcome measurements prior to the study (Park et al., 2020). Higher scores on the RBANS indicate better cognitive functioning. The assessment was conducted within 4 weeks post-intervention.

Changes in serum BDNF levels were investigated after the multidomain intervention. Fasting blood samples were collected at approximately 9 am using serum separator tubes (SSTs) within 4 weeks before and after the intervention. The SSTs were kept at room temperature for 30 min, centrifuged for 10 min at 3000 rpm, and sent to a central laboratory. Serum samples were stored at −70°C or lower until analysis. Serum BDNF levels were measured using a quantitative sandwich enzyme-linked immunosorbent assay (ELISA) (DBD00; R&D Systems, Inc., Minneapolis, MN, USA) in accordance with the manufacturer's instructions.

2.4. MRI acquisition and processing

Diffusion-weighted MRI data at each clinical site were acquired with the following MR systems and DTI parameters: 3 T Achieva, Philips with a 8-channel SENSE head coil [32 diffusion sampling directions; *b*-value, 1,000 s / mm^2; 256 × 256 acquisition matrix with 80 slices; repetition time (TR), 11.659 s; echo time (TE), 75 ms; flip angle, 90°; voxel size, 0.89 × 0.89 × 2 mm^3; field of view, 230 mm] at the Ajou University Hospital, 3 T Achieva, Philips with a 8-channel SENSE head coil (32 diffusion sampling directions; b-value, 1,000 s / mm^2; 128 × 128 acquisition matrix with 80 slices; TR, 11.659 s; TE, 92.222 ms; flip angle, 90°; voxel size, 1.79 × 1.79 × 2 mm^3; field of view, 230 mm) at the Ewha Woman's University Medical Center, and 3 T Signa Architect, GE with a 34-channel array head coil, at the Inha University Hospital (30 diffusion sampling directions; *b*-value, 1,000 s / mm^2; 256 × 256 acquisition matrix with 70 slices; TR, 15 s; TE, 79.371 ms; flip angle, 90°; voxel size, 0.89 × 0.89 × 2 mm^3; field of view, 230 mm). The same imaging parameters and MRI scanners were used for the baseline and 24-week scans. Regular phantom scans were performed within each site, although the phantom was not shared among three centers.

The diffusion-weighted images were processed using FMRIB's Software Library (FSL).[1] The Brain Extraction Tool (BET) was used to remove skull and non-brain tissue to extract non-diffusion-weighted volume (b0 volume) brain regions. The EDDY tool[2] (Andersson and Sotiropoulos, 2016) was used to estimate and correct for susceptibility-induced off-resonance field, volume movement, and eddy current distortions. The low-frequency MR intensity inhomogeneity and its effects on the diffusion images were estimated for the b0 volume and the estimated bias field map was applied to all diffusion-weighted volumes using the N4BiasFieldCorrection tool from Advanced Normalization Tools (ANTs) (Tustison et al., 2010). To correct for geometric distortions due to MR susceptibility in the diffusion data, previous studies have used additional diffusion-weighted images with reversed phase-encoding direction using the TOPUP tool[3] (Andersson et al., 2003). However, most diffusion-weighted studies struggle to apply the TOPUP tool due to a lack of reversed data (Wang et al., 2017). Alternatively, nonlinear registration for a structural T1 MRI was performed to correct for distortions using symmetric regularization (SyN) implemented in ANTs (Avants et al., 2008). The bias-corrected and skull-stripped T1 MRI was inverted prior to non-linear registration for the similar contrast characteristics of the source and the target images. The dtifit tool was used to fit the diffusion tensor model and computed diffusion scalar maps for FA, mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) using the tensor eigenvalues.[4] Finally, we performed feature extraction by aligning JHU-ICBM-labels atlas to the native FA image using a SyN and calculating the average FA, MD, AD, and RD values for each region of interest (ROI) (Mori et al., 2005). Based on the results of previous imaging analyses from the SUPERBRAIN studies (Moon et al., 2022a,b), specific ROIs were selected where changes in white matter integrity were anticipated. These ROIs consisted of the cingulum cingulate gyrus (CgC), cingulum hippocampus (CgH), superior longitudinal fasciculus (SLF), as well as the uncinate fasciculus (UF) on both hemispheres (Figure 2).

2.5. Statistical analysis

Group differences at baseline were analyzed by *t*-test (MRI vs. non-MRI groups) or one-way analyses of variance (ANOVA, FMI vs. HMI vs. controls) for continuous variables and the chi-square test for categorical variables. In addition, two-way repeated measures ANOVA, with time and groups as independent factors, was used to compare changes in the RBANS and serum BDNF levels from baseline to the study endpoint. The groups were considered similar when $p > 0.05$. *Post hoc* analyses were done by Dunnett test.

Individual FA, MD, AD, and RD at baseline were compared among groups using one-way analyses of covariance (ANCOVA) with age, sex, years of education, and imaging site effects added as covariates of no interest. In addition, to compare changes in the FA, MD, AD, and RD from baseline to the study endpoint, we used two statistical analyses. First, two-way repeated measures ANOVA was used, with time and groups as independent factors and age, sex, years

1 http://www.fmrib.ox.ac.uk/fsl

2 https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/eddy

3 https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/topup

4 https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/dtifit

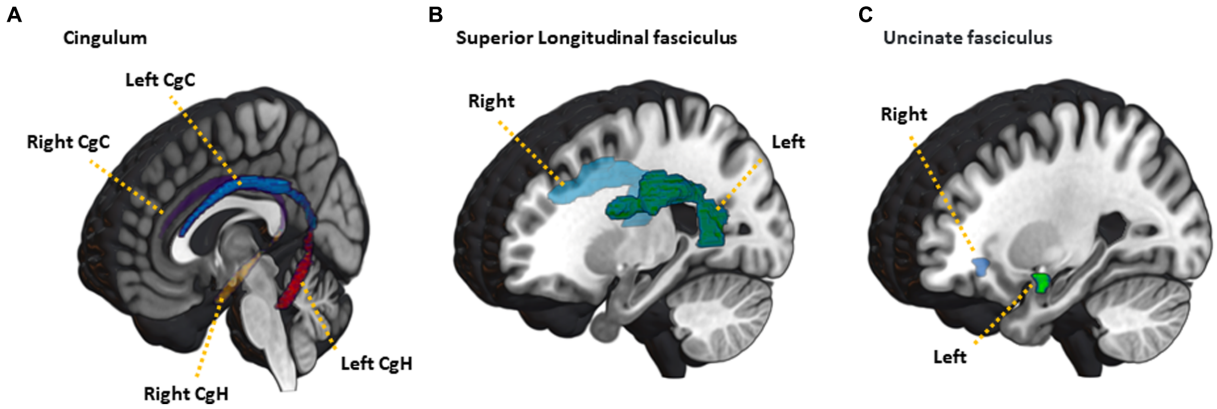

FIGURE 2
Illustration of JHU-ICBM-labels atlas ROIs used in the analysis. **(A)** cingulum, **(B)** superior longitudinal fasciculus, **(C)** uncinated fasciculus. CgC, cingulum cingulate gyrus; CgH, cingulum hippocampus.

of education, and imaging site effects added as covariates of no interest. Secondly, ROI-wise paired *t*-tests were used to analyze longitudinal changes in white matter integrity for each group (FMI, HMI or controls) and combined intervention groups (FMI + HMI), respectively, using age, sex, years of education, and site effects as covariates. The statistical significance level was set at Bonferroni corrected *value of* $p < 0.05$. Significant brain image measures in previous paired *t*-test were compared between each group pair (FMI vs. control; HMI vs. control; FMI + HMI vs. control) using ANCOVA with changes as dependent variables and age, sex, education, and site as covariates. Finally, correlations between clinical parameters (total and standard scores cognitive domains of the RBANS) or the serum BDNF level and changes in significant brain image measures were evaluated after controlling for age, sex, and years of education at a statistical significance level of $p < 0.05$ (uncorrected for multiple corrections). Specifically, the statistical analyses were conducted using statsmodels.api.OLS package.[5]

3. Results

The population undergoing MRI was younger, more educated, and had a higher baseline RBANS total scale index than the population not undergoing MRI in SUPERBRAIN. However, there were no differences in intervention adherence, sex distribution, APOE ε4 carriers, and group distribution between the two populations (Supplementary Table S1). The intervention and control groups in the SUPERBRAIN exploratory MRI sub-study were not significantly different in demographic, clinical, cognitive, and MRI characteristics at baseline (Table 1). The adherence rates in the FMI and HMI groups were 96.0 and 97.0%, respectively.

The two-way repeated measures ANOVA showed significant group × time interaction in the RBANS total scale index scores, delayed recall and visuospatial/construction (Table 2). *Post hoc* analyses revealed that longitudinal changes in the visuospatial/construction significantly differed between the FMI group and the control ($p = 0.039$) or between the HMI group and the control ($p = 0.042$). Serum BDNF levels did not show any significant group × time interaction among groups (Table 2).

3.1. Longitudinal changes in FA, MD, AD, and RD

The FA, MD, AD, and RD at each ROI at the baseline were not different among groups after Bonferroni correction. In the first statistical analysis using two-way repeated measures ANOVA, any significant difference in longitudinal changes in the FA, MD, AD, and RD was not revealed. The second statistical analysis, which analyzed longitudinal changes in white matter integrity for each group, revealed the results as follows: FA increase (p-value = 0.0003, t value = −4.625) and RD decrease (p-value = 0.0026, t value = 3.599) of the left UF in the control group; MD decrease (p-value = 0.0061, t value = 3.106) of the left CgH in the FMI; AD decrease (p-value = 0.0009, t value = 3.939) of the right CgH in the HMI. However, the difference in these longitudinal changes between groups was not significant. Additionally, in the combined intervention groups (FMI + HMI), ROI-wise paired *t*-tests showed significant longitudinal changes in white matter integrity of the cingula and right UF (Table 3). Among the significant regions in paired *t*-test of the combined intervention groups, compared with the control group, the FMI, HMI, and intervention group yielded significantly more beneficial effects on the AD of the CgC (Table 4; Figure 3).

3.2. Correlations between AD of the CgC and clinical variables

Correlations between AD of the CgC and clinical variables were evaluated in participants. Although longitudinal AD changes of the CgC did not correlate significantly with changes in the RBANS, longitudinal AD changes of the left CgC correlated with the BDNF changes ($r = 0.280$, $p = 0.048$).

5 https://www.statsmodels.org/dev/generated/statsmodels.regression.linear_model.OLS.html

TABLE 1 Baseline clinical characteristics in the intervention and control groups.

	FMI (*n* = 19)	HMI (*n* = 20)	Control (*n* = 16)	Value of *p*
Age, y	68.0 ± 4.7	68.8 ± 4.7	67.3 ± 4.4	0.657
Education, y	12.1 ± 3.8	11.6 ± 4.0	9.8 ± 4.3	0.314
Female, n (%)	13 (68.4)	12 (60.0)	14 (87.5)	0.314
APOE ε4 carriers, *n* (%)	3 (15.7)	2 (10.0)	3 (18.8)	0.724
RBANS indexes				
Total	119.9 ± 13.6	109.6 ± 19.1	105.5 ± 18.8	0.672
Attention	112.3 ± 14.1	112.3 ± 16.5	104.8 ± 18.1	0.257
Immediate recall	104.7 ± 16.2	106.1 ± 15.7	101.1 ± 15.2	0.658
Delayed recall	98.4 ± 11.6	99.7 ± 18.3	99.9 ± 17.4	0.942
Visuospatial/Construction	99.3 ± 11.2	101.5 ± 14.2	95.6 ± 13.4	0.433
Language	108.6 ± 15.1	111.8 ± 10.3	111.2 ± 15.1	0.769
BDNF, ng/ml	29.8 ± 11.3	29.9 ± 11.4	40.5 ± 22.1	0.158

FMI, facility-based multidomain intervention; HMI, home-based multidomain intervention; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; BDNF, brain-derived neurotrophic factor. Data for continuous variables are presented as the mean ± standard deviation. Group differences were analyzed by one-way analyses of variance (ANOVA) for continuous variables and the chi-square test for categorical variables. *P*-values represent the results from the ANOVA or chi-square test for the comparison of three groups (FMI vs HMI vs Control).

TABLE 2 Changes in clinical characteristics after 24 weeks in the intervention and control groups.

	FMI (*n* = 19)	HMI (*n* = 20)	Control (*n* = 16)	*P*-value		
				Group	Time	Group×time
RBANS indexes						
Total	7.0 ± 6.3	5.2 ± 9.7	−2.3 ± 9.8	0.195	0.007	0.005
Attention	1.4 ± 8.1	−0.5 ± 9.0	−2.7 ± 9.1	0.085	0.683	0.357
Immediate recall	6.1 ± 9.3	7.3 ± 14.1	3.3 ± 10.4	0.401	0.001	0.702
Delayed recall	10.5 ± 10.8	11.0 ± 9.3	2.9 ± 7.9	0.732	<0.001	0.027
Visuospatial/Construction	3.0 ± 9.3	−0.9 ± 16.4	−8.4 ± 13.4	0.035	0.200	0.044
Language	2.0 ± 12.0	0.1 ± 11.5	−3.1 ± 11.1	0.873	0.947	0.391
BDNF, ng/ml	14.6 ± 24.5	4.2 ± 2.2	−3.7 ± 2.6	0.750	0.099	0.088

FMI, facility-based multidomain intervention; HMI, home-based multidomain intervention, RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; BDNF, brain-derived neurotrophic factor. The two-way repeated measures one-way analyses of variance (ANOVA), with time and groups as independent factors, was used to compare changes in the RBANS and serum BDNF levels from baseline to the study endpoint. *P*-values represent the results from the two-way repeated measures ANOVA to exam groups (FMI vs HMI vs Control) × time (baseline vs. post-intervention) effects.

4. Discussion

Our study revealed that among the regions with significant longitudinal changes in the intervention group, compared with the control group, the FMI, HMI, and intervention group yielded significantly more beneficial effects on the AD of the CgC. In addition, longitudinal AD changes of the left CgC positively correlated with the BDNF changes. Therefore, in this study, enhanced cognitive reserve after the multidomain lifestyle intervention could be revealed by changes in brain imaging for white matter integrity.

Previous imaging analyses from the SUPERBRAIN studies (Moon et al., 2022a,b) have shown that group preventive strategies implemented at the facility can be beneficial in promoting structural or functional neuroplastic changes in brain areas that are involved in learning. These areas included the bilateral frontotemporal lobes, cingulate gyri, insula, and the left medial orbitofrontal gyrus. Based on these findings, we specifically selected the cingulum, SLF, and the UF on both hemispheres as ROIs where we expected to observe changes in white matter integrity. Among the chosen ROIs, our analyses demonstrated that the FMI, HMI, and intervention groups exhibited significantly more positive effects on the AD of the CgC compared to the control group. Furthermore, longitudinal AD changes in the left CgC were found to be positively correlated with changes in the BDNF. The cingulum bundle is one of the most distinctive fiber tracts in the brain, forming a near-complete ring from the orbital frontal cortices, along the dorsal surface of the corpus callosum, then down the temporal lobe towards the pole (Bubb et al., 2018). The cingulum is a complex pathway consisting of both short and long sagittal association fibers. Additionally, it contains fibers that extend across the tract, connecting cortical and subcortical regions. Among these sagittal connections, there are numerous short cortico-cortical association fibers, often referred to as "U-fibers," which interconnect the medial regions of the frontal, parietal, and temporal lobes. Given the length and intricacy of the cingulum bundle, there are various ways to subdivide it. For our analysis, we employed the JHU-ICBM-labels atlas, which divides the cingulum into two subdivisions: the CgC and

TABLE 3 Longitudinal changes between baseline and post-intervention in white matter integrity in each group.

	Baseline				Changes (from baselines to study end)				*value of p*			
	FMI	HMI	FMI + HMI	Control	FMI	HMI	FMI + HMI	Control	FMI	HMI	FMI + HMI	Control
	(*n* = 19)	(*n* = 20)	(*n* = 39)	(*n* = 16)	(*n* = 19)	(*n* = 20)	(*n* = 39)	(*n* = 16)				
FA												
CgC, right	0.0980(0.0075)	0.1013(0.0076)	0.0999(0.0077)	0.1008(0.0064)	0.0005(0.0047)	−0.0002(0.0047)	0.0001(0.0047)	−0.0001(0.0052)	0.6336	0.7831	0.892	0.8926
CgC, Left	0.1029(0.0072)	0.1071(0.0096)	0.1054(0.0089)	0.1054(0.0071)	0.0008(0.0052)	−0.0002(0.0054)	0.0002(0.0053)	−0.0001(0.0062)	0.5146	0.8657	0.7409	0.9385
CgH, right	0.1183(0.0096)	0.1202(0.0086)	0.1193(0.0089)	0.1174(0.0108)	0.0051(0.0102)	0.0033(0.0124)	0.0041(0.0113)	0.0011(0.0106)	0.424	0.2505	0.0563	0.6796
CgH, Left	0.1085(0.0100)	0.1121(0.0103)	0.1106(0.0102)	0.1069(0.0090)	0.0056(0.0101)	0.0042(0.0108)	0.0049(0.0103)	0.0061(0.0121)	0.0516	0.0966	***0.0051***	0.0611
SLF, right	0.1179(0.0075)	0.1248(0.0091)	0.1215(0.0088)	0.1227(0.0079)	0.0007(0.0040)	−0.0001(0.0055)	0.0002(0.0048)	0.0002(0.0051)	0.4534	0.9096	0.7284	0.8533
SLF, left	0.1154(0.0056)	0.1218(0.0082)	0.1189(0.0079)	0.1196(0.0056)	0.0008(0.0040)	0.0008(0.0044)	0.0008(0.0041)	0.0005(0.0041)	0.3552	0.4204	0.2145	0.6028
UF, right	0.0893(0.0078)	0.0943(0.0080)	0.0922(0.0084)	0.0888(0.0080)	0.0008(0.0023)	−0.0001(0.0041)	0.0003(0.0034)	−4.26E-05(0.0050)	0.138	0.8606	0.5509	0.9736
UF, left	0.0753(0.0097)	0.0802(0.0068)	0.0779(0.0085)	0.0754(0.0080)	0.0011(0.0050)	0.0019(0.0050)	0.0015(0.0049)	0.0031(0.0026)	0.3152	0.1077	0.0581	***0.0003***
MD												
CgC, right	0.0001(4.78E-06)	0.0001(5.79E-06)	0.0001(5.44E-06)	0.0001(6.43E-06)	1.49E-06(4.28E-06)	1.67E-06(4.63E-06)	1.58E-06(4.41E-06)	−5.31E-07(6.93E-06)	0.1454	0.1219	0.0502	0.7633
CgC, Left	0.0001(6.08E-06)	0.0001(6.84E-06)	0.0001(6.68E-06)	0.0001(8.13E-06)	8.65E-07(4.49E-06)	1.31E-06(5.29E-06)	1.09E-06(4.86E-06)	−1.56E-06(6.42E-06)	0.4122	0.2801	0.167	0.3465
CgH, right	0.0001(1.01E-05)	0.0001(1.20E-05)	0.0001(1.09E-05)	0.0001(1.03E-05)	−9.13E-06(1.36E-05)	−5.80E-06(1.06E-05)	−7.42E-06(1.21E-05)	−3.54E-06(1.40E-05)	0.0514	0.051	***0.0004***	0.3295
CgH, Left	0.0001(1.24E-05)	0.0001(8.76E-06)	0.0001(1.11E-05)	0.0001(9.12E-06)	−1.07E-05(1.50E-05)	−6.36E-06(1.37E-05)	−8.50E-06(1.43E-05)	−6.49E-06(1.36E-05)	***0.0061***	0.0515	***0.0006***	0.0765
SLF, right	0.0001(7.67E-06)	0.0001(8.00E-06)	0.0001(7.92E-06)	0.0001(6.63E-06)	1.24E-06(4.00E-06)	1.53E-06(5.56E-06)	1.39E-06(4.80E-06)	1.12E-06(6.84E-06)	0.1919	0.2316	0.0777	0.5223
SLF, left	0.0001(1.12E-05)	0.0001(7.09E-06)	0.0001(9.91E-06)	0.0001(6.70E-06)	7.47E-07(5.74E-06)	1.24E-06(5.10E-06)	1.00E-06(5.35E-06)	−4.29E-07(4.69E-06)	0.5775	0.2872	0.2488	0.7192
UF, right	0.0001(4.43E-06)	0.0001(5.77E-06)	0.0001(5.30E-06)	0.0001(9.14E-06)	2.65E-06(6.86E-06)	3.33E-06(5.99E-06)	3.00E-06(6.35E-06)	2.74E-06(9.01E-06)	0.1083	0.0512	***0.0054***	0.2414
UF, left	0.0001(8.74E-06)	0.0001(1.04E-05)	0.0001(9.81E-06)	0.0001(7.59E-06)	−5.88E-07(4.08E-06)	1.11E-06(7.92E-06)	2.87E-07(6.32E-06)	−2.60E-06(4.54E-06)	0.5374	0.5348	0.7783	0.057
AD												

(Continued)

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TABLE 3 (Continued)

	Baseline				Changes (from baselines to study end)				*value of p*			
	FMI	HMI	FMI + HMI	Control	FMI	HMI	FMI + HMI	Control	FMI	HMI	FMI + HMI	Control
	(*n* = 19)	(*n* = 20)	(*n* = 39)	(*n* = 16)	(*n* = 19)	(*n* = 20)	(*n* = 39)	(*n* = 16)				
CgC, right	0.0002(9.00E-06)	0.0002(1.06E-05)	0.0002(9.64E-06)	0.0002(9.84E-06)	3.32E-06(5.33E-06)	2.64E-06(4.34E-06)	2.98E-06(4.80E-06)	−1.23E-06(7.53E-06)	0.0512	0.0534	***0.0004***	0.5211
CgC, Left	0.0002(1.12E-05)	0.0002(1.20E-05)	0.0002(1.13E-05)	0.0002(1.20E-05)	2.25E-06(4.62E-06)	2.21E-06(5.05E-06)	2.23E-06(4.78E-06)	−3.04E-06(7.30E-06)	0.0511	0.0648	***0.0059***	0.116
CgH, right	0.0002(1.34E-05)	0.0002(1.50E-05)	0.0002(1.40E-05)	0.0002(1.77E-05)	−1.18E-05(1.75E-05)	−7.45E-06(8.46E-06)	−9.61E-06(1.36E-05)	−6.03E-06(1.59E-05)	0.0502	***0.0009***	***<0.0001***	0.1503
CgH, Left	0.0002(2.60E-05)	0.0002(1.34E-05)	0.0002(2.05E-05)	0.0002(1.35E-05)	−1.40E-05(2.10E-05)	−7.43E-06(1.77E-05)	−1.06E-05(1.94E-05)	−5.05E-06(1.84E-05)	0.051	0.0766	***0.0015***	0.2909
SLF, right	0.0002(1.08E-05)	0.0002(1.17E-05)	0.0002(1.10E-05)	0.0002(8.60E-06)	2.48E-06(5.43E-06)	2.37E-06(5.93E-06)	2.42E-06(5.62E-06)	2.08E-06(7.41E-06)	0.0619	0.0898	0.0504	0.2783
SLF, left	0.0002(1.54E-05)	0.0002(8.72E-06)	0.0002(1.22E-05)	0.0002(8.88E-06)	1.74E-06(7.15E-06)	3.10E-06(6.31E-06)	2.44E-06(6.68E-06)	−2.96E-08(6.96E-06)	0.3016	0.0501	0.058	0.9866
UF, right	0.0002(1.09E-05)	0.0002(1.01E-05)	0.0002(1.04E-05)	0.0002(1.12E-05)	5.01E-06(1.04E-05)	5.60E-06(9.31E-06)	5.32E-06(9.75E-06)	4.74E-06(1.13E-05)	0.0507	0.0544	***0.0015***	0.1156
UF, left	0.0001(1.43E-05)	0.0001(1.38E-05)	0.0001(1.38E-05)	0.0001(1.34E-05)	8.26E-07(5.44E-06)	4.27E-06(1.03E-05)	2.59E-06(8.40E-06)	−6.20E-07(7.47E-06)	0.5167	0.0801	0.0612	0.7443
RD												
CgC, right	7.52E-05 (6.57E-06)	7.22E-05 (6.99E-06)	7.33E-05(7.08E-06)	7.31E-05(7.02E-06)	5.81E-07(5.28E-06)	1.19E-06(5.61E-06)	8.93E-07(5.39E-06)	−1.78E-07(7.42E-06)	0.6371	0.3551	0.3073	0.9244
CgC, Left	7.38E-05 (7.02E-06)	6.98E-05 (9.37E-06)	7.13E-05(8.79E-06)	7.17E-05(8.80E-06)	1.73E-07(5.81E-06)	8.69E-07(6.73E-06)	5.30E-07(6.23E-06)	−8.17E-07(7.70E-06)	0.898	0.5709	0.5983	0.6771
CgH, right	8.90E-05 (1.10E-05)	8.61E-05 (1.14E-05)	8.74E-05(1.10E-05)	8.78E-05(1.07E-05)	−7.76E-06(1.32E-05)	−4.97E-06(1.27E-05)	−6.33E-06(1.29E-05)	−2.29E-06(1.42E-05)	0.05	0.098	***0.004***	0.5274
CgH, Left	8.99E-05 (9.93E-06)	8.45E-05 (9.77E-06)	8.68E-05(1.03E-05)	8.95E-05(9.33E-06)	−9.11E-06(1.36E-05)	−5.83E-06(1.29E-05)	−7.42E-06(1.31E-05)	−7.21E-06(1.32E-05)	0.0511	0.0577	***0.0011***	0.056
SLF, right	0.0001 (8.51E-06)	0.0001 (9.44E-06)	0.0001(9.49E-06)	0.0001(8.40E-06)	6.28E-07(4.52E-06)	1.12E-06(6.43E-06)	8.80E-07(5.52E-06)	6.37E-07(7.10E-06)	0.5524	0.4456	0.3252	0.7245
SLF, left	0.0001 (1.01E-05)	0.0001 (9.25E-06)	0.0001(1.07E-05)	0.0001(7.36E-06)	2.47E-07(5.76E-06)	3.20E-07(5.38E-06)	2.84E-07(5.50E-06)	−6.30E-07(4.96E-06)	0.8534	0.7932	0.748	0.6188
UF, right	7.76E-05 (6.67E-06)	7.24E-05 (7.63E-06)	7.47E-05(7.69E-06)	7.77E-05(1.00E-05)	1.48E-06(5.50E-06)	2.19E-06(5.67E-06)	1.84E-06(5.53E-06)	1.75E-06(8.57E-06)	0.2566	0.1002	0.0539	0.4267
UF, left	7.55E-05 (1.09E-05)	6.87E-05 (1.02E-05)	7.19E-05(1.08E-05)	7.41E-05(8.50E-06)	−1.29E-06(5.63E-06)	−4.59E-07(7.76E-06)	−8.67E-07(6.73E-06)	−3.59E-06(3.99E-06)	0.3289	0.7943	0.4264	***0.0026***

FA, fractional anisotropy; MD, mean diffusivity; AD, axial diffusivity; RD, radial diffusivity; CgC, cingulum cingulate gyrus; CgH, cingulum hippocampus; SLF, superior longitudinal fasciculus; UF, uncinate fasciculus; FMI, facility-based multidomain intervention; HMI, home-based multidomain intervention. Data are presented as the mean (standard deviation). Regions of intertest-wise paired *t*-tests were used to analyze longitudinal changes in white matter integrity for each group (FMI, HMI or controls) and combined intervention groups (FMI + HMI), respectively, using age, sex, years of education, and site effects as covariates. The statistical significance level was set at Bonferroni corrected value of $p < 0.05$ (bolded and italicized). *P*-values represent the results from the paired *t*-tests in each group.

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TABLE 4 Comparison between intervention group and the control of white matter integrity in the regions with significant longitudinal change in each group.

	Value of *p*		
	FMI vs. Control	HMI vs. Control	Intervention vs. Control
FMI			
MD			
CgH, Left	0.472	0.6674	0.9283
HMI			
AD			
CgH, right	0.4748	0.9627	0.6161
FMI + HMI			
FA			
CgH, Left	0.6149	0.4551	0.4961
MD			
CgH, right	0.2935	0.6842	0.3961
CgH, Left	0.492	0.6608	0.9288
UF, right	0.8694	0.9535	0.9764
AD			
CgC, right	0.1018	0.101	0.0469
CgC, Left	***0.0357***	***0.0352***	***0.0073***
CgH, right	0.4748	0.9627	0.6161
CgH, Left	0.235	0.9936	0.5641
UF, right	0.8323	0.747	0.8332
RD			
CgH, right	0.2535	0.5851	0.3472
CgH, Left	0.8827	0.4663	0.7453
Controls			
FA			
UF, left	0.1471	0.3877	0.1928
RD			
UF, left	0.2003	0.0902	0.0831

FA, fractional anisotropy; MD, mean diffusivity; AD, axial diffusivity; RD, radial diffusivity; CgC, cingulum cingulate gyrus; CgH, cingulum hippocampus; SLF, superior longitudinal fasciculus; UF, uncinate fasciculus; FMI, facility-based multidomain intervention; HMI, home-based multidomain intervention. Significant brain image measures in previous paired *t*-test in each group were compared between each group pair (FMI vs. control; HMI vs. control; FMI + HMI vs. control) using one-way analyses of covariance with changes as dependent variables and age, sex, education, and site as covariates. Significant *P*-value ($p < 0.05$) was bolded and italicized.

the CgH. Previous research has suggested that the CgC is associated with attention and executive functions, whereas the CgH is more closely related to learning and episodic memory. In our study, we found that longitudinal changes in the CgC did not significantly correlate with changes in the RBANS. However, it is worth highlighting that previous studies have shown that multidomain lifestyle interventions or exercise can have a positive impact on various cognitive domains, including global cognition, processing speed/attention, and executive function (Ngandu et al., 2015; Gomes-Osman et al., 2018). These cognitive functions are associated with the CgC. Therefore, it is possible that interventions targeting multidomain lifestyle or exercise could potentially affect the CgC and contribute to improvements in attention, processing speed, and executive function.

Several studies indicate that the effects of aging on the cingulum are not uniform and can vary across different regions. Evidence suggests an age-related gradient along the long axis of the cingulum, with the frontal parts of the bundle being most affected (Bubb et al., 2018). Conversely, consistent findings have shown microstructural changes in the posterior and parahippocampal cingulum, which are associated with both mild cognitive impairment and Alzheimer's disease (Yu et al., 2017). In our study, we observed significantly more beneficial effects on the AD of the CgC in the FMI, HMI, and intervention groups. Furthermore, we found a positive correlation between longitudinal AD changes in the left CgC and changes in BDNF. The possible mechanisms of dementia protection by multidomain lifestyle intervention involve increasing or maintaining cognitive reserve in the presence of pathology and neuropathological damage (Livingston et al., 2017, 2020). These cognitive reserve mechanisms may include preserved metabolism or increased connectivity in temporal and frontal brain areas. A previous study has suggested that increased resilience against cognitive impairment in the early stages of Alzheimer's disease is partially associated with enhanced connectivity between the left frontal cortex and brain hubs (Franzmeier et al., 2018). Building upon these findings, our study contributes further evidence regarding the mechanisms underlying dementia prevention through multidomain lifestyle interventions. Specifically, we observed improved white matter integrity in the CgC, providing support for the beneficial effects of such interventions on maintaining the structural integrity of this region. Our multidomain lifestyle intervention revealed only beneficial effects on the AD among various DTI parameters. AD refers to the magnitude of diffusion parallel to fiber tracts. Lower AD might reflect axonal injury, reduced axonal caliber, or less coherent orientation of axons. FA refers to the fraction of diffusion that is directionally dependent (anisotropic). Lower FA might reflect damage to the myelin sheath surrounding axons, enlarged axonal diameter, reduced axonal packing density, or increased membrane permeability. MD is the overall directionally averaged magnitude of diffusion, and its increase reflects reduced white matter integrity due to either axonal or myelin degradation. Finally, RD refers to the magnitude of diffusion perpendicular to fiber tracts. RD may be relatively more sensitive to myelin, but higher RD might reflect myelin loss, or loss of axons and/or reduced axonal packing density. Together, FA and MD provide information about changes to barriers to diffusion; increased AD has been associated with axonal degeneration and increased RD has been linked to demyelination (Bosch et al., 2012; Bennett and Madden, 2014; Kantarci, 2014; Alves et al., 2015). In addition, there is evidence that AD is not influenced by myelin. Therefore, the AD is differentiated from other DTI parameters in terms of its specific relation to the axonal change. The Amyloid Cascade Hypothesis (Hardy and Higgins, 1992) predicts that axonal degeneration is a result of Wallerian degeneration and precedes neuronal loss. The close association of tau with both axonal integrity and with the cognitive symptoms of Alzheimer's disease suggests that white matter changes may occur independently and perhaps prior to changes in gray matter. Building upon these findings, our study contributes further evidence regarding the mechanisms underlying dementia prevention through multidomain lifestyle interventions. Specifically, we observed improved white matter integrity through the effect on the AD, providing support for the beneficial effects of such

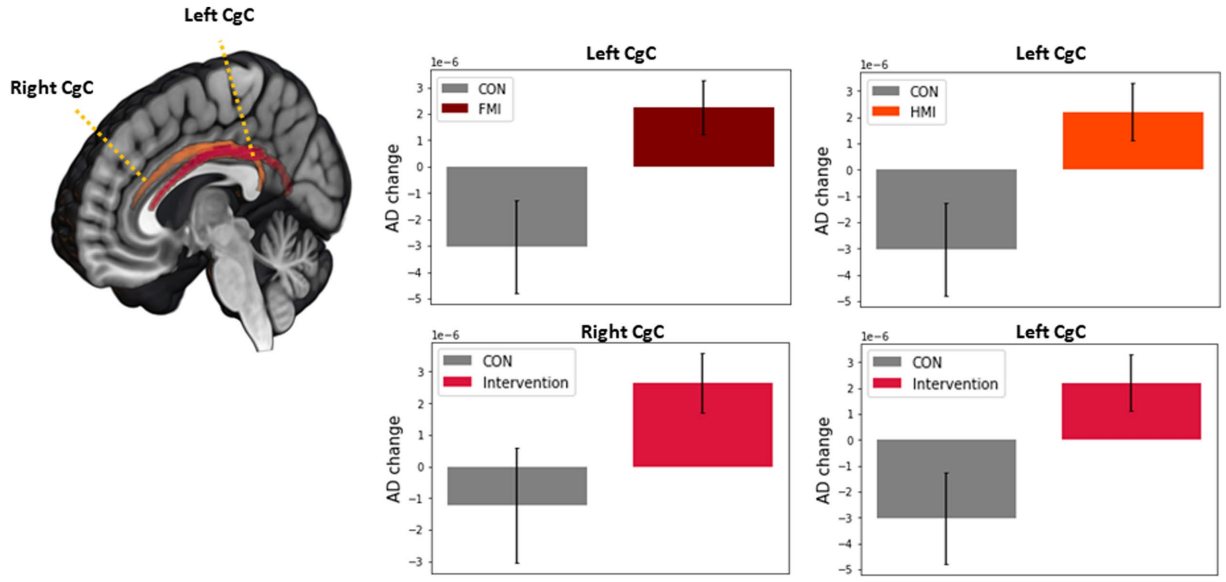

FIGURE 3
Comparison between intervention group and the control of white matter integrity in the regions with significant longitudinal change in the intervention group. Among the significant regions in paired *t*-test of the intervention group, compared with the control group, the FMI, HMI, and intervention group yielded significantly more beneficial effects on the AD of the CgC. AD, axial diffusivity; CgC, cingulum cingulate gyrus; FMI, facility-based multidomain intervention; HMI, home-based multidomain intervention; CON, control.

interventions on maintaining the structural integrity against the axonal degeneration rather than changes in the myelin integrity.

The main strengths of this study are the randomized controlled design, the multidomain intervention, and the availability of MRI scans at baseline and 6 month. The main limitation of this study is that the MRI scanners differed between sites; however, this was adjusted for during analysis. Additionally, as this was a SUPERBRAIN MRI exploratory sub-study, the results should be interpreted with caution. Future studies including white matter integrity as a primary outcome measure are necessary to confirm the impact of multidomain lifestyle interventions on white matter integrity.

In conclusion, significant changes in white matter integrity in at-risk elderly without substantial impairment after the multidomain lifestyle intervention suggest that multidomain lifestyle intervention may confer cognitive benefits through neuroplastic changes of functional processing circuits in the brain areas which play a crucial role in adaptive learning.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ajou University Hospital institutional review board. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

SM, JJ, CH, YP, J-ML, and SC: conceptualization and methodology. SM and SK: formal analysis and investigation. SM, SL, and SK: writing – original draft preparation. SM, JJ, CH, YP, J-ML, and SC: writing – review and editing. SM, JJ, CH, YP, J-ML, and SC: funding acquisition. All authors contributed to manuscript revision, read, and approved the submitted version.

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Conflict of interest

SM received a research grant from Hyundai Pharmaceutical Co. Ltd. CH receives research support from Eisai Korea Inc. JJ receives research grants from Chong Kun Dang Pharmaceutical Corp., Jeil Pharmaceutical Co. Ltd., and Kuhnil Pharmaceutical Co. Ltd., and consults for PeopleBio Co. Ltd. SM, CH, JJ, YP, HN, and SC are shareholders of Rowan Inc. YP consults for Pulmuone Co. Ltd. HN

consults for Hyundai Pharmaceutical Co. Ltd. SC consults for Hyundai Pharmaceutical Co. Ltd. and PeopleBio Co. Ltd.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2023.1242295/full#supplementary-material

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Cardiovascular disease risk models and dementia or cognitive decline: a systematic review

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Background: Health cognitive promotion and protection is a critical topic. With the world's aging population and rising life expectancy, there will be many people living with highly age-related dementia illnesses. Cardiovascular disease (CVD) and dementia share the same risk factors, such as unhealthy lifestyles and metabolic factors. These recognized risks associated with CVD and dementia frequently co-occur. CVD risk models may have a close association with dementia and cognitive decline. So, this systematic review aimed to determine whether CVD risk models were connected with dementia or cognitive decline and compare the predictive ability of various models.

Methods: PubMed, Web of Science, PsychINFO, Embase, Cochrane Library, CNKI, Sinomed, and WanFang were searched from 1 January 2014 until 16 February 2023. Only CVD risk models were included. We used the Newcastle-Ottawa scale (NOS) for the quality assessment of included cohort studies and the Agency for Healthcare Research and Quality (AHRQ) for cross-sectional studies. The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement's guidelines were followed in this systematic study.

Results: In all, 9,718 references were screened, of which 22 articles were included. A total of 15 CVD risk models were summarized. Except for the Cardiovascular Health in Ambulatory Care Research Team (CANHEART) health index, the other 14 CVD risk models were associated with dementia and cognitive decline. In comparison, different CVD risk models and domain-specific cognitive function correlation variation depended on cohort characteristics, risk models, cognitive function tests, and study designs. Moreover, it needed to be clarified when comparing the predicting performance of different CVD risk models.

Conclusion: It is significant for public health to improve disease risk prediction and prevention and mitigate the potential adverse effects of the heart on the brain. More cohort studies are warranted to prove the correlation between CVD risk models and cognitive function. Moreover, further studies are encouraged to compare the efficacy of CVD risk models in predicting cognitive disorders.

KEYWORDS

cardiovascular disease risk models, cardiovascular health, dementia, cognitive decline, health promotion

1. Introduction

With the aging population and increasing life expectancy, people now have significantly higher chances of developing highly age-related dementia disorders (Livingston et al., 2020). Age-related dementia is caused by a complex combination of hereditary and environmental variables (Fayosse et al., 2020). In low- and middle-income nations, the number of people with dementia is increasing faster than in high-income countries, owing to a greater risk factor burden (Livingston et al., 2020). With less knowledge of the underlying pathology and no targeted treatments, modifiable factors have drawn particular attention for dementia prevention. According to the World Health Organization, health cognitive promotion and protection is a public health priority to achieve the goal of universal cognitive health coverage (WHO, 2020).

Increasing evidence demonstrates that heart and brain health are inextricably linked (Zhao et al., 2023). Patients diagnosed with cardiovascular disease (CVD) usually had poorer cognition than those without CVD (Covello et al., 2021). According to the most recent descriptions of novel pathological reasons, mixed dementia (Alzheimer's disease and cerebrovascular injuries) is more common among the oldest seniors (those over 90 years old; Livingston et al., 2020). More and more population-based cohort studies have discovered that dementia and CVD may share the same risk factors. Modifiable health and lifestyle factors such as blood pressure (BP), total cholesterol (TC), blood glucose, physical activity, dietary habits, and smoking could improve vascular health and potentially reduce the risk of cognitive decline and dementia (Rasmussen et al., 2020). Cardiovascular risk factors may hasten cognitive decline by generating cerebral hypoperfusion, hypoxia, embolism, or infarcts, which result in vascular and degenerative brain lesions (Bancks et al., 2019; Lane et al., 2020). According to neuropathological research, dementia and CVD share pathogenic mechanisms linked to cardiovascular risk factors, and CVD may lower the threshold for cognitive impairment (Song et al., 2020).

According to the Lancet Commission on Dementia Prevention, 12 modifiable risk factors, namely, less education, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes, low social contact, excessive alcohol consumption, traumatic brain injury, and air pollution, account for nearly 40% of all dementia cases globally, and this estimate highlights how relatively important potentially modifiable risk factors are in dementia (Livingston et al., 2020). Given that multiple risk factors overlap and may have an additive or synergistic effect (Lee et al., 2019), some risk models that treated incident dementia as the outcome were built, such as Cardiovascular Risk Factors, Aging, and Dementia (CAIDE) risk algorithms (Kivipelto et al., 2006). These models, however, were mainly developed based on predictors that are challenging to obtain in primary prevention, such as apolipoprotein E Ɛ4 (ApoE Ɛ4), mean corpuscular volume, and peak expiratory flow (Exalto et al., 2014; You et al., 2022). In contrast, CVD risk models have been extensively constructed and applied. The Framingham risk models, which contain health parameters simple to measure, are the most frequently utilized in research and clinical settings (Peloso et al., 2020).

Surprisingly, relevant studies found that CVD risk models are associated with dementia and cognitive decline (Harrison et al., 2014). Using CVD risk models to predict dementia not only impedes the incidence of CVD but also favors putting off the progression of dementia. Harrison conducted a systematic review in 2014 to conclude the association between various CVD risk models and dementia or cognitive impairment (Harrison et al., 2014). In recent years, with the deepening of research, new CVD risk models have been constructed, such as the prediction for atherosclerotic cardiovascular disease (ASCVD) risk in China (China-PAR) (Yang et al., 2016) and Life's Essential 8 (LE8) (Lloyd-Jones et al., 2022). Furthermore, some scholars have paid more attention to whether CVD risk models can predict dementia and which models have better forecast performance. So, it is necessary to find more evidence and update the results. This review has two objectives: (1) to comprehensively review the association between various CVD risk models and dementia or cognitive decline and (2) to compare the better risk models for predicting dementia and cognitive decline.

2. Methods

2.1. Search strategy

This systematic review followed the procedures of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement (Page et al., 2021). The present study was registered in PROSPERO. Available at: https://www.crd.york.ac.uk/prospero/display_record.php? ID=CRD42023316549. Since Harrison reported related research in 2014 (Harrison et al., 2014), we have systematically reviewed articles from 1 January 2014 until 16 February 2023. PubMed, Web Of Science, PsychINFO, Embase, Cochrane Library, CNKI, Sinomed, and WanFang were searched. Combinations of the following terms were explored: "cognit*," "dementia," "Alzheimer's disease," "cognitive dysfunction," "cognitive impair*," "cognitive decline," "heart disease risk factors," "cardiovascular risk," "cardiovascular risk model," "cardiovascular risk score," "cardiovascular health," "cardiovascular health metrics," and "Framingham". The search strategy of PubMed is presented in Table 1.

2.2. Inclusion and exclusion criteria

The inclusion criteria for studies were the following: (1) assessed CVD risk models; (2) had access to specific information on cognitive test results (or how they changed); and (3) used a cross-sectional, longitudinal cohort study design. Articles were disqualified if they only examined a single risk factor or included dementia or cognitive impairment data in their risk models. Studies written in languages other than English or Chinese, those with incomplete abstracts, and those lacking full texts were also disqualified.

2.3. Data extraction and assessment for study quality

From each eligible study, we extracted data on (1) article information: authors, publication year, and country; (2) cohort information: name of the study, number of participants, percentage of women, mean age, and race/ethnicity; (3) study design: cross-sectional study, longitudinal cohort study (follow-up time); (4) CVD risk models: details of the risk model used and any modifications made; (5) primary outcome (dementia diagnoses, cognitive decline, or cognitive function); and (6) analytical strategy: details on models' prognostic performance including odds ratio (OR), 95% confidence

TABLE 1 PubMed search strategy.

Search formula		Result
#1	[M.H.] = dementia OR cognitive dysfunction OR Alzheimer's disease	221,674
#2	[TIAB] = cognit* OR Dementia OR Alzheimer's disease OR cognitive dysfunction OR MCI OR cognitive impair* OR cognitive decline	608,329
#3	#1 OR #2	693,047
#4	[M.H.] = Heart Disease Risk Factors	5,336
#5	[TIAB] = Heart Disease Risk Factors OR cardiovascular risk OR cardiovascular risk model OR cardiovascular risk score OR cardiovascular health OR cardiovascular health metrics OR Framingham	98,294
#6	#4 OR #5	100,480
#7	#3 AND #6	3,434
#8	#7 AND [2014:2023 (pdat)]	2,249

interval (95% CI), hazard ratio (HR), β coefficients, the area under the receiver operating characteristic curve (AUC), or C-statistic.

2.4. Risk of bias assessment

Cohort studies were evaluated for quality using the Newcastle-Ottawa scale (NOS) (Lo et al., 2014). In more detail, the scores of the related items in three domains–four items for the chosen domain, one item for the comparability domain, and three items for the resulting part–were added up to create a total score of the risk of bias. High-quality studies were those with a total score of six or higher. The Agency for Healthcare Research and Quality (AHRQ) provided an 11-item checklist for evaluating the methodological quality of the cross-sectional studies (Newman, 2000). If a question was answered "NO" or "UNCLEAR," the item received a score of "0" and if the reply was "YES," the item received a score of "1". Low-quality articles were given a score of 0–3, moderate quality ones of 4–7, and high-quality ones of 8–11. The prediction model Risk Of Bias ASsessment Tool (PROBAST) includes 20 signaling questions across four domains: participants, predictors, outcome, and analysis (Moons et al., 2019). It is used to assess a prediction model's risk of bias and applicability concerns. It can be downloaded from www.probast.org.

2.5. Data synthesis

Due to the variation among studies, including variations in the variables included in the CVD risk models, the small number of studies using the same models, and even variations in adjusted variables across studies using the same models, as well as differences in cognitive outcomes and variations in the reporting of effect sizes, synthesis with meta-analysis is not possible.

3. Results

3.1. Description of included studies

The search yielded a total of 9,718 articles. Of these, 3,250 were duplicates, and 6,417 were irrelevant after title and abstract reviews. A total of 51 articles underwent full-text screening and 34 were excluded due to unmet criteria. Other 5 extra studies were obtained from the references of the included articles and the citation retrieval of related systematic reviews, and 22 full-text articles, including 14 cohort studies and 8 cross-sectional studies, were included. Figure 1 summarizes the study selection process.

The included research was conducted in 10 different countries. The most significant articles came from the United States, China, Italy, France, Thailand, the Republic of Korea, and the United Kingdom. A total of 19 studies were derived from datasets based on data from a population-based cohort. Most studies used the National Alzheimer Coordinating Center (NACC) database (Jefferson et al., 2015; Viswanathan et al., 2015; Pelcher et al., 2020). Sample sizes ranged from 300 to 429,033 and were racially diverse as they included White people, Black people, Hispanic/Latino (H/L) people, and non-H/L people. The mean age at baseline ranged from 45 to 79.5 years. In cohort studies, the follow-up duration ranged from 1 to 26.2 years. Detailed information on the study cohort, sample traits, CVD risk models, cognitive function or dementia assessments, and model details are presented in Table 2.

3.2. Quality of the included studies

After the studies' quality assessment, the 14 cohort studies were rated as good quality, and the 8 cross-sectional studies were rated moderate to high. The deduction items are concentrated in 6 and 9–11. The key concern is that several cardiovascular parameters (physical activity and diet) were dependent on self-reports. In addition, some studies substituted similar variables because existing cohorts did not contain the desired variables. For example, Washington Heights-Inwood Community Aging Project Risk Score (WHICAP) studies used Body Mass Index (BMI) instead of the waist-to-hip ratio (Torres et al., 2020). The quality assessment of the reviewed studies is shown in Tables 3, 4.

3.3. Quality of the included CVD risk models

A total of 22 studies described 15 CVD prediction models (Kannel et al., 1976; D'Agostino et al., 1994, 2008; Conroy et al., 2003; Sacco et al., 2009; Lloyd-Jones et al., 2010; Reitz et al., 2010; Goff et al., 2014;

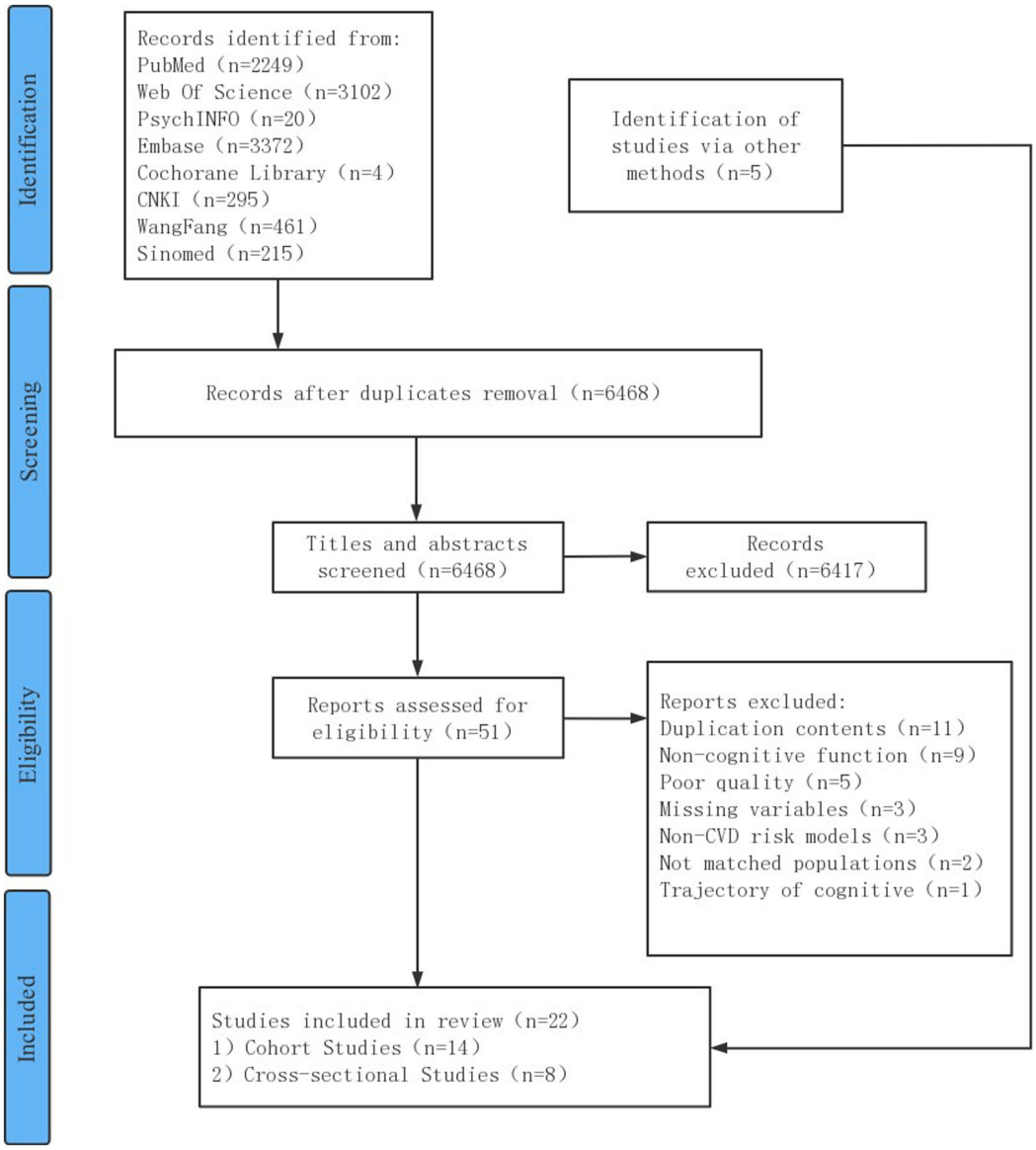

FIGURE 1
PRISMA 2020 flow diagram presenting study screening and selection process.

Jee et al., 2014; Maclagan et al., 2014; Tsao and Vasan, 2015; Yang et al., 2016; Dufouil et al., 2017; Hageman et al., 2021; Buawangpong et al., 2022). Among them were two models without evaluation (Lloyd-Jones et al., 2010; Maclagan et al., 2014). Life's Simple 7 (LS7) was defined as the concept and determining of the metrics done by the Goals and Metrics Committee of the Strategic Planning Task Force of the American Heart Association (AHA) (Lloyd-Jones et al., 2010). Furthermore, the Cardiovascular Health in Ambulatory Care Research Team (CANHEART) health index was a modified version of the AHA's definition of ideal cardiovascular health (CVH) for Canadians (Maclagan et al., 2014). Besides, WHICAP claimed good prediction performance, with no specific values discovered (Reitz et al., 2010). Others found AUC or C-statistics ranging from 0.51 to 0.86. Except for the Thai Cardiovascular Risk score (TCVR) (Buawangpong et al., 2022), most of the models demonstrated good to acceptable discrimination (Receiver Operator Characteristic Curve>0.7). No studies exhibited a low risk of bias owing to insufficient analytical domain reporting (Tables 5, 6). The explanation could be that the CVD risk models were built and verified before the PROBAST report was proposed, and there needed to be a uniform and standard reporting checklist, resulting in a low assessment score. In contrast, its predictive performance was quite good, particularly for the Framingham series models.

3.4. The different CVD risk models and dementia or cognitive decline

Framingham risk models and CAIDE, and other nine CVD risk models were used to predict dementia or cognitive decline, namely, the Korean Coronary Heart Disease Risk score (KPS), Systematic COronary Risk Evaluation (SCORE), SCORE2, atherosclerotic cardiovascular disease pooled cohort equation (ASCVD-PCE), TCVR, CANHEART, Global Vascular Risk score

TABLE 2 Summary characteristics of the included studies.

First author/ publication year	Country	Cohort	Sampling				CVD risk model	Outcome	Study design	Follow-up duration (year)	Effect values
			N	Mean age	Gender (Females %)	Multiethnic					
Zheng et al. (2022)	China	UK Biobank cohort	429,033	57.1	53.8%	N	SCORE2 SCORE CAIDE	Dementia (AD, VD)	Cohort	12.8	C-indices: 0.750 (0.745 to 0.755)
Buawangpong et al. (2022)	Thailand	/	421	63.39	64%	N	TCVR	MCI	Cohort	7	AuROC: 0.58–0.61
McGrath et al. (2022)	United States	FHS Original and Offspring cohort	4,899 2,386	55 80	57.2% 62.1%	N	FSRP (rFSRP) PGRS	Dementia	Cohort	10	HR: 1.160 (1.06–1.26)
Tin et al. (2022)	United States	ARIC	8,823EA 2,738AA	54.3EA 53.5AA	53.1%EA 63.1%AA	N	LS7	Dementia	Cohort	26.2	HR (EA): 1.440 (1.37–1.51) HR (AA): 1.260 (1.16–1.36)
Ji et al. (2022)	China	CHARLS	6,402	57.8	49.0%	N	FGCRS	Cognitive function	Cohort	6.9	β: −0.001 (−0.006 to −0.004)
Schaich et al. (2022)	United States	MESA	4,392	60.1	53%	Y	CAIDE FSRP ASCVD-PCE	Cognitive decline	Cohort	16	FSRP: HR: 1.500 (1.30–1.74); AUC: 0.66 ASCVD-PCE: HR: 1.620 (1.40–1.88); AUC: 0.65
Song et al. (2020)	China	MAP (northeastern Illinois)	1,588	79.5	76%	N	FGCRS	Cognitive function MCI Dementia	Cohort	21	β: −0.019 (−0.035 to −0.003)
Rundek et al. (2020)	United States	NOMAS	1,290	64	60%	Y	CAIDE GVRS	Cognitive decline	Cohort	6	SE: −0.247
Samieri et al. (2018)	France	Three city Study	6,626	73.3	63.4%	N	LS7	Cognitive decline	Cohort	12–16	HR: 0.920 (0.89–0.96)
Viticchi et al. (2017)	Italy	Amnestic MCI	385	72.29	49.4%	N	FCRP	AD	Cohort	1	AUC: 0.682 (0.577–0.786)
Harrison et al. (2017)	United Kingdom	Newcastle 85+ Study Leiden 85-plus Study LiLACS NZ Study	616 444 396	85+ 85-plus	60.1% 65.4% 52%	N	FSRP CAIDE Oxi-inflammatory load	Cognitive function	Cohort	60 months annually for 5 annually for 3	HR: 1.460 (1.08–1.98)

(Continued)

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TABLE 2 (Continued)

First author/ publication year	Country	Cohort	Sampling				CVD risk model	Outcome	Study design	Follow-up duration (year)	Effect values
			N	Mean age	Gender (Females %)	Multiethnic					
Viswanathan et al. (2015)	United States	NACC	2,975	72.1	66.1%	N	rFSRP	Cognitive function	Cohort	3.18 ± 1.35	β: −0.059 (−0.188 to −0.069)
Jefferson et al. (2015)	United States	NACC	3,117MCI 6,603NC	74 72	56% 68%	N	FSRP	Dementia MCI Cognitive function	Cohort	2.2 ± 2.2MCI 3.0 ± 2.5NC	β: −0.01 (−0.03–0.02)
Thacker et al. (2014)	United States	REGARDS	17,761	45+	55%	Y	LS7	Cognitive function	Cohort	A mean of 4	HR: 0.630 (0.51–0.79)
Wei et al. (2022)	United States	NHANES	2,585	≥60	54%	N	LS7	Cognitive function	Cross-sectional	/	β: 0.05 (0.02–0.07)
Mun et al. (2023)	Republic of Korea	NHIS	8,600	69.74	60.5%	N	KRS	Cognitive decline	Cross-sectional	/	OR: 1.339 (1.034–1.734)
Jeon et al. (2021)	Republic of Korea	CMERC	2,622	57.2	68.3%	N	CANHEART health index	Cognitive function	Cross-sectional	/	β: 1.99 (1.01–3.92)
Bao-Shan et al. (2021)	China	/	300	61.93	60%	N	China-PAR	Cognitive function	Cross-sectional	/	OR: 2.586 (1.023–6.533)
Torres et al. (2020)	United States	FRONTIER	541	61.6	68.9%	N	CAIDE FRS WHICAP	Cognitive function	Cross-sectional	/	β (FRS): −0.08 β (WHICAP): −0.04
Pelcher et al. (2020)	United States	NACC-UDS	19,309	72.84	56.9%	N	rFSRP	Dementia MCI Cognitive function	Cross-sectional	/	β: 0.02 (0.001–0.01)
Tarraf et al. (2020)	United States	HCHS/SOL	7,650	56	55.6%	N	FCRS GVRS	Cognitive function	Cross-sectional	/	β (FGCRS): −0.019 β (GVRS): −0.042
Badran et al. (2019)	United Kingdom	/	346	57	54%	N	Framingham Vascular Age	Cognitive function	Cross-sectional	/	β: −0.005

SCORE, Systematic COronary Risk Evaluation; CAIDE, Cardiovascular Risk Factors, Aging, and Dementia; AUC, area under the receiver operating characteristic curve; TCVR, Thai Cardiovascular Risk score; MCI, mild cognitive impairment; FHS, Framingham Heart Study; PGRS, a polygenic risk score; NHIS, National Health Insurance Service; ARIC, Atherosclerosis Risk in Communities; LS7, Life's Simple 7; CAIDE, Cardiovascular Risk Factors, Aging, and Incidence of Dementia; AD, Alzheimer's disease; VD, Vascular disease; FSRP, Framingham Stroke Risk Profile; ASCVD-PCE, atherosclerotic cardiovascular disease pooled cohort equation; MAP, The Rush Memory and Aging Project; FGCRS, The Framingham General Cardiovascular Risk Score; NOMAS, Northern Manhattan Study; NACC, National Alzheimer Coordinating Center; NC, normal cognitive; REGARDS, Reasons for Geographic And Racial Differences in Stroke; NHANES, National Health and Nutrition Examination Survey; KPS, Korean coronary heart disease risk score; OR, odds ratio; CMERC, The Cardiovascular and Metabolic Diseases Etiology Research Center study; CANHEART, Cardiovascular Health in Ambulatory Care Research Team; China-PAR, Prediction for ASCVD Risk in China; FRONTIER, Facing Rural Obstacles to Healthcare Now Through Intervention, Education & Research; FRS, Framingham Risk Score; WHICAP, Washington Heights-Inwood Community Aging Project Risk Score; NACC-UDS, National Alzheimer's Coordinating Center Uniform Data Set; rFSRP, revised Framingham Stroke Risk Profile; HCHS/SOL, Hispanic Community Health Study/Study of Latinos; FCRS, Framingham Cardiovascular Risk Score; GVRS, Global Vascular Risk Score; N, No; Y, Yes; U, Unclear; FSRP, Framingham Stroke Risk Profile; CHARLS, the China Health and Retirement Longitudinal Study; EA, European American; AA, African American; HR, Hazard Ratio; β, β coefficients; SE, standard error.

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TABLE 3 The quality assessments of the cohort studies.

Cohort star template(NOS)			
Study author (publication date, country)	Selection	Comparability	Outcome
Zheng et al. (2022), China	★★★★	★★	★★★
Buawangpong et al. (2022), Thailand	★★★★	★★	★★
McGrath et al. (2022), United States	★★★★	★★	★★★
Tin et al. (2022), United States	★★★★	★★	★★★
Ji et al. (2022), China	★★★★	★★	★★★
Schaich et al. (2022), United States	★★★★	★★	★★★
Song et al. (2020), China	★★★★	★★	★★★
Rundek et al. (2020), United States	★★★★	★★	★★★
Samieri et al. (2018), France	★★★★	★★	★★★
Viticchi et al. (2017), Italy	★★★★	★★	★★
Harrison et al. (2017), United Kingdom	★★★★	★★	★★★
Viswanathan et al. (2015), United States	★★★★	★★	★★
Jefferson et al. (2015), United States	★★★★	★★	★★★
Thacker et al. (2014), United States	★★★★	★★	★★

TABLE 4 The quality assessments of cross-sectional studies.

Cross-sectional study quality(AHRQ)												
Study author (publication date, country)/items	1	2	3	4	5	6	7	8	9	10	11	Quality score
Wei et al. (2022), United States	Y	Y	Y	Y	Y	U	Y	Y	U	Y	U	8
Mun et al. (2023), Republic of Korea	Y	Y	Y	Y	N	U	Y	Y	U	Y	Y	8
Jeon et al. (2021), Republic of Korea	Y	Y	Y	Y	N	N	Y	Y	U	Y	U	7
Bao-Shan et al. (2021), China	Y	Y	Y	Y	N	U	Y	Y	U	N	U	6
Torres et al. (2020), United States	Y	Y	N	Y	N	U	Y	Y	U	Y	U	6
Pelcher et al. (2020), United States	Y	Y	Y	Y	N	U	Y	Y	U	Y	U	7
Tarraf et al. (2020), United States	Y	Y	N	Y	Y	U	Y	Y	U	N	U	6
Badran et al. (2019), United Kingdom	Y	Y	N	Y	N	N	Y	Y	U	Y	U	6

1. Define the source of information (survey, record review); 2. List inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous publications; 3. Indicate time used for identifying patients; 4. Indicate whether or not subjects were consecutive if not population-based; 5. Indicate if evaluators of subjective study components were masked to other aspects of the status of the participants; 6. Describe any assessments undertaken for quality assurance purposes(e.g., test/retest of primary outcome measurements); 7. Explain any patient exclusions from analysis; 8. Describe how confounding was assessed and controlled; 9. If applicable, explain how missing data were handled in the analysis; 10. Summarize patient response rates and completeness of data collection; 11. Clarify what follow-up, if any, was expected and the percentage of patients for which incomplete data or follow-up was obtained. Y, Yes; N, No; U, Unclear.

(GVRS), China-PAR, and LS7. Generally, the included CVD risk models had 5 to 15 factors. GVRS had the most number of factors, whereas SCORE had the least (Conroy et al., 2003; Sacco et al., 2009). Except for CANHEART and LS7, other models all included sex, age (age-stratified), systolic blood pressure (SBP), and smoking habits. Notably, race was taken into consideration by ASCVD-PCE, GVRS, and WHICAP (Rundek et al., 2020; Tarraf et al., 2020; Torres et al., 2020; Schaich et al., 2022). WHICAP is a simple summary risk score for predicting Alzheimer's disease (AD) in older adults (Reitz et al., 2010). Given that its construction was based on cardiovascular risk factors, we decided that WHICAP could be included. All of the risk factors can be divided into traditional factors, behavioral factors, and anthropometric factors, including demographic data (age and sex), laboratory data (BP, blood glucose, and APOE Ɛ4), questionnaire data (physical activity and dietary habits) and self-report data (physical activity, dietary habits, and smoking habits). Please see Tables 7, 8 for more details.

Compared with previous research, more studies focused on cognitive function than dementia (Harrison et al., 2014). Dementia was further diagnosed in different subcategories, including AD and vascular disease (VD) (Zheng et al., 2022). There were two ways for included studies to assess outcomes: one was cognitive diagnoses, including International Classification of Diseases 9 or 10 (ICD-9, ICD-10), an expert committee, clinical examination, or Clinical Dementia Rating (CDR), and the other way was neuropsychological assessments including Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MOCA), or domain-specific tests. Furthermore, global cognitive function could be acquired by calculating Z scores.

TABLE 5 The analysis of four domains of CVD risk models.

Included Study	①	②	③	④	⑤	⑥	⑦	⑧	⑨	⑩	⑪	⑫	⑬	⑭	⑮	⑯	⑰	⑱	⑲	⑳	Performance
FSRP	Y	Y	Y	Y	Y	Y	Y	Y	Y	NI	Y	Y	Y	Y	NI	Y	NI	Y	Y	Y	For men: 10-Year Probability of Stroke: 9.6% For women: 10-Year Probability of Stroke: 6.5%
rFSRP	Y	Y	Y	Y	Y	Y	Y	Y	Y	NI	Y	Y	N	Y	Y	Y	NI	Y	N	Y	For men: Calibration chi-squares: 64.0/12.1 For women: Calibration chi-squares: 42.5/4.1
FRS	Y	Y	Y	Y	Y	Y	Y	Y	Y	NI	Y	Y	N	Y	NI	Y	NI	N	N	Y	For men: C-Index =0.74 For women: C-Index =0.77
FCRS	Y	Y	Y	Y	Y	Y	Y	Y	Y	NI	Y	Y	NI	Y	Y	Y	NI	Y	Y	Y	C-Index: 0.756 (95%CI: 0.739–0.773)
Framingham Vascular Age	Y	Y	Y	Y	Y	Y	Y	Y	Y	NI	Y	Y	NI	Y	Y	Y	NI	Y	Y	Y	C-Index: 0.756 (95%CI: 0.739–0.773)
KPS	Y	Y	Y	Y	Y	Y	Y	Y	Y	NI	Y	Y	NI	Y	Y	Y	NI	Y	N	Y	For men: AUC =0.764 For women: AUC =0.815
SCORE	Y	Y	Y	Y	Y	Y	Y	Y	Y	NI	Y	Y	NI	Y	NI	Y	NI	Y	Y	Y	ROC: 0.71–0.84
SCORE2	Y	Y	Y	Y	Y	Y	Y	Y	Y	NI	Y	Y	NI	Y	Y	Y	NI	Y	N	Y	C-Index: 0.81 (0.76–0.86)
TCVR	Y	Y	Y	PY	Y	Y	Y	Y	Y	NI	PY	N	Y	Y	Y	Y	NI	Y	Y	Y	AuROC = 0.58–0.61
China-PAR	Y	Y	Y	PY	Y	Y	Y	Y	Y	NI	Y	Y	Y	Y	Y	Y	NI	Y	NI	Y	For men: C-Index: 0.794 (95%CI: 0.775–0.814) For women: C-Index: 0.811 (95%CI: 0.787–0.835)
WHICAP	Y	Y	Y	PY	Y	Y	Y	Y	Y	NI	PY	Y	NI	N	Y	Y	NI	N	N	Y	NI
GVRS	Y	Y	Y	PY	Y	Y	Y	Y	Y	NI	Y	Y	Y	Y	NI	Y	NI	Y	Y	Y	ROC = 0.747
ASCVD-PCE	Y	Y	Y	PY	Y	Y	Y	Y	Y	NI	Y	Y	NI	Y	NI	Y	NI	Y	N	Y	C-Index: 0.713–0.818

Y, Yes; PY, Probably Yes; N, No; PN, Probably No; NI, No Information; CI, Confidence Interval; AUC, Area Under the Receiver Operating Characteristic Curve; ROC, Receiver Operator Characteristic Curve ①Were appropriate data sources used, e.g., cohort, randomized controlled trial, or nested case–control study data? ②Were all inclusions and exclusions of participants appropriate? ③Were predictors defined and assessed in a similar way for all participants? ④Were predictor assessments made without knowledge of outcome data? ⑤Are all predictors available at the time the model is intended to be used? ⑥Was the outcome determined appropriately? ⑦Was a prespecified or standard outcome definition used? ⑧Were predictors excluded from the outcome definition? ⑨Was the outcome defined and determined in a similar way for all participants? ⑩Was the outcome determined without knowledge of predictor information? ⑪Was the time interval between predictor assessment and outcome determination appropriate? ⑫Were there a reasonable number of participants with the outcome? ⑬Were continuous and categorical predictors handled appropriately? ⑭Were all enrolled participants included in the analysis? ⑮Were participants with missing data handled appropriately? ⑯Was selection of predictors based on univariable analysis avoided? (Model development studies only) ⑰Were complexities in the data (e.g., censoring, competing risks, sampling of control participants) accounted for appropriately? ⑱Were relevant model performance measures evaluated appropriately? ⑲Were model overfitting and optimism in model performance accounted for? (Model development studies only) ⑳Do predictors and their assigned weights in the final model correspond to the results from the reported multivariable analysis? (Model development studies only).

TABLE 6 The PROBAST results of CVD risk models.

Included Study	ROB				Applicability			Overall	
	Participants	Predictors	Outcome	Analysis	Participants	Predictors	Outcome	ROB	Applicability
FSRP	+	+	?	?	+	+	+	?	+
rFSRP	+	+	?	–	+	+	+	–	+
FRS	+	+	?	–	+	+	+	–	+
FCRS	+	+	?	?	+	+	+	?	+
Framingham vascular age	+	+	?	?	+	+	+	?	+
KPS	+	+	?	–	+	+	+	–	+
SCORE	+	+	?	?	+	+	+	?	+
SCORE2	+	+	?	–	+	+	+	–	+
TCVR	+	+	?	–	+	+	?	–	?
China-PAR	+	+	?	?	+	+	+	?	+
WHICAP	+	+	?	–	+	+	?	–	?
GVRS	+	+	?	?	+	+	+	?	+
ASCVD-PCE	+	+	?	–	+	+	+	–	+

PROBAST, Prediction model Risk Of Bias ASsessment Tool; ROB, risk of bias. * + indicates low ROB/low concern regarding applicability; – indicates high ROB/high concern regarding applicability; and? indicates unclear ROB/unclear concern regarding applicability.

Except for one study (Jeon et al., 2021), the various risk models were found to be significantly connected with a higher chance of dementia in the future. In this study, CVH levels did not correlate with early cognitive decline in the Korean study population. The validity of the CANHEART model used to measure CVH was not established for the Korean population because it was initially developed by Canadian academics for the Canadian population. In addition, the CANHEART model used in Canadian samples for predicting cognitive decline was unclear.

The results were ambiguous. AUC was the prognostic performance metric in only four studies (Viticchi et al., 2017; Buawangpong et al., 2022; Schaich et al., 2022; Zheng et al., 2022). More studies just analyzed β efficiency. According to the individual risk factor profiles in midlife, the CAIDE risk score was explicitly created as an easy method to forecast the likelihood of dementia in the future (Kivipelto et al., 2006). With an initial C-index of 0.78 and a repeated C-index of 0.75 following external validation, the score accurately predicted dementia (Exalto et al., 2014).

3.5. The Framingham CVD risk models and dementia or cognitive decline

A total of 12 studies used the Framingham risk model: five studies used the Framingham General Cardiovascular Risk Score (FGCRS) (Viticchi et al., 2017; Song et al., 2020; Tarraf et al., 2020; Torres et al., 2020; Ji et al., 2022), three studies used the Framingham Stroke Risk Profile (FSRP) (Jefferson et al., 2015; Harrison et al., 2017; Schaich et al., 2022), while three studies used the revised Framingham Stroke Risk Profile (rFSRP) (Viswanathan et al., 2015; Pelcher et al., 2020; McGrath et al., 2022), which eliminates left ventricular hypertrophy (LVEF), and one study used Framingham Vascular Age (Badran et al., 2019). All studies found higher Framingham risk scores associated with an increased risk of subsequent cognitive decline or impairment. Which cognitive abilities were linked to a higher risk of CVD or stroke varied among research due to various measures of cognitive function, sample sizes, or statistical performance.

3.6. Specific CVD risk models and dementia or cognitive decline

Except for Framingham models, we concluded that nine specific CVD risk models may be associated with dementia and cognitive decline. Five CVD risk models were designed for a single country (Bao-Shan et al., 2021; Jeon et al., 2021; Buawangpong et al., 2022; Zheng et al., 2022; Mun et al., 2023). KPS, TCVR, the China-PAR, SCORE2, and the CANHEART health index were developed to measure cardiovascular risk among Korean, Thai, Chinese, European, and Canadian populations.

Four risk models were for the multiethnic cohort. A longitudinal cohort of non-Hispanic White people and African Americans served as the basis for the ASCVD-PCE (Schaich et al., 2022) and has since been validated for predicting atherosclerotic CVD risk in Asian and multiethnic populations, including Hispanics. A diverse group with almost equal representations of White people (34.2%), Black people (30.6%), and H/L (33.3%) participants created the WHICAP summary risk score to predict AD in older adults based on their vascular profiles

TABLE 7 The details of Framingham risk models.

Framingham risk models		
CVD risk model	Population	Variables included
FSRP	White American	Age, sex, SBP, use of antihypertension therapy, DM, CVD, AF, left ventricular hypertrophy, and cigarette smoking
rFSRP	White American	Age, sex, SBP, current smoking status, prevalent CVD, prevalent or past AF, prevalent or past DM, and antihypertensive medication use
FRS	White American	Age, gender, current smoking status, TC, HDL-c, SBP, and use of blood pressure medications
FCRS	White American	Age, sex, TC, HDL-c, SBP, and blood pressure treatment, smoking, and DM
Framingham Vascular Age	White American	Age, gender, SBP, antihypertensive medication, smoking, Type 2 DM, and BMI

FSRP, Framingham Stroke Risk Profile; FRS, Framingham Risk Score; FCRS, Framingham Cardiovascular Risk Score; rFSRP, revised Framingham Stroke Risk Profile; SBP, Systolic Blood Pressure; TC, Total Cholesterol; LDL_c, Low-density Lipoprotein Cholesterol; HDL_c, High-density Lipoprotein Cholesterol; BMI, Body Mass Index; AF, atrial fibrillation; CVD, Cardiovascular Disease; DM, Diabetes Mellitus.

TABLE 8 The details of specific CVD risk models.

Specific CVD risk models		
CVD risk model	Population	Variables included
KPS	Korean	Sex, age, SBP, DBP, TC, HDL-c, smoking status, and diabetes history
SCORE	European	Sex, age, smoking, SBP, TC, or cholesterol/HDL-c ratio
SCORE2	European	Age, current smoking, SBP, diabetes, TC, and HDL-c
TCVR	Thai	Age, gender, DM, SBP, WC, height, TC, HDL-c, and LDL-c The TCVR can be calculated using six models: 1. age, gender, DM, smoking status, SBP, and WC; 2. age, gender, DM, smoking status, SBP, WC, and height; 3. age, gender, DM, smoking status, SBP, and TC; 4. age, gender, DM, smoking status, SBP, TC, and HDL-c; 5. age, gender, DM, smoking status, SBP, HDL, and LDL-c; 6. age, gender, DM, smoking status, SBP, and LDL-c.
CANHEART	Canadian	Smoking status, physical activity, healthy diet, obesity, DM, and hypertension history
China-PAR	Chinese	Age, treated or untreated SBP, TC, HDL-C, current smoking, DM, WC, geographic region, urbanization, and family history of ASCVD
LS7	General	Smoking status, BMI, physical activity, diet, TC, blood pressure, and fasting blood glucose
WHICAP	34.2% White population 30.6% Black population 33.3% Hispanic/Latino population	Sex, age, presence of DM or hypertension, current smoking status, low HDL, waist-to-hip ratio (BMI), education, ethnicity, and APOE ε4 allele status
GVRS	52.7% Hispanic population 24.9% African American population 19.9% White population	Age, gender, African American, Hispanic Ethnicity, waist, alcohol, former or current smoker, moderate or moderate-to-heavy activity, SBP, DBP, antihypertensive medication, peripheral vascular disease, fasting blood glucose, HDL-c, and TC
ASCVD-PCE	Asian and multiethnic populations that include Hispanic people	Age, sex, SBP, TC, HDL-c, antihypertensive medication use, DM, current smoker, and race

KPS, Korean coronary heart disease risk score; SCORE, Systematic Coronary Risk Evaluation; CAIDE, Cardiovascular Risk Factors, Aging, and Incidence of Dementia; ASCVD_PCE, atherosclerotic cardiovascular disease pooled cohort equation; TCVR, Thai Cardiovascular Risk score; CANHEART, Cardiovascular Health in Ambulatory Care Research Team; WHICAP, Washington Heights_Inwood Community Aging Project Risk Score; GVRS, Global Vascular Risk Score; China-PAR, Prediction for ASCVD Risk in China; LS7, Life's Simple 7; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; TC, Total Cholesterol; LDL_c, Low-density Lipoprotein Cholesterol; HDL_c, High-density Lipoprotein Cholesterol; BMI, Body Mass Index; DM, Diabetes Mellitus; WC, White Cell; ASCVD, Atherosclerotic Cardiovascular Disease.

associated with late-onset AD (Torres et al., 2020). GVRS is a model for assessing global vascular risk developed in the Northern Manhattan Study (NOMAS) that incorporates traditional, behavioral, and anthropometric risk factors and uses continuous variables (Rundek et al., 2020; Tarraf et al., 2020). A simple tool, LS7 only has seven modified factors, including four behavioral and three biological factors, similar to CANHEART (Lloyd-Jones et al., 2010). The AHA first suggested this metric for keeping CVH and has since been advised for brain health (Gorelick et al., 2017).

Other than CANHEART, specific CVD risk models were associated with a lower risk for dementia or cognitive decline (Covello et al., 2021; Jeon et al., 2021; Speh et al., 2021). CVD risk models from multiethnic cohorts were proven to predict dementia or cognitive decline in diverse race populations, such as White, H/L, Black, or Asian. Specifically, an article reported the association between QRISK and cognitive function, but we did not report it due to its poor quality (Hsu et al., 2015).

Only SCORE2, FSRP, ASCVD-PCE, and FCRP reported the models' performance for dementia (Viticchi et al., 2017; Schaich et al.,

2022; Zheng et al., 2022). The AUC or C-statistics of these models ranged from 0.65 to 0.75. Additionally, the C-indices of SCORE2 risk could distinguish between incident all-cause dementia, AD, VD, and all-cause death (Zheng et al., 2022).

3.7. Comparing the association between different CVD risk models and dementia or cognitive decline

Seven studies compared the predictive performance of two or three risk models (Harrison et al., 2017; Rundek et al., 2020; Tarraf et al., 2020; McGrath et al., 2022; Schaich et al., 2022; Zheng et al., 2022). CAIDE, as a reference substance, was used for five articles. Some studies reported that CAIDE is better for predicting dementia. For instance, one study that evaluated FSRP, ASCVD-PCE, and CAIDE concluded that CAIDE had more robust relationships with cognitive performance than FSRP and ASCVD-PCE but that ASCVD-PCE's associations with the Digit Symbol Coding (DSC) and Digit Span (DS) were comparable to CAIDE's ($\beta = -0.57$ and -0.21, respectively) (Schaich et al., 2022).

Other studies showed that CAIDE had an inferior association with dementia or cognitive function compared with other risk models, such as SCOPE2, WHICAP, or GVRS. One study that compared SCORE2 with SCORE and CAIDE showed that the C-index of SCORE2 risk for discriminating against all-cause dementia was 0.750, which was significantly higher than the C-indices of SCORE and CAIDE risk (SCORE2 vs. SCORE: 0.014; SCORE2 vs. CAIDE: 0.093). The study further found that SCORE2 risk significantly improved the ability to distinguish between AD and VD (Zheng et al., 2022). Two studies showed that higher GVRS presented stronger associations with lower cognitive function than the FCRS or CAIDE (Rundek et al., 2020; Tarraf et al., 2020).

4. Discussion

This systematic review synthesizes the current trends regarding the association between different CVD risk models and incident dementia or cognitive decline. We updated Harrison's systematic review and searched the articles from 2014 to 2023 (Harrison et al., 2014). As a result, 22 studies were included, and 15 CVD risk models were included; besides the Framingham series of models (FSRP, rFSRP, FRS, FGCRS, and Framingham vascular age), there were also specific CVD risk models, namely, KPS, TCVR, China-PAR, SCORE1, SCORE2, CANHEART, ASCVD-PCE, WHICAP, GVRS, and LS7. Our results show that higher CVD risk scores were associated with an increased risk of subsequent dementia or cognitive impairment. Furthermore, compared to the traditional dementia predicting model, multiethnic CVD risk models had a higher connection with cognitive tests.

Regarding the target outcome, only CAIDE was built to predict incident dementia, while other risk models treated fatal or non-fatal CVD events as outcomes. However, more studies found that CVD risk models were associated with dementia and cognitive impairment, and even some articles that compared CAIDE with CVD risk models proved that some CVD risk models' dementia-predicting performance may be similar to or better than CAIDE. Kaffashian et al. (2013) discovered that the Framingham risk scores may be more accurate at predicting future cognitive decline than the CAIDE score by contrasting the FGCRS and FSPR with the CAIDE risk score (Kaffashian et al., 2013). One study compared CAIDE, FSRP, and ASCVD-PCE with exceptional cognitive performance in 4,392 multiethnic studies of participants with atherosclerosis and found that CAIDE had stronger associations with cognitive abilities performance than the FSRP and ASCVD-PCE. However, associations of ASCVD-PCE with processing speed and working memory were similar to CAIDE (Schaich et al., 2022). It is clear that Framingham risk models, consisting of cardiovascular factors, are more appropriate for predicting cognitive impairment. Similar to how SCORE2, WHICAP, and GVRS were created to address a variety of incident CVD risk variables, the findings of this study showed that those models could also predict incident dementia better than the CAIDE risk algorithm (Rundek et al., 2020; Tarraf et al., 2020; Torres et al., 2020; Zheng et al., 2022).

Higher scores from the CVD risk models have been linked to an increased risk of cognitive deterioration or dementia in many studies. Still, when specific cognitive domains have been examined, the results have been mixed regarding which cognitive domains have higher cardiovascular risk (Harrison et al., 2014; Wu et al., 2023). Notably, the identified studies had different primary cognitive outcome measures, which impede inferences regarding which vascular risk scores are the most responsive to specific cognitive domains. Many cognitive tests were used to identify incident dementia or cognitive decline, including verbal fluency, short-term and long-term memory, computation, processing speed, and exclusion function. Some studies reported that FGCRS and GVRS were associated with episodic memory, while others proved that no association was observed for episodic memory when the rFSRP was used (Viswanathan et al., 2015). However, in the NACC cohort, after controlling for age, FSRP independently contributed to a decline in processing speed (Jefferson et al., 2015). The variation of cohort characteristics (e.g., ethnicity and education level), methodological variances, follow-up time, and cognitive assessment instruments may all contribute to the differences in the results.

Traditional risk factors for CVD, such as hypertension, diabetes, dyslipidemia, obesity, and smoking, have been linked to a rapid loss of cognitive function. Moreover, most studies that showed an association between CVD risk models and worse cognitive function were focused on a single population, such as White people, whereas there were fewer studies conducted within non-White populations, such as H/L. It has been shown that race/ethnicity, as a critical element, modified associations (Tarraf et al., 2020; Torres et al., 2020; Schaich et al., 2022). Schaich et al. (2022) found that associations between CAIDE and dementia were more significant in African Americans and Hispanics than in White individuals (difference in $\beta = 0.69$ and 1.67, respectively). CVD risk models, such as the multiethnic GVRS, that are tailored to specific risks based on racial/ethnic background and that can offer significant insight into cognitive risk are practical to use in primary care settings as opposed to FCRP, which ignores race (Tarraf et al., 2020).

Better than GVRS, which contains too many factors, LS7 and CANHEART emphasize modifiable risk factors more than other risk models and may have more immediate implications for health promotion and disease prevention. As Canadian researchers originally created the CANHEART for the Canadian population, it does not

have the TC constraint and its validity has not been demonstrated for the Korean population. Unlike CANHEART, LS7 was proposed by the AHA and includes seven modifiable cardiovascular risk factors. The relationships between the seven individual components and cognitive outcomes have been extensively researched. Nonetheless, the results were mixed since the connections between vascular risk factors and dementia are frequently complex, non-linear, and age-dependent. It is generally accepted that midlife CVH tends to have a linear association with late-life dementia risk.

In contrast, a J-shaped association was seen between the late-life CVH score and dementia, according to a systematic review and meta-analysis (Wu et al., 2023). Furthermore, in 2022, the AHA updated LS7 to LE8, optimizing the scoring algorithm and adding sleep information (Lloyd-Jones et al., 2022). Following the AHA's CVH recommendations and keeping CVH at its best will significantly lower the risk of developing dementia in old age.

A limitation of this review is that it did not involve quantifying the association between CVD risk models and cognitive function through meta-analysis. Another limitation is that we included cross-sectional studies. Furthermore, only cross-sectional studies were used to explore the correlation between CVD risk models and dementia because the latest models have not yet been used for longitudinal cohorts. We aimed to maximize the search for suitable studies on the correlation between CVD risk models and dementia, therefore, cross-sectional and longitudinal cohorts were included. It is expected that more cohorts can be conducted in the future. The aim of this analysis was not to come to any firm conclusions about risk models' powers to predict performance on cognitive decline, but to provide an overarching viewpoint on this trend that can inform future efforts to regulate CVD and dementia and promote health.

5. Implications for clinical practice and policy

Growing evidence points to a tight link between heart and brain health, with CVD possibly leading to brain illnesses such as stroke, dementia, and cognitive impairment. The overall picture of the anatomical and functional connections between the heart and the brain is still unknown at this time. Early detection and prompt management of modifiable risk factors are essential for CVD or dementia, therefore, there is a need for medical professionals to focus more on health promotion.

By understanding human health from a multi-organ perspective, medical professionals can improve disease risk prediction and prevention and mitigate the adverse effects of disease in one organ on other organs at risk. Using mature CVD risk models to predict cognitive decline or dementia incidence has several implications for optimizing clinical practice in escalating care among professional staff. First, two outcomes, CVD and dementia incidence, may be acquired at a one-time assessment, simplifying the preventive services. Second, compared with CAIDE, CVD risk models have few items and few experimental indicators, which are easier to collect, and patients also have the opportunity to self-monitor and self-manage. Finally, it is critical to increase public awareness of the link between CVD and dementia and to reaffirm the significance of preventing and controlling CVD risk factors. Keeping the heart healthy can help prevent cognitive decline in non-CVD or CVD patients.

6. Conclusion

The current systematic review shows the rapidly spreading use of present CVD risk models to predict dementia or cognitive decline. With the rapid development of CVD risk scores, we updated Harrison's study published in 2014 (Harrison et al., 2014). This review presents findings from a large variety of cross-sectional studies and cohorts published between 2014 and 2023, showing significant progress in this field. Our findings prove that a positive association was observed between nationally or multiethnic-based CVD risk scores and subsequent dementia or cognitive impairment. Although meta-analysis was not conducted for different models' risk, this study supports findings that indicate that the included models may be associated with CVD, cognitive function, and dementia.

Given that these factors are easily accessible in clinical and research settings and may be used to identify the members of a population who are most at risk for future cognitive decline and dementia, future efforts should be concentrated on developing vascular factor-based dementia or cognitive decline risk models. More cohorts could clarify the link between CVD risk models and dementia or cognitive decline by unifying the outcome assessment. Additionally, constructing models applicable to low-income and middle-income countries or multiethnic populations is becoming increasingly significant.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

RRJ: Data curation, Methodology, Writing – original draft. QW: Methodology, Supervision, Writing – review & editing. HYH: Data curation, Methodology, Writing – review & editing. TL: Supervision, Writing – review & editing. CFY: Supervision, Writing – review & editing. YLY: Data curation, Methodology, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Glossary

CVD	Cardiovascular Disease
BP	Blood Pressure
TC	Total Cholesterol
CAIDE	Cardiovascular Risk Factors, Aging, and Dementia
ApoE Ɛ4	Apolipoprotein E Ɛ4
ASCVD	Atherosclerotic Cardiovascular Disease
China-PAR	Prediction for ASCVD Risk in China
LE8	Life's Essential 8
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analysis
OR	Odds Ratio
CI	Confidence Interval
HR	Hazard Ratio
AUC	Area Under the Receiver Operating Characteristic Curve
NOS	Newcastle-Ottawa Scale
AHRQ	Agency for Healthcare Research and Quality
PROBAST	Prediction model Risk Of Bias ASsessment Tool
NACC	National Alzheimer Coordinating Center
H/L	Hispanic/Latino
WHICAP	Washington Heights-Inwood Community Aging Project Risk Score
BMI	Body Mass Index
LS7	Life's Simple 7
AHA	American Heart Association
CANHEART	Cardiovascular Health in Ambulatory Care Research Team
TCVR	Thai Cardiovascular Risk score
KPS	Korean Coronary Heart Disease Risk Score
SCORE	Systematic COronary Risk Evaluation
ASCVD-PCE	Atherosclerotic Cardiovascular Disease Pooled Cohort Equation
GVRS	Global Vascular Risk Score
CVH	Cardiovascular Health
SBP	Systolic Blood Pressure
AD	Alzheimer's disease
MCI	Mild Cognitive Function
AD	Alzheimer's disease
VD	Vascular Disease
ICD-9, ICD-10	International Classification of Diseases Version 9 or 10
CDR	Clinical Dementia Rating
MMSE	Mini-Mental State Examination
MOCA	Montreal Cognitive Assessment
FGCRS	Framingham General Cardiovascular Risk Score
FSRP	Framingham Stroke Risk Profile
rFSRP	Revised Framingham Stroke Risk Profile
LVEF	Left Ventricular Hypertrophy
NOMAS	Northern Manhattan Study
ROC	Receiver Operator Characteristic Curve
DSC	Digit Symbol Coding
DS	Digit Span

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Association between cerebrospinal fluid clusterin and biomarkers of Alzheimer's disease pathology in mild cognitive impairment: a longitudinal cohort study

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Background: Clusterin, a glycoprotein implicated in Alzheimer's disease (AD), remains unclear. The objective of this study was to analyze the effect of cerebrospinal fluid (CSF) clusterin in relation to AD biomarkers using a longitudinal cohort of non-demented individuals.

Methods: We gathered a sample comprising 86 individuals under cognition normal (CN) and 134 patients diagnosed with MCI via the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. To investigate the correlation of CSF clusterin with cognitive function and markers of key physiological changes, we employed multiple linear regression and mixed-effect models. We undertook a causal mediation analysis to inspect the mediating influence of CSF clusterin on cognitive abilities.

Results: Pathological characteristics associated with baseline $A\beta_{42}$, Tau, brain volume, exhibited a correlation with initial CSF clusterin in the general population, Specifically, these correlations were especially prominent in the MCI population; CSF $A\beta_{42}$ (P_{CN}=0.001; P_{MCI}=0.007), T-tau (P_{CN}<0.001; P_{MCI}<0.001), and Mid temporal (P_{CN}=0.033; P_{MCI}=0.005). Baseline CSF clusterin level was predictive of measurable cognitive shifts in the MCI population, as indicated by MMSE (β = 0.202, p = 0.029), MEM (β = 0.186, p = 0.036), RAVLT immediate recall (β = 0.182, p = 0.038), and EF scores (β = 0.221, p = 0.013). In MCI population, the alterations in brain regions (17.87% of the total effect) mediated the effect of clusterin on cognition. It was found that variables such as age, gender, and presence of *APOE ε4* carrier status, influenced some of these connections.

Conclusion: Our investigation underscored a correlation between CSF clusterin concentrations and pivotal AD indicators, while also highlighting clusterin's potential role as a protective factor for cognitive abilities in MCI patients.

KEYWORDS

Alzheimer's disease, cerebrospinal fluid, biomarkers, cognition, clusterin

1. Introduction

Dementia, a neurological disorder marked by a steady deterioration of cognitive abilities, impacts memory, thought processes, and behavior. Alzheimer's disease (AD) predominates as the most frequently diagnosed type of dementia, comprising about 70% of all cases (Duong et al., 2017). The amyloid cascade theory suggests that the accumulation of amyloid-beta (Aβ) peptide in cerebral regions marks a critical incident in AD's progression. This event, occurring quite early, has the potential to set off tau-related pathology, provoking detrimental cellular reactions that may result in neuronal dysfunction and cellular death (Karran et al., 2011; Pooler et al., 2015).

The tau-related pathology observed in neurons aligns closely with the cognitive deterioration typical of the disease's final stage. There are theories that this process occurs in a continuous cascade (Karran and De Strooper, 2022). Clusterin is a multifunctional glycoprotein encoded by the CLU gene (a single copy gene located on chromosome 8 at the p21-p12 locus), also known as apolipoprotein J (Foster et al., 2019; Yuste-Checa et al., 2022). The protective effect of this protein against cellular stress has been reported in studies of cardiac injury and tumor survival (Djeu and Wei, 2009; Foster et al., 2019). Apart from curtailing the development of amyloid polypeptide fibrils, a key marker of Alzheimer's pathology, it further mitigates apoptosis and oxidative stress. It exhibits the capability to bind Aβ polypeptides, thus thwarting excessive inflammation (Wu et al., 2012).

One study observed a significant association between single nucleotide polymorphisms (SNPs) at the CLU gene (also known as APOJ) (rs11136000) at a genome-wide level (Harold et al., 2009). It has been reported that clusterin is associated with neuroprotective effects in AD (Wojtas et al., 2020) and has been associated with major AD pathological markers (Tang et al., 2022). Recent researches suggested that the CLU protein may promote the propagation of tau pathology, and an animal study also observed an increase in tau levels in mice treated with CLU (Martin-Rehrmann et al., 2005; Yuste-Checa et al., 2021). The processes through which clusterin influences AD pathology remain ambiguous. The primary focus of our research was to find the correlation between clusterin in CSF, AD pathophysiological processes, and cognitive abilities. Furthermore, we sought to determine the risk factors for AD, such as age, gender, and presence of *APOE ε4* carrier status, influence these correlations (Rosselli et al., 2022).

Additionally, our goal was to determine the degree to which other pertinent biomarkers might influence these correlations. Gaining a comprehensive understanding of how clusterin ties into the onset and clinical presentation of AD could also serve as a beneficial guide for early detection and management of AD. To achieve our goals, we analyzed several biomarkers related to AD pathophysiology such as $A\beta_{42}$, tau protein abnormalities (phosphorylated tau protein, P-tau protein), and indicators of neurodegeneration including total tau protein (T-tau protein) and MRI findings. These biomarkers were chosen for their representation of crucial stages in the AD progression and their extensive research in the context of this disorder (Wang et al., 2020). Our analyses were conducted on a population of non-demented individuals to better understand the early stages of the disease (Giau et al., 2019; Talwar et al., 2021).

2. Materials and methods

2.1. ADNI database

ADNI is a large-scale research effort launched in 2003, an international multicenter, ongoing, observational object, helps improve our understanding of AD and other disorders of the nervous system through a longitudinal study. Participants undergo regular clinical assessments, neuroimaging scans, and blood and CSF tests. The data collected from participants are stored in a central database and made available to researchers worldwide, see the ADNI website for the latest information https://adni.loni.usc.edu/ (Veitch et al., 2019, 2022).

2.2. Participants

Data was retrieved from the ADNI database, encompassing clinical attributes, CSF details, MRI scan results, and cognitive information from 220 participants. The ADNI database classifies subjects as clinically cognitively normal (CN), including those with subjective memory symptoms (MMSE >24, CDR = 0), those with mild cognitive impairment (MCI; MMSE >24, CDR = 0.5), and those with dementia. Participants underwent periodic evaluations for clinical data collection and participation in biomarker studies, which included CSF extraction. The inclusion of 220 individuals necessitated the presence of clusterin protein, demographic information, *APOE* gene carriage status, cognitive diagnosis. Simultaneously, we incorporated cognitive assessment scores of participants meeting these criteria and brain structural organizational data, despite the potential for missing data. Following the baseline examination, biomarker measurements and clinical cognitive assessments were conducted at baseline (BL), 12, 48, 72, 96, 120, 144, 168, and 180 months (Supplementary Table S1). All participants were made aware of the study's aim and granted their approval via signed consent forms (Aisen et al., 2010).

2.3. Measurements of biomarkers

Measurement of $A\beta_{42}$, T-tau, and P-tau in CSF by the INNO-BIA AlzBio3 kit (Shaw et al., 2009). CSF samples were analyzed using an automated Roche Elecsys® platform at the University of Pennsylvania. Further details can be found in previously published literature (Schindler et al., 2018). Repeated biomarker assays in CSF were averaged, and CSF clusterin was quantified using liquid chromatography-tandem mass spectrometry multiple reaction monitoring (LC/MS-MRM) with the peptide sequence IDSLLENDR. The ADNI database was used to collect all observed data (Kennedy et al., 2014; Liu et al., 2022).

2.4. MRI assessment

The MRI Core has established a standardized and publicly accessible data analysis set through the implementation of precise and fully automated brain and hippocampal segmentation algorithms, which have been validated in previously published studies. In our study, we focused on the following regions of interest (ROI): the whole

brain, hippocampus, entorhinal, fusiform, and middle temporal areas. Previous large cohort studies, such as the Add Neuro Med project in Europe and the ADNI database study, have demonstrated the research value of these brain regions (Mangialasche et al., 2013; Falahati et al., 2017; Yu et al., 2021).

2.5. Cognitive assessment

We retrieved the composite memory score (MEM), as well as the commonly used cognitive measures, including ADAS-Cog which full name is the AD Assessment Scale-Cognitive subscale and executive functioning (EF) scores, the Brief Mental State Evaluation Scale (MMSE), and the Rey Auditory Word Learning Immediate Test (RAVLT immediate), from the ADNI Neuropsychological Test to monitor the cognitive measures' trajectory. All of them are psychometrically optimized composite scores, which have been previously validated and proven to be reliable and externally valid (Folstein et al., 1975; Crane et al., 2012; Gibbons et al., 2012; Xu et al., 2022).

2.6. Statistical analysis

CSF clusterin concentrations were analyzed and found to be approximately normally distributed (Supplementary Table S1). To ensure the reliability of the results, We defined outliers as those with a standard deviation of 4 SD above or below the mean, and all analyses in this study were performed using transformed log10 values. We compared continuous demographics, clinical outcomes, and biomarkers using Student's *t*-test or Wilcoxon rank sum tests, while nominal variables were compared with chi-square test or one-way ANOVA, followed by *post hoc* comparisons. The correlation of baseline CSF clusterin with biomarker and cognitive data was assessed using linear regression models. In each model, CSF clusterin levels were used as the form of independent variables, and dependent variables included cognitive measures and biomarkers. We employed a technique previously adopted by other researchers wherein a Linear Mixed Effects (LME) model was fitted, designating different measures as the dependent variable, The independent variable is time, while adjusting for random slope and intercept (Ma et al., 2021).

We also used the model to extract the rate of change of each variable for further subsequent analysis. We used the main biomarkers mentioned above as our hypothetical mediators to analyze the mediation between CSF clusterin and multiple cognitive performance, all tests are bootstrapped with 10,000 replications and adjusted for covariates. The cumulative risk of cognitive progression during follow-up was compared between groups stratified by clusterin level using Kaplan–Meier curves. Furthermore, the relationship between clusterin and the incidence of cognitive progression during follow-up was analyzed using multivariate Cox regression models. In the present study, we introduce a novel variable derived from the product of AD risk factors and CSF clusterin to the model to evaluate the interactive effects of clusterin levels and known AD risk factors (such as age, gender, and *APOE ε4* status) on the dependent variables. Moreover, we utilized a pre-established and verified cut-off value: a critical concentration of 976.6 pg./mL of CSF $A\beta_{42}$, enabling us to categorize subjects into A+ and A− groups for further analys (Tang et al., 2022).

All statistical analyses were performed in R 0.4.2.2. All regression analyses were corrected for age level, participant gender, educational level, and presence of *APOE ε4* carrier status.

3. Results

The main characteristics of the study population, according to cognitive state, are reported in Table 1. We divided the participants into two groups: normal cognitive ability (CN; $n = 86$) and mild cognitive impairment (MCI; $n = 134$).

As expected, cognitive test scores differed significantly between the CN and MCI groups (ADAS11, $p < 0.001$; ADAS13, $p < 0.001$; ADASQ4, $p < 0.001$; MMSE, $p < 0.001$, AVLT immediate, $p < 0.001$; MEM, $p < 0.001$; EF, $p < 0.001$).

Almost all neuroimaging variables, except the whole brain volume and fusiform volume, showed significant differences between the two cognitive groups (ventricles volume, $p = 0.001$; hippocampus volume, $p < 0.001$; entorhinal volume, $p < 0.001$; mid temporal volume, $p < 0.001$). MCI group had higher T-tau ($p < 0.001$), P-tau ($p < 0.001$), and relatively lower levels of CSF $A\beta_{42}$ ($p < 0.001$). There was no clear difference in CSF clusterin and years of education between the two groups which closely resembled previous findings (Tang et al., 2022). The MCI population had a higher proportion of *APOE ε4* carriers compared to the CN group. Additionally, we observed a progressive increase in dementia prevalence from the CN (11.5%) to the MCI group (63.9%), which is by previously reported findings in the literature (Chen et al., 2022).

3.1. Cross-sectional CSF biomarker analysis

In our primary analysis, we computed the correlations between clusterin and all biomarkers as well as cognitive measures after adjustment of age, gender, educational level, *APOE ε4* carriers' status, and intracranial volume. A positive correlation was found between clusterin and biomarkers remained significant in the MCI group (CSF Aβ, $\beta = 0.225$, $p = 0.007$; Total tau, $\beta = 0.440$, $p < 0.001$; P-tau, $\beta = 0.384$, $p < 0.001$). EF was found to have a positive correlation with clusterin ($\beta = 0.191$, $p = 0.035$), whereas other cognitive factors had no correlation with clusterin. The high level of clusterin correlated with the bigger volumes of the hippocampus ($p = 0.02$), fusiform ($p = 0.001$), mid-temporal ($p = 0.005$), and smaller volumes of ventricles ($p < 0.001$). No significant associations were listed between baseline clusterin and other neuroimaging variables in a cross-sectional study. Further analyses suggested that CSF Aβ, tau, MRI imaging markers, and clusterin directly impact cognitive measurement (Figures 1, 2).

3.2. Age, gender, and *APOE ε4* interactions with CSF clusterin on biomarkers

In this analysis, we aimed to examine the interactions between CSF clusterin levels and age, gender, and *APOE ε4* status on various biomarkers in the CN and MCI groups. The main findings were as follows:

Our observations revealed an interaction between CSF clusterin levels and age on T-tau, MRI (hippocampus volume,

TABLE 1 Clinical characteristics of participants in individual groups in the current study.

Characteristics	CN (n = 86)	MCI (n = 134)	p value
Age (years)	75.70 ± 5.54	74.69 ± 7.34	0.278
Gender = male (%)	44 (51.2)	91 (67.9)	0.019
Education (years)	15.64 ± 2.97	16.02 ± 2.98	0.353
APOE ε4 carriers (%)	21 (22.8)	71 (77.2)	<0.001
$A\beta_{42}$	1060.58 ± 386.15	713.68 ± 299.97	<0.001
T-tau	242.35 ± 76.67	313.44 ± 113.11	<0.001
P-tau	22.36 ± 8.10	31.00 ± 12.87	<0.001
Clusterin	20.61 ± 0.44	20.63 ± 0.48	0.712
ADAS11	6.02 ± 2.94	11.49 ± 4.13	<0.001
ADAS13	9.24 ± 4.25	18.91 ± 5.93	<0.001
ADASQ4	2.84 ± 1.79	6.33 ± 2.26	<0.001
MMSE	29.04 ± 1.02	26.99 ± 1.78	<0.001
RAVLT immediate	45.19 ± 8.46	32.04 ± 8.56	<0.001
MEM	0.980 ± 0.50	−0.150 ± 0.57	<0.001
EF	0.600 ± 0.72	−0.110 ± 0.80	<0.001
Ventricles	34480.78 ± 17056.81	43755.98 ± 20122.09	0.001
Hippocampus	7191.51 ± 846.89	6315.79 ± 1099.98	<0.001
Whole brain	997298.94 ± 102276.17	1005024.17 ± 108157.33	0.600
Entorhinal	3792.09 ± 696.59	3305.62 ± 749.94	<0.001
Fusiform	17087.26 ± 2378.97	16643.06 ± 2296.11	0.207
Mid temporal	19588.08 ± 2848.87	18728.40 ± 2901.55	0.049
Dementia at follow up (%)	10 (11.5)	85 (63.9)	<0.001

Categorical variables are reported as numbers and percentages; continuous variables are reported as means ± SDs. Gender, the gender of the participants; Education, Years of education of the participants; CN, cognitively normal; MCI, mild cognitive impairment; APOE, Apolipoprotein E; $A\beta_{42}$, Amyloid-β_{42}; T-tau, Total tau; P-tau, Phosphorylated tau; ADAS, Alzheimer's disease assessment scale-cognitive; ADASQ4, ADAS delayed word recall; MMSE, mini mental state examination; RAVLT immediate, Rey auditory verbal learning test immediate recall; MEM, memory function composite score; EF, executive function composite score.

whole brain volume, and mid-temporal volume), and cognitive measurements (EF) exclusively in MCI participants. In the CN group, the initial interaction effect we examined involved the correlation between CSF clusterin and other measures, with *APOE ε4* status affecting baseline MRI (mid-temporal volume). Interaction effects were noted for longitudinal MRIand cognitive measurements (EF). Interactions are statistically significant between CSF clusterin and gender on longitudinal ADAS11. As for the relationship between age and CSF clusterin, it was noteworthy for longitudinal MRI (ventricles and mid temporal) (Supplementary Tables S8, S9).

3.3. Prediction of longitudinal changes of CSF biomarkers, cognitive score, and neuroimaging variables using baseline CSF clusterin

In the longitudinal analysis, we examined the relationship between baseline CSF clusterin levels and changes in CSF biomarkers, cognitive scores, and neuroimaging variables over time. We hypothesized that the upregulation of clusterin would be related to an increase in overall cognitive ability. After adjusting for relevant covariates, we found the following results for the MCI group:

A higher baseline CSF clusterin level was significantly associated with a higher increased rate not only of global cognition (MMSE, $\beta = 0.202$, $p = 0.029$), composite memory (MEM, $\beta = 0.186$, $p = 0.036$) but also of short-term auditory-verbal memory (i.e., RAVLT immediate, $\beta = 0.182$, $p = 0.038$), executive function (EF, $\beta = 0.221$, $p = 0.013$), Additionally, lower baseline CSF clusterin level predicted greater decline in hippocampus volume ($\beta = 0.170$, $p = 0.043$), the whole brain volume ($\beta = 0.176$, $p = 0.047$), mid temporal volume ($\beta = 0.177$, $p = 0.039$). A higher baseline clusterin level was significantly associated with a higher increased rate of CSF Aβ ($\beta = 0.243$, $p = 0.003$). Meanwhile, the upregulation of baseline clusterin predicted a decrease in the rate of change of P-tau ($\beta = -0.227$, $p = 0.013$). However the effects of baseline clusterin on longitudinal biomarkers and cognitive were not statistically significant in cognitively normal populations (CN) (Figure 3).

3.4. Mediation analyses

Our initial regression studies across various groups unveiled the relationships between the index of pathology and cognitive parameters within a model that accounted for factors such as age, gender, education level, and *APOE ε4* status. We delved into whether the connection between baseline CSF clusterin and

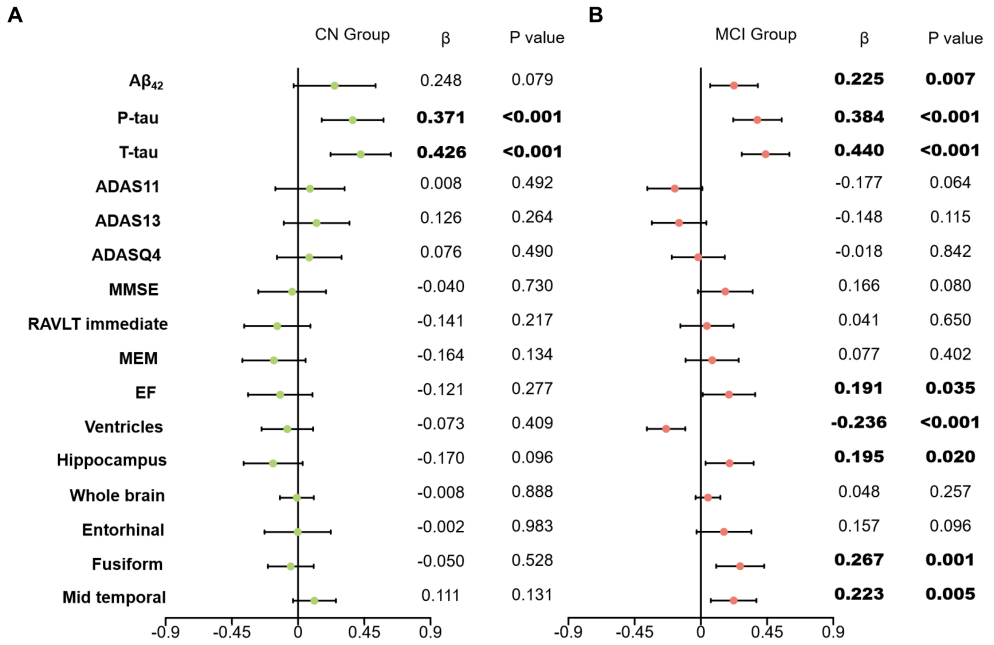

FIGURE 1
Effects of clusterin with biomarkers and cognitive data. Associations of baseline clusterin on baseline biomarkers and cognitive measurements in two group. All analyses were corrected for age, gender, educational level, *APOE ε4* status, and intracranial volume. **(A)** results of CN group; **(B)** results of MCI group; CN, cognitively normal; MCI, mild cognitive impairment; $A\beta_{42}$, Amyloid-β_{42}; T-tau, Total tau; P-tau, Phosphorylated tau; ADAS, Alzheimer's disease assessment scale-cognitive; ADASQ4, ADAS delayed word recall; MMSE, mini-mental state examination; RAVLT immediate, Rey auditory verbal learning test immediate recall; MEM, memory function composite score; EF, executive function composite score.

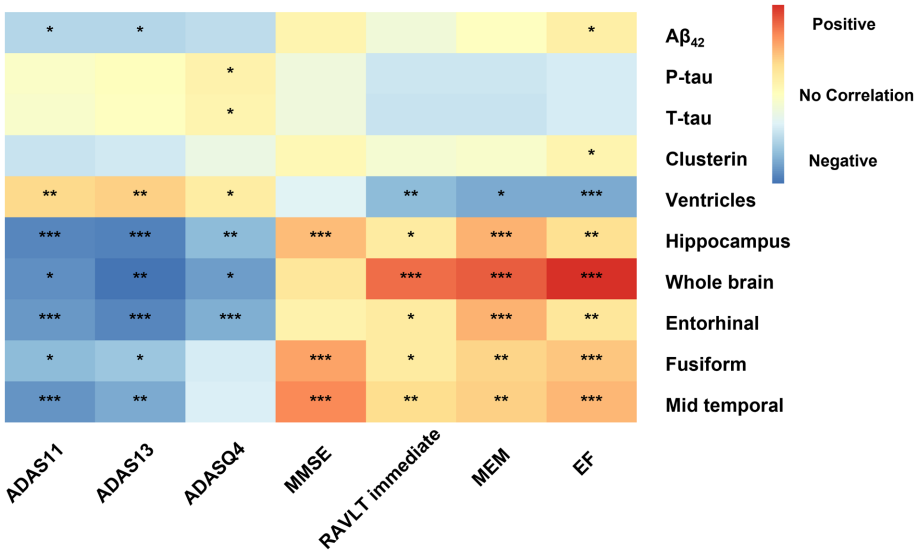

FIGURE 2
Effects of biomarkers on cognitive measures within MCI participants. Correlation of AD biomarker cognitive measurements at baseline. All analyses were corrected for age, gender, educational level, *APOE ε4* status, and intracranial volume. Significance have been marked with the symbol ***, **, and *: *p* value<0.001 and *p* value <0.01, and *p* value<0.05. $A\beta_{42}$, Amyloid-β_{42}; T-tau, Total tau; P-tau, Phosphorylated tau; ADAS, Alzheimer's disease assessment scale-cognitive; ADASQ4, ADAS delayed word recall; MMSE, mini-mental state examination; RAVLT immediate, Rey auditory verbal learning test immediate recall; MEM, memory function composite score; EF, executive function composite score.

cognitive parameters was influenced by factors such as CSF $A\beta_{42}$, tau-related pathology, and neuroimaging variables. For a graphical representation of the mediation concept, see Figure 4A. There is no evidence found to suggest that the effects of CSF clusterin on cognitive impairments are mediated by its modulation of other AD markers in cross-sectional.

Figure 4 demonstrates the ultimate models of MCI participants, wherein some mediators exhibited a minimum of the trend toward

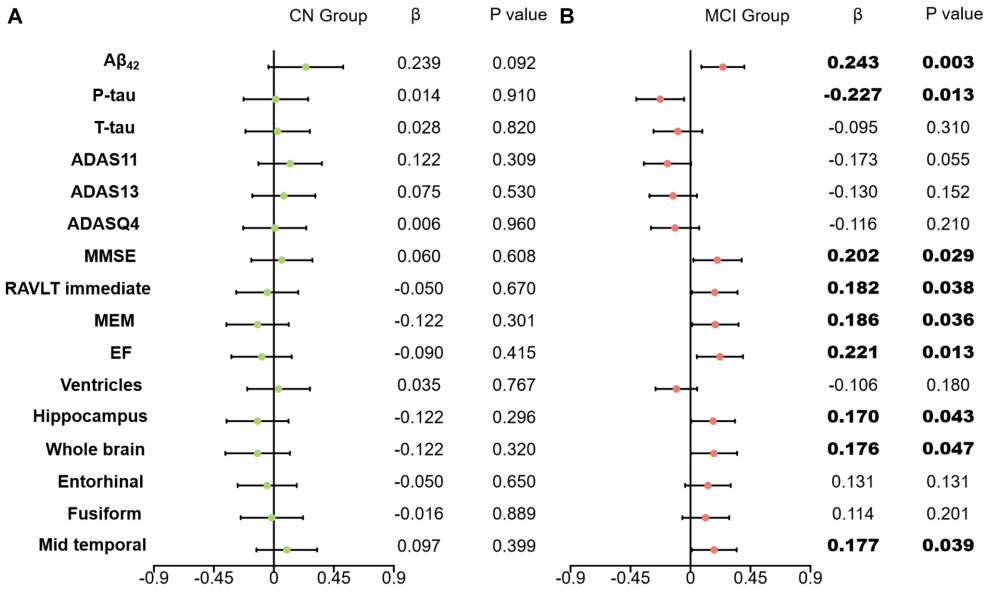

FIGURE 3
Effects of clusterin on longitudinal biomarkers and cognitive score. All analyses were corrected for age, gender, educational level, *APOE ε4* status, and intracranial volume. **(A)** results of CN group; **(B)** results of MCI group; CN, cognitively normal; MCI, mild cognitive impairment; $A\beta_{42}$, Amyloid-β_{42}; T-tau, Total tau; P-tau, Phosphorylated tau; ADAS, Alzheimer's disease assessment scale-cognitive; ADASQ4, ADAS delayed word recall; MMSE, mini-mental state examination; RAVLT immediate, Rey auditory verbal learning test immediate recall; MEM, memory function composite score; EF, executive function composite score.

significance in the mediation pathway. Our findings suggest that the association between baseline clusterin and cognitive impairment, specifically executive function (EF), was partially mediated by longitudinal neurodegeneration as indicated by hippocampus volume, accounting for approximately 17.84% of the total effect. As for other possible mediation relationships, no meaningful mediating effects were observed in models with these biomarkers as mediating variables (CSF Aβ, tau pathology, whole brain volume, and mid-temporal volume) (Figure 4).

An estimation of hazard ratios (HRs) was performed using Cox proportional hazards regression analysis based on tertiles of baseline clustering. However, no significant results was observed in the analysis (Supplementary Table S7). We examined the correlation between CSF clusterin and biomarkers in both A− and A+ subjects. Our analysis showed a significant association between CSF clusterin and both CSF Aβ and tau pathology in the A+ subgroup, which is similar to the results observed in the whole MCI population (Supplementary Tables S11–S13).

4. Discussion

Current cohort studies of CSF clusterin were few and most have focused on plasma clusterin (Lidström et al., 1998; Thambisetty et al., 2010). The association between clusterin and AD pathology is unclear, and we used this study, a large longitudinal cohort of non-demented individuals was used to comprehensively investigate the predictive value of CSF clusterin in relation to various indicators of AD pathology. The findings revealed that baseline CSF clusterin was a predictor of longitudinal cognitive impairment in individuals with MCI, and that baseline CSF clusterin concentrations were more predictive in females under the age of 65. These results provide valuable insights into the potential role of CSF clusterin in the pathogenesis and progression of AD.

A significant negative correlation was found between plasma clusterin concentration and cognitive score in a study investigating the association between plasma clusterin and AD cognition (Thambisetty et al., 2010). However, in contrast to their result, our findings revealed a significant association between CSF clusterin levels and executive function in the MCI population in cross-sectional. In a study of plasma clusterin levels, lower clusterin groups were also found to have lower cognitive scores, which was consistent with our findings (Romagnoli et al., 2021).

Our findings suggest that CSF clusterin levels are associated with changes in pathology related to AD: decreased CSF clusterin levels in early AD (MCI) is associated with abnormal Aβ pathology, previous research has suggested that the correlation between clusterin and CSF $A\beta_{42}$ may be related to the specific interaction of clusterin with amyloid. Several mechanisms may underlie these associations. Firstly, clusterin has been found to interact with prefibrillar species, inhibiting amyloid plaque formation in a substrate-dependent manner when the ratio of clusterin to Aβ peptide is relatively high (Yerbury et al., 2007). This association is more likely to be detected in the early stages of AD, consistent with our findings. Secondly, clusterin is sensitive to oxidative stress and has been reported to have several oxidative stress-related loci on its gene promoter. It is involved in various cellular stress responses such as the acute myocardial injury response and enhanced antioxidation in tumor cells. In the context of AD pathology, Aβ can trigger the generation of reactive oxygen species (ROS) by activating NMDA receptors. This stressful environment may lead to the upregulation of clusterin (Tiwari et al., 2019; Kalvaityte et al., 2022).

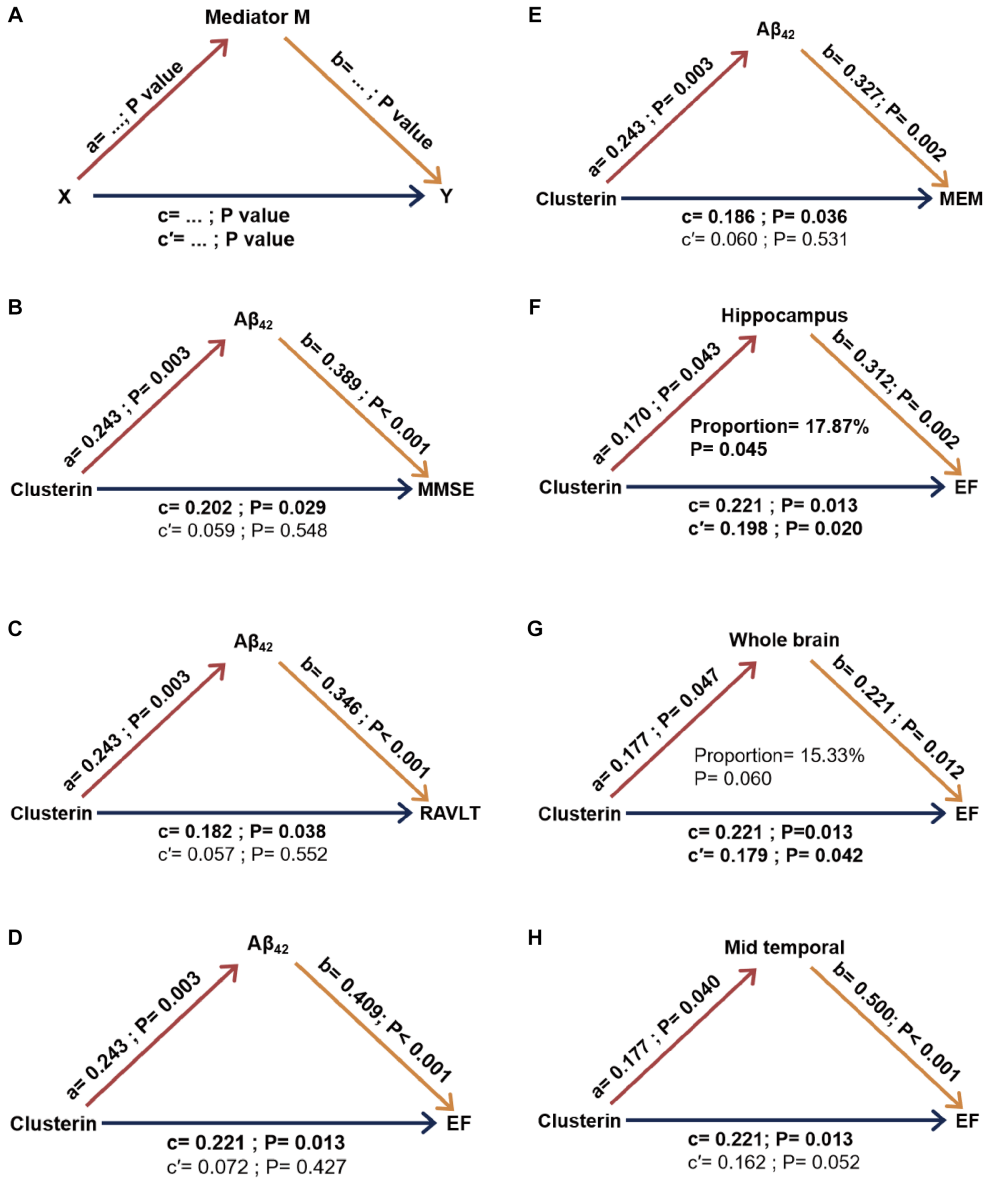

FIGURE 4
Mediation analysis results concerning clusterin's impact on longitudinal cognition with biomarkers serving as mediators in MCI. The concept of mediation is visually interpreted in part **(A)**. Specific results in part **(B-H)**. a, b, c, c' were took into account factors such as age, gender, education level, *APOE ε4* carrier status, and intracranial volume. $A\beta_{42}$, Amyloid-β_{42}; MMSE, Mini-Mental State Examination; RAVLT, Rey auditory verbal learning test immediate recall; MEM, memory function composite score; EF, executive function composite score. X, independent variable; Y, dependent variable; M, mediating variable; proportion, percentage of mediation (obtained using a bootstrap method). a: clusterin's effect on biomarker levels. b: biomarkers' effect on cognitive scores. c: Total effect of clusterin on cognitive scores without mediation. c': direct effect of clusterin on cognitive scores considering mediation.

Rik Ossenkoppele et al. suggested that tau protein aggregation plays a pivotal role in the development of clinical AD. Their study revealed a strong link between a high burden of tau protein and cognitive decline. *In vitro* studies further support this relationship, showing that tau pathology can induce synaptic loss and reduce neural network function, thereby emphasizing the close association between tau protein pathology, neurodegeneration, and the onset of clinical symptoms (Ossenkoppele et al., 2022). Hyperphosphorylated tau can impair synaptic function and increase excitotoxicity and is also implicated in Aβ-induced neuronal death (Leschik et al., 2007; Khan and Bloom, 2016).

The causal relationship between increased CSF clusterin aggregates and tau protein pathology, changes in neurons is unclear. Patricia Yuste-Checa et al. found elevated CSF clusterin levels in individuals with tau pathology and Manifestations of neurodegeneration (Martin-Rehrmann et al., 2005; Yuste-Checa et al., 2021).

In our cross-sectional study, the tau pathology and neurodegeneration are associated with increased CSF clusterin levels. These findings are consistent with previous studies (Martin-Rehrmann et al., 2005; Deming et al., 2016). The cross-sectional correlation between tau and clusterin may suggest an upregulated response of clusterin to tau pathology (Nuutinen et al., 2009; Wojtas et al., 2020).

Furthermore, this relationship is observed in cognitively normal populations and clusterin correlates with age, suggesting that this effect may be associated with normal aging (O'Bryan et al., 1993).

AD pathology typically begins in the temporal lobe region, particularly the medial temporal lobe (MTL), this particular area is involved in learning memory, stress and emotional response, consisting of structures such as the parahippocampal cortices, hippocampus and entorhinal (Jin et al., 2022), then spreads to the limbic regions of the medial and inferior temporal lobes, the posterior cingulate cortex, and finally to the isocortical areas of the brain (Serrano-Pozo et al., 2011). Clusterin was associated with several brain regions associated with cognition in our study, such as the hippocampus and middle temporal gyrus, which are mentioned in the Results section.

A previous meta-analysis showed that the mean volume of the hippocampus was smaller in the MCI population compared to the normal elderly group, which is consistent with our finding (Shi et al., 2009). Hippocampal atrophy has been found in people with MCI and has been linked to cognitive decline in a meta-analysis, which is consistent with our findings (Nickl-Jockschat et al., 2012).

Higher levels of clusterin at baseline correlate with a baseline volume of the hippocampus, similar associated brain regions also encompass the middle temporal gyrus, which primarily functions in explicit memory, language processing, and social cognition (Xu et al., 2019) suggesting that processing clusterin may be involved in the protection of neurons in relevant brain regions. Previous research indicates that clusterin may have neuroprotective properties, and in AD, reduced levels of this protein may be linked to neuronal degeneration and cell death (Giannakopoulos et al., 1998).

We identified a significant positive correlation between executive function (EF) and the level of clusterin. This finding suggests that higher levels of clusterin are associated with better executive functioning. The positive correlation with EF might be grounded on the neuroprotective role of clusterin, where higher levels could be indicative of a better neuronal health and, consequently, better cognitive performance, particularly in tasks requiring executive control.

Only a few cohort studies have systematically investigated longitudinal changes in biomarkers within MCI populations. A previous study identified a correlation between clusterin levels and rates of change in cognitively relevant brain regions (Thambisetty et al., 2012). Their research demonstrated that elevated clusterin levels correlated with a slower pace of brain atrophy. We observed similar results to theirs, particularly in the region of the temporal lobe and hippocampus. Our results echo previous research findings, showcasing that elevated levels of clusterin are associated with a slower rate of brain atrophy, notably in critical regions implicated in cognitive functions such as the hippocampus and the broader brain structure. The results indicate that higher clusterin levels are associated with a slower decline in the volume of both the hippocampus and the whole brain over time, suggesting a potential protective role of clusterin in preserving brain volume. Additionally, we found that clusterin levels were associated with cognitive changes in the MCI population, especially in memory and executive function. Over time, higher levels of clusterin proteins are associated with a slower decline in cognitive scores. Interestingly, we found a correlation between clusterin and longitudinal changes in tau pathology. Higher levels of clusterin were associated with a slower accumulation of tau pathology over time. The interaction mechanism between clusterin and tau pathology remains a subject of debate. One possible explanation is that the body responds to stressors, such as phosphorylated tau protein aggregation or cerebrovascular disease induction, by increasing clusterin concentration. The presence of clusterin impeded the formation and accumulation of tau aggregates, as reported in a cellular experiment (Mok et al., 2018; Dhiman et al., 2019; Wojtas et al., 2020; Yuste-Checa et al., 2022).

Based on these results, we conducted mediation analyses to determine which factors mediate the relationship between clusterin levels and cognitive performance. In the CN population, we did not observe a significant effect. However, in the mild cognitive impairment (MCI) population, our analysis suggested that the impact of clusterin on cognitive measures was partially mediated by neurodegeneration, specifically in the hippocampus. Previous research has also demonstrated that hippocampal atrophy can be observed in individuals with MCI and is associated with cognitive decline. Moreover, hippocampal atrophy has been established as a sensitive and specific marker for early detection of AD (Hampel et al., 2005). While we conducted a mediation analysis with AD biomarkers as intermediaries, and the results indicate that clusterin does not exert its influence on brain regions through the major biomarkers, including tau protein (Supplementary Table S10).

Our study's findings imply that clusterin may exhibit neuroprotective effects during the initial stages of AD. Nonetheless, additional research is required to validate these findings and elucidate the underlying mechanisms connecting clusterin, hippocampal atrophy, and cognitive function.

Several limitations to our study should be acknowledged. Firstly, the lack of complete follow-up in our cohort may limit the reliability of our findings. Secondly, our analyses were based on CSF protein measurements which may not be as accurate as PET imaging data. Thirdly, there is variability in the results of different studies on clusterin which may require clarification through larger and more diverse cohorts. Lastly, the sampling of CSF clusterin is an invasive procedure that is not accessible to all patients, which may limit the generalizability of our findings. Due to the absence of long-term follow-up data on clusterin protein, we are unable to provide a comprehensive explanation for causality.

To sum up, our study has revealed a link between clusterin and important biomarkers of AD and has evaluated the protein's long-term effect on the disease's pathology using a longitudinal cohort. Our findings pave the way for further investigations into the complex role of this glycoprotein.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by the Alzheimer's Disease Neuroimaging Initiative (ADNI).

All participants were made aware of the study's aim and granted their approval via signed consent forms.

Author contributions

HW: Data curation, Formal analysis, Investigation, Methodology, Software, Writing – original draft. L-ZM: Formal analysis, Conceptualization, Data curation, Methodology, Writing – review & editing. Z-HS: Data curation, Formal analysis, Methodology, Supervision, Validation, Writing – original draft. J-YL: Methodology, Writing – original draft, Data curation. W-YY: Data curation, Writing – original draft. FG: Data curation, Writing – original draft. WZ: Conceptualization, Supervision, Writing – review & editing. LT: Conceptualization, Supervision, Writing – review & editing, Project administration.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The handling editor J-TY declared a past co-authorship with the author LT.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2023.1256389/full#supplementary-material

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Effects of the multidomain intervention with nutritional supplements on cognition and gut microbiome in early symptomatic Alzheimer's disease: a randomized controlled trial

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Background: The SoUth Korean study to PrEvent cognitive impaiRment and protect BRAIN health through lifestyle intervention in at-risk elderly people (SUPERBRAIN) is a part of the World-Wide Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (WW-FINGERS) network. This study aimed to demonstrate the effects of the SUPERBRAIN-based multidomain intervention with nutritional supplements in amyloid positive emission tomography (PET) proven early symptomatic Alzheimer's disease patients.

Methods: Forty-six participants who were diagnosed with mild cognitive impairment or mild dementia and were positive in the amyloid PET study randomized into three groups: group A, the multidomain intervention with nutritional supplements; group B, nutritional supplements only; and a control group. The primary outcome was a change in the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) total scale index score after an 8-week intervention. Secondary outcomes, including gut microbiome data, were also analyzed.

Results: The RBANS total scale index score improved significantly in group A compared with group B ($p < 0.032$) and compared with the control group ($p < 0.001$). After intervention, beta diversity of the gut microbiome between group A and the control group increased, and patients in group A were more enriched with *Bifidobacterium*.

Conclusion: SUPERBRAIN-based multidomain intervention with nutritional supplements improves cognition and gut microbiota in patients with early symptomatic Alzheimer's disease who were amyloid-positive by PET.

KEYWORDS

Alzheimer's disease, dementia, mild cognitive impairment, prevention, multidomain intervention, nutritional supplements, gut microbiome

1. Introduction

Alzheimer's disease (AD) and related dementias are the most common neurodegenerative diseases (World Health Organization, 2012, 2017). However, as curative pharmacological treatments for AD dementia are still lacking (Hung and Fu, 2017; Alzheimer's Association, 2022), nonpharmacological treatments to prevent and modify cognitive impairment have been employed. Although single-domain interventions have shown modest outcomes and inconsistent results (Hill et al., 2017; de Souto et al., 2018; Radd-Vagenas et al., 2018; Ding et al., 2020), multidomain interventions have emerged as an alternative approach that considers the multifactorial causes of AD dementia (Coley et al., 2008; Scarmeas et al., 2009; Andrieu et al., 2015).

The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) trial reported that participants who received 24 months of multidomain intervention had better cognitive outcomes than control participants (Ngandu et al., 2015). To better adapt this intervention for use in other countries (World Health Organization, 2019), the World-Wide FINGERS (WW-FINGERS) network was launched. As a part of this worldwide network, the SoUth Korean study to PrEvent cognitive impaiRment and protect BRAIN health through lifestyle intervention in at-risk elderly people (SUPERBRAIN) was established as a multidomain intervention adjusted to the Korean context (Park et al., 2020). The feasibility study of the SUPERBRAIN presented significant improvement in cognition in intervention groups compared with a control group (Moon et al., 2021), and its magnetic resonance imaging results showed interval cortical thickening in facility-based multidomain intervention groups compared with the other groups (Moon et al., 2022).

In contrast, other clinical trials, such as the Multidomain Alzheimer Preventive Trial (MAPT) and Prevention of Dementia by Intensive Vascular Care (PreDIVA) trials, did not reveal significant effects from the interventions (van Charante et al., 2016; Andrieu et al., 2017). These inconsistent results require explanation, considering the positive results from the FINGER trial because of its well-selected target population (Solomon et al., 2021). The ancillary study of the MAPT revealed that a positive amyloid status could indicate a target population for multidomain intervention (Delrieu et al., 2019). Furthermore, a subgroup analysis of the original FINGER study reported that *APOE* ε4 carriers, who may have higher levels of brain amyloid pathology, showed a beneficial effect of the multidomain intervention on general cognition and memory within the group compared to non-carriers (Solomon et al., 2018). These findings called for further studies of the effects of multidomain interventions in amyloid-positive participants.

Recent trials have focused on a population at risk of dementia; that is, those not yet diagnosed with dementia. However, multidomain intervention might also be effective for patients with dementia because components of multidomain interventions are still available as treatment options for patients with dementia (Livingston et al., 2017, 2020). Consequently, this study targeted individuals with amyloid PET-proven early symptomatic AD, encompassing those with mild cognitive impairment (MCI) as well as individuals with dementia with Clinical Dementia Rating Scale Sum of Boxes (CDR-SB) score of less than 5.

We also enhanced the SUPERBRAIN multidomain intervention protocol for nutrition. Despite receiving nutritional guidance, patients with cognitive impairment find it challenging to eat balanced meals every day. To compensate for this, a nutritional supplement in the form of a multinutrient drink was added to the nutrition protocol of the SUPERBRAIN.

Therefore, this study investigated whether the effects of the multidomain intervention with nutritional supplements are superior to nutritional supplements alone or to no intervention (the control group) and whether the effects of nutritional supplements are superior to those of the control group.

2. Materials and methods

2.1. Study design

This study was a single-center, outcome assessor–blinded randomized controlled trial with a three-arm parallel design, and the intervention period was 8 weeks. The participants in group A received multidomain intervention with nutritional supplements, whereas those in group B received only nutritional supplements. A waitlist control group was also established in which participants were informed that the multidomain intervention program would be provided to them after the study. The baseline study was executed within 8 weeks before the start of the intervention, and the final study was completed within 4 weeks after the end of the last intervention. This study was registered with the Clinical Research Information Service (KCT0007253).

The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practices Guidelines (Dixon, 1998). Written informed consent was obtained from all participants before enrollment. The Ewha Womans University, Seoul Hospital Institutional Review Board (IRB) approved this trial (SEUMC 2020-08-008-001).

2.2. Participants

The minimum number of participants required for adequate statistical power was calculated based on the effect size of changes in the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) total scale index score from a previous study (Calapai et al., 2017). The calculation was performed using G*Power version

3.1.9.7 (Heinrich Heine University, Düsseldorf, Germany). For 80% of the statistical power, at least 13 participants were required in each group. Considering a drop-out rate of approximately 20%, the final sample size was determined to be 16 participants per group.

Participants were recruited from individuals who visited the outpatient clinic of Ewha Womans University Seoul Hospital because of cognitive decline from March 2, 2021, to August 13, 2022. The inclusion criteria were: older adults aged 60–85 years; clinically diagnosed with MCI (Albert et al., 2011) or probable AD dementia (McKhann et al., 2011); Korean Mini-Mental State Examination Second Edition (K-MMSE-2) score of 17–27 (Han et al., 2008; Baek et al., 2016); Clinical Dementia Rating (CDR) (Morris, 1991) score of 0.5–1; CDR-SB (Choi et al., 2003) score of 0.5–5; having a caregiver with whom they could attend interviews and programs; and the subject agrees to participate in the study with written consent.

Participants were excluded if they had organic brain diseases or degenerative diseases known to be major causes of cognitive decline, including brain tumor, stroke, normal pressure hydrocephalus, Parkinson's disease, Lewy body dementia, vascular dementia, and autoimmune encephalitis. In addition, individuals were excluded if they had infectious or metabolic diseases that may cause cognitive impairment, such as neurosyphilis, AIDS dementia, vitamin B12 deficiency, folate deficiency, and hypothyroidism. Other exclusion criteria were major psychiatric illness, epilepsy with intractable seizures, acute illness or acute infectious disease, probable encephalopathy caused by chronic liver or kidney disease, chronic pulmonary or cardiovascular disease under treatment, and any medical condition that would prevent cooperation with the interventions. Participants were also excluded if they had significant vision or hearing impairment, were illiterate, were unable to cooperate until the end of the study, were unable to safely complete the exercise program, had concurrent participation in another intervention trial, or refused to participate in the study.

Amyloid PET scans were conducted on the recruited participants. Participants who were determined as having amyloid pathology were enrolled in the study. Ultimately, the enrolled participants were amyloid PET-proven early symptomatic AD with a CDR-SB score below 5.

2.3. Amyloid PET

We used ^{18}F-florbetaben manufactured by DuChemBio Co., Ltd. (Seoul, Korea) following the approval process of the Korean Ministry of Food and Drug Safety. Delayed-phase 3D list-mode dynamic PET images were acquired over a 20-min period 90–110 min after the bolus injection of 308.12 ± 10.93 MBq ^{18}F-florbetaben. A spiral computed tomography scan of the brain was performed with the following parameters: 120 kV, 30 mA, and a slice thickness of 1.0 mm to correct for attenuation in the PET emission data. The participants' heads were fixed with a head holder and a vacuum fixation cushion to reduce motion artifacts. The standard PET data were reconstructed into a 128 × 128 matrix (voxel size: 3.18 × 3.18 × 2.02 mm^3) using the built-in 3D ordered subset expectation maximization algorithm (iteration: 4; subset: 12).

A visual reading by a nuclear medicine specialist was used to determine amyloid PET positivity.

2.4. Randomization

Participants were randomized to each group in a 1:1:1 ratio. The permuted block randomization method was applied using a macro in SAS software (SAS Institute Inc., Cary, NC, USA) with a block size of six. Only the independent statistical specialists knew the whole allocation sequence. Outcome assessors were not involved in the interventions, and participants were prohibited from discussing their assigned group when they met the outcome assessors.

2.5. Nutritional supplements

Memory Pack Plus (Daesang Life Science Corporation, Korea) was used as the nutritional supplement for this study. It is a multinutrient drink designed for brain health that contains eicosapentaenoic acid, docosahexaenoic acid, and phosphatidylserine (Supplementary material 1). It is aseptically packed as a 150 mL carton, and each carton contains 150 kcal.

2.6. Interventions

The protocol and contents of the multidomain intervention were based on the facility-based multidomain intervention of SUPERBRAIN (Park et al., 2020), which includes the following five components: the monitoring and managing of metabolic and vascular risk factors, cognitive training, physical exercise, nutritional guidance, and motivational enhancement. The number and frequency of each session were adjusted for a shorter study period than the previous SUPERBRAIN. Education on vascular risk factors was provided at the first visit with a booklet for the participants. The blood pressure, alcohol drinking, smoking, body weight, and abdominal circumference of each participant were monitored, and the results were discussed with each participant every 4 weeks. Each week, exercise and cognitive training sessions were done twice on the same visit day. Cognitive training sessions and nutritional guidance sessions were conducted with individual participants, whereas exercise sessions were conducted in a group of two participants. The participants attended nutritional guidance sessions once every 3 weeks. The details of the activities are described in Supplementary material 2. The motivation program was given as an in-person session at the beginning of the intervention and was followed by weekly text messages sent by the study coordinator.

Memory Pack Plus cartons were provided to group A and B participants. Both groups were told to drink two cartons daily. Participants in the control group received dementia-prevention education from a guideline booklet at the beginning of the study, and general medical care was provided to them.

2.7. Adherence and adverse events

Adherence to cognitive training, exercise, vascular-risk-factor monitoring, and nutritional guidance was assessed using the cumulative attendance rate for the 8-week intervention. The adherence to intake of nutritional supplements was assessed by calculating the number of remaining supplement cartons.

Adherence (%) to nutrient supplements

$$= \left(1 - \frac{number\ of\ remaining\ nutrient\ supplements}{number\ of\ distributed\ nutrient\ supplements}\right) \times 100$$

The study coordinator monitored the occurrence of adverse events.

2.8. Primary outcome

The primary outcome was a change in the total scale index score of the RBANS from baseline to after intervention and using a reference population of Korean adults to normalize the data (Randolph et al., 1998). We also evaluated five subdomain index scores: immediate memory, delayed memory, visuoconstruction, language and attention. Higher scores indicate better performance for all index scores.

2.9. Secondary outcomes

The secondary outcomes included global cognition, evaluated using K-MMSE-2 and CDR-SB. We also evaluated activities of daily living by the Korean Instrumental Activities of Daily Living scale (K-IADL) (Chin et al., 2018), depression by the 15-item Geriatric Depression Scale (GDS-15), and caregiver burden by the Zarit Burden Interview (ZBI). Physical performance was evaluated using the Short Physical Performance Battery (SPPB), grip power, and 30-s sit-to-stand test (endurance evaluation). Body composition was assessed using the body mass index and measurements of body fat, skeletal muscle mass, and visceral fat. The Nutrition Quotient for Elderly (NQ-E) was used to assess consumption of vegetables, fruits, beans, fish, milk, dairy products, eggs, water, fast food, pastries, and sweet food (Chung et al., 2018). Higher scores indicate better performance for K-MMSE-2, SPPB, and NQ-E. Lower scores indicate better performance for CDR-SB, K-IADL, GDS-15, and ZBI.

The secondary outcomes were modified from the first clinical trial enrollment. According to the results of the previous feasibility study of SUPERBRAIN (Moon et al., 2021), outcomes related to cognition, caregiver burden and physical performance were added. To assess nutrition, we replaced the mini-nutrition assessment that was a registered item in the initial trial registration with the NQ-E, which had shown a significant effect in the feasibility study. These changes were reported to the IRB, and further approval was obtained.

2.10. Exploratory outcomes

Fasting blood samples were collected from all participants in serum separation tubes and K2EDTA tubes. Total plasma cortisol and serum brain-derived neurotrophic factor (BDNF) were measured at baseline and after the interventions. BDNF was measured by Human Free BDNF enzyme-linked immunosorbent assay kit (R&D Systems, Minneapolis, MN, USA), and cortisol was measured using an ADVIA Centaur chemiluminescence immunoassay kit (Siemens Healthcare GmbH, Munich, Germany).

Stool collection kits containing buffer (CJ Bioscience Inc., Seoul, Korea) were provided to participants, and they were instructed on how to collect stools. Stool was collected 0–2 days before the baseline and final study visits. The kits were stored at room temperature and were shipped to CJ Bioscience Inc. for analysis within 1 week of the collection date.

We conducted 16S ribosomal RNA (rRNA) gene sequencing, taxonomic profiling, and functional profiling. The V3–V4 hypervariable region of the 16S rRNA gene was amplified with primers 341F and 805R using the direct polymerase chain reaction method. NEBNext Ultra II FS DNA Library Prep Kit for Illumina (New England Biolabs Inc., Ipswich, MA, USA) was used to construct DNA libraries. Sequencing of prepared DNA libraries by CJ Bioscience Inc. was conducted using the Illumina MiSeq platform (Illumina, San Diego, CA, USA) with 2 × 300 base pair kits.

The paired-end raw 16S rRNA sequence data were uploaded to the EzBioCloud and processed using a web-based EzBioCloud microbiome taxonomic profile tool.[1] High-quality sequence reads were assigned to the "species group" at 97% sequence similarity using the PKSSU4.0 database.

Sex is a potential confounder of the microbiome outcome as it may influence both behavior that related to adherence to intervention components and the gut microbiome (Shobeiri et al., 2022). We confirmed that there were no significant differences in demographic characteristics, including sex, between the three experimental groups before conducting the microbiome analysis, thus controlling for the effect of sex.

Electroencephalogram data were obtained, but the data could not be read because of a technical problem. Therefore, analysis of electroencephalogram data was omitted from this study. This change was reported to the IRB, and further approval was obtained.

2.11. Statistical analyses

Statistical analyses were performed using a modified intention-to-treat approach. Baseline characteristics of each group were analyzed using analysis of variance (ANOVA) for continuous variables and chi-squared tests for categorical variables. To assess the effect of each intervention, outcomes were analyzed using a linear mixed-effect model. Comparisons between two groups were conducted using Bonferroni-adjusted *post hoc* analyses. Subgroup analyses for RBANS index scores were performed by disease stages (MCI and mild dementia) and sex. The analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA).

For gut microbiome analyses, the EzBioCloud Media Transfer Protocol server was used. The alpha diversity was calculated using the Chao1 and Shannon matrices, and its significance was assessed by Mann–Whitney U test. The generalized UniFrac metric was used for calculating the beta diversity, and the significance was assessed with permutational multivariate analysis of variance (PERMANOVA). Linear discriminant analysis effect size was performed to investigate the taxonomic differences among the groups. We also compared three experimental groups with an external healthy population (healthy control), and this microbiome analyses were performed using the Ez-Mx platform (CJ Bioscience Inc., Seoul, Korea) (Oh et al., 2022).

Statistical significance for each analysis was set at $p < 0.05$.

1 https://www.ezbiocloud.net/contents/16smtp

3. Results

3.1. Baseline characteristics of participants

Between October 12, 2020, and November 23, 2021, 76 patients were assessed for eligibility: 3 withdrew consent, and 24 failed screening due to negative amyloid PET results. We randomly assigned 49 participants with positive amyloid PET results and who were diagnosed with MCI or mild dementia to three groups: group A ($n = 16$), group B ($n = 16$), and the control group ($n = 17$). After randomization, three participants, one from each group, withdrew consent before the start of the interventions (Figure 1).

There were no significant differences in sex, age, education, and frequency of *APOE* ε4 carriers among the three groups. There were no significant differences among the three groups regarding the number of participants with diabetes mellitus, hyperlipidemia, or history of cardiac disease or stroke, but the number of participants with hypertension was significantly different among the three groups. The presence of hypertension was adjusted as a covariate in the analyses of primary and secondary outcomes. Cognitive function, physical performance, and nutritional status were similar among the three groups at baseline (Tables 1–3 and Supplementary material 3).

3.2. Adherence and adverse events

In group A, the adherence rates were 96.1% for the cognitive program, 94.0% for the exercise program, 100.0% for the vascular risk-factor monitoring, and 100.0% for the nutritional guidance. The adherence rate for the intake of nutritional supplements was 99.1% in group A and 83.7% in group B.

In group A, male participants showed adherence rates of 93.8% for the cognitive program, 87.5% for the exercise program, and 100.0% for supplement intake, while female participants demonstrated adherence rates of 99.5, 99.5, and 98.9%, respectively. In Group B, adherence rates for nutritional supplement intake were 83.3% for males and 84.8% for females.

No adverse event was reported during the entire intervention period.

3.3. Primary outcome

At baseline, there were no differences in the RBANS total scale index score and subdomain index scores among the three groups (Table 2). After intervention, the linear mixed-effect model revealed a significant difference in changes in RBANS total scale index score among the three groups. The adjusted means (95% confidence intervals) were as follows: group A, 9.00 (5.15, 12.85); group B, 1.80 (−2.05, 5.65); and control group, −4.56 (−8.29, 0.83); $p < 0.001$, effect size $f^2 = 0.530$. *Post hoc* analysis revealed that the total scale index scores improved more for group A than for group B ($p = 0.032$) and more for group A than for the control group ($p < 0.001$). The visuoconstruction domain index score improved significantly different among the groups ($p < 0.001$), and *post hoc* analysis showed that the index score of group A improved more than that of the control group ($p < 0.001$, effect size $f^2 = 0.362$). In the attention domain, the difference among the three groups was significant ($p = 0.046$), but a *post hoc* analysis found only a borderline significance in that group A improved more than the control group ($p = 0.079$) (Table 2).

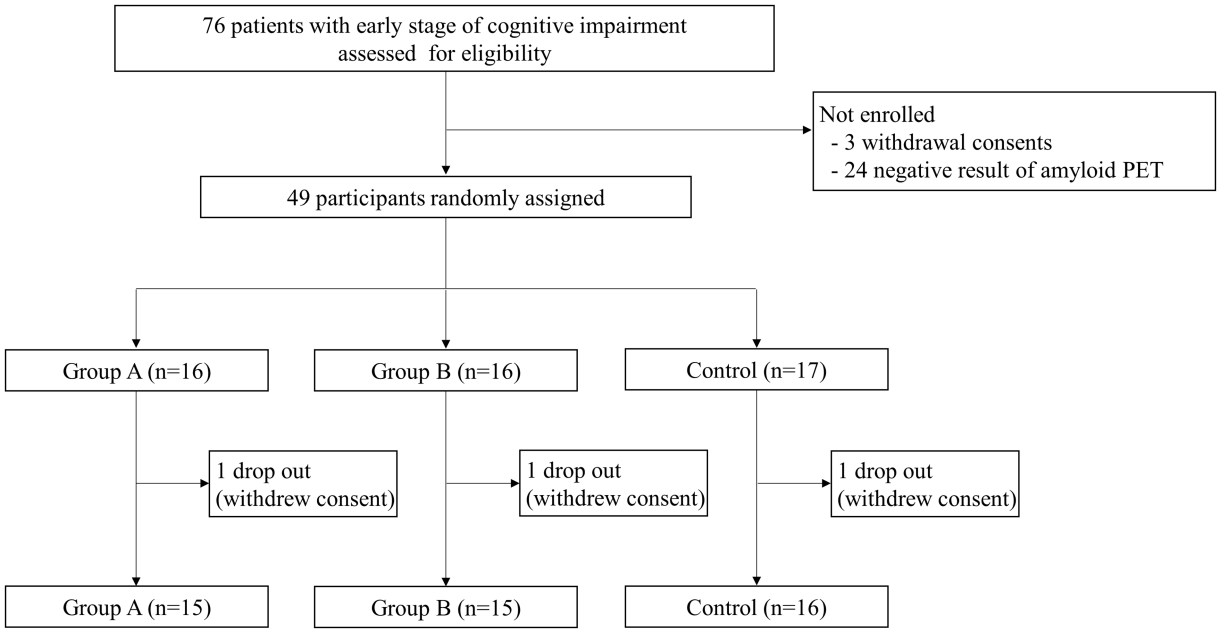

FIGURE 1
Study design. A total of 76 patients were screened for eligibility. Of those, 27 patients were not enrolled due to consent withdrawal or negative amyloid PET results. Thus, 49 participants with early-stage Alzheimer's disease were randomly divided into three groups. Of these, three participants (one from each group) dropped out due to withdrawal of consent, and 46 participants completed the study.

TABLE 1 Baseline characteristics of participants.

	Group A ($n = 16$)	Group B ($n = 16$)	Control ($n = 17$)	p
Sex, female	10 (62.5)	6 (37.5)	13 (76.5)	0.071
Age, years†	74.81 (5.74)	76.06 (5.64)	75.77 (6.67)	0.830
Education, year†	9.72 (3.56)	11.03 (4.53)	8.68 (4.57)	0.291
APOE ε4 carrier	8 (50.0)	6 (40.0)	4 (23.5)	0.283
HTN	7 (43.8)	4 (25.0)	12 (70.6)	**0.031***
DM	5 (31.2)	5 (31.2)	8 (47.1)	0.550
Dyslipidemia	7 (43.8)	3 (18.8)	8 (47.1)	0.188
Cardiac disease	1 (6.2)	1 (6.2)	1 (5.9)	0.999
Stroke	0 (0.0)	0 (0.0)	1 (5.9)	0.383
Smoking	2 (12.5)	0 (0.0)	0 (0.0)	0.116
Alcohol consumption‡	0 (0.0)	1 (6.2)	0 (0.0)	0.349
CDR				0.946
0.5	12 (75.0)	12 (75.0)	12 (70.6)	
1	4 (25.0)	4 (25.0)	5 (29.4)	
AChEI use	14 (87.5)	15 (93.8)	17 (100.0)	0.326

Values are expressed as number (percent), except where noted otherwise.
*$p < 0.05$.
†Values are expressed as mean (standard deviation).
‡Drinking alcohol more than four times a day or for seven times a week.
AChEI, acetylcholinesterase inhibitor; CDR, Clinical Dementia Rating; DM, Diabetes mellitus; HTN, hypertension. We highlighted significant or borderline-significant values in bold in the letter.

3.4. Secondary outcomes

At baseline, there were no differences among the three groups for the K-MMSE-2, K-IADL, GDS-15, ZBI, physical performance, body composition, and nutrition score (Table 3).

After intervention, changes in K-MMSE-2 scores differed significantly among the three groups ($p = 0.016$) and the changes were the highest in treatment group A ($p = 0.014$) (Table 3). The change in the sit-to-stand time was significantly improved in group A compared with the control group ($p = 0.032$). The SPPB score improved significantly in group A compared with group B ($p = 0.002$) and in group A compared with the control group ($p < 0.001$) (Table 3).

3.5. Exploratory outcomes

At baseline and after intervention, there were no differences in plasma cortisol and serum BDNF concentrations among the three groups (Figures 2A,B). However, after intervention, serum BDNF concentrations increased in groups A and B but decreased in the control group; these differences were not statistically significant ($p = 0.288$) (Figure 2A). There were no differences in plasma cortisol concentration among the three groups after intervention ($p = 0.787$) (Figure 2B).

The gut microbiome data analysis showed that the changes in alpha diversity were not statistically different in the three groups (Figures 3A–C). PERMANOVA for beta diversity showed no

TABLE 2 Mean changes in the scores of the RBANS.

	Baseline				Changes from baseline to study end							
	Group A ($n = 15$)	Group B ($n = 15$)	Control ($n = 16$)	p	Group A ($n = 15$)	Group B ($n = 15$)	Control ($n = 16$)	p	Post-hoc			
									A vs. B	A vs. C	B vs. C	
Total scale index score	78.60 (16.89)	74.67 (11.54)	79.50 (15.88)	0.332	9.00 (5.15, 12.85)	1.80 (−2.05, 5.65)	−4.56 (−8.29, −0.83)	**<0.001***	**0.032***	**<0.001***	**0.063†**	A > B A > C
Immediate memory	81.07 (12.81)	74.53 (11.11)	81.81 (14.41)	0.360	5.20 (−0.6, 11)	4.33 (−1.46, 10.13)	−0.56 (−6.18, 5.05)	0.306	>0.999	0.471	0.681	
Delayed memory	68.40 (19.99)	65.40 (18.45)	64.56 (17.41)	0.663	7.53 (1.44, 13.62)	3.73 (−2.36, 9.82)	0.06 (−5.83, 5.96)	0.218	>0.999	0.248	>0.999	
Visuo-construction	99.00 (14.81)	98.00 (12.71)	97.75 (15.70)	0.791	3.80 (−1.33, 8.93)	−3.40 (−8.53, 1.73)	−11.44 (−16.4, −6.47)	**<0.001***	0.155	**<0.001***	**0.085†**	A > C
Language	85.87 (13.80)	87.33 (12.87)	93.81 (9.45)	0.055	6.20 (0.76, 11.64)	6.13 (0.7, 11.57)	−1.63 (−6.89, 3.64)	**0.066†**	>0.999	0.129	0.134	
Attention	92.20 (12.81)	91.87 (19.41)	91.44 (15.17)	0.650	6.07 (1.54, 10.59)	−0.8 (−5.33, 3.73)	−1.13 (−5.51, 3.26)	**0.046***	0.108	**0.079†**	>0.999	

Values of baseline index scores are expressed as mean (standard deviation). Values of the changes in index scores are expressed as the adjusted mean (95% CI).
Higher scores indicate better performance for all index scores.
*$p < 0.05$.
†$0.05 < p < 0.1$, borderline significance.
A vs. B, group A versus group B. We highlighted significant or borderline-significant values in bold in the letter; A vs. C, group A versus control group; B vs. C, group B versus control group; CI, confidence interval; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status.

TABLE 3 Mean changes in the secondary outcomes.

	Baseline				Changes from baseline to study end							
	Group A ($n = 15$)	Group B ($n = 15$)	Control ($n = 16$)	p	Group A ($n = 15$)	Group B ($n = 15$)	Control ($n = 16$)	p	Post-hoc			
									A vs. B	A vs. C	B vs. C	
Cognitive function & Caregiver burden												
MMSE†	23.73 (3.17)	21.53 (2.50)	22.75 (3.38)	0.153	1.53 (0.42, 2.65)	0.67 (−0.45, 1.78)	−0.75 (−1.83, 0.33)	**0.016***	0.818	**0.014***	0.215	A > C
CDR-SB	2.93 (1.35)	3.53 (0.86)	3.44 (1.30)	0.373	0.03 (−0.09, 0.16)	0.00 (−0.13, 0.13)	0.16 (0.03, 0.28)	0.185	>0.999	0.513	0.251	
K-IADL	0.41 (0.30)	0.45 (0.18)	0.54 (0.31)	0.396	0.00 (−0.03, 0.03)	0.03 (0.00, 0.06)	0.03 (0.00, 0.05)	0.344	0.603	0.633	>0.999	
GDS-15	3.87 (4.00)	2.67 (2.74)	3.31 (3.03)	0.664	−0.13 (−1.34, 1.07)	0.33 (−0.87, 1.54)	−0.94 (−2.10, 0.23)	0.310	>0.999	>0.999	0.401	
ZBI	11.67 (10.89)	16.47 (12.11)	19.94 (15.91)	0.079	−0.8 (−4.88, 3.28)	−0.13 (−4.21, 3.95)	1.75 (−2.20, 5.70)	0.644	>0.999	>0.999	>0.999	
Physical performances												
Left grip (kg)†	19.20 (6.93)	21.76 (7.17)	18.38 (8.24)	0.435	1.37 (0.01, 2.74)	1.16 (−0.21, 2.52)	0.18 (−1.10, 1.45)	0.389	>0.999	0.611	0.888	
Right grip (kg)†	20.54 (6.88)	23.81 (7.02)	19.63 (7.66)	0.252	1.21 (−0.28, 2.69)	0.27 (−1.21, 1.75)	−0.36 (−1.75, 1.02)	0.305	>0.999	0.379	>0.999	
Sit-to-stand (times/30 s)†	11.67 (3.74)	12.33 (3.13)	13.06 (4.39)	0.597	1.98 (0.65, 3.30)	0.17 (−1.16, 1.50)	−0.44 (−1.68, 0.81)	**0.031***	0.179	**0.032***	>0.999	A > C
SPPB total score†	9.23 (0.42)	9.67 (0.43)	10.43 (0.41)	0.156	1.35 (0.63, 2.06)	−0.48 (−1.2, 0.24)	−0.94 (−1.61, −0.26)	**<0.001***	**0.002***	**<0.001***	>0.999	A > B A > C
Body composition & Nutrition												
BMI (kg/m^2)	22.96 (4.05)	23.21 (2.17)	23.75 (1.91)	0.729	0.15 (−0.25, 0.55)	0.16 (−0.25, 0.58)	0.06 (−0.33, 0.45)	0.920	>0.999	>0.999	>0.999	
Body fat (%)	33.63 (9.66)	29.30 (6.98)	34.19 (3.61)	0.176	−0.27 (−1.50, 0.96)	0.56 (−0.72, 1.83)	−0.06 (−1.25, 1.13)	0.626	>0.999	>0.999	>0.999	
SMM (kg)†	20.22 (3.74)	20.14 (4.93)	20.90 (4.47)	0.295	0.13 (−0.28, 0.54)	0.24 (−0.18, 0.66)	0.08 (−0.32, 0.47)	0.842	>0.999	>0.999	>0.999	
VF (level)	9.47 (4.47)	7.47 (2.26)	9.25 (2.70)	0.200	0.00 (−0.72, 0.72)	0.42 (−0.32, 1.16)	0.00 (−0.69, 0.69)	0.639	>0.999	>0.999	>0.999	
NQ-E†	56.52 (11.55)	61.98 (9.13)	60.85 (9.87)	0.312	6.17 (3.16, 9.18)	−0.25 (−3.26, 2.76)	−0.01 (−2.91, 2.90)	**0.005***	**0.012***	**0.014***	>0.999	A > B A > C

Values of baseline index scores are expressed as mean (standard deviation). Values of the changes in index scores are expressed as the adjusted mean (95% CI).

*$p < 0.05$.

†Higher scores indicate better performance for all index scores.

A vs. B, group A versus group B; A vs. C, group A versus control group; B vs. C, group B versus control group; CDR-SB, Clinical Dementia Rating Sum of Boxes; CI, confidence interval; GDS-15, Geriatric Depression Scale-15 items; K-IADL, Korean Instrumental Activities of Daily Living; MMSE, Korean Mini-Mental State Examination 2nd Edition; NQ-E, Nutrition Quotient for elderly; SPPB, Short Physical Performance Battery; BMI, Body Mass Index; SMM, Skeletal Muscle Mass; VF, Visceral Fat; ZBI, Zarit's Burden Index. We highlighted significant or borderline-significant values in bold in the letter.

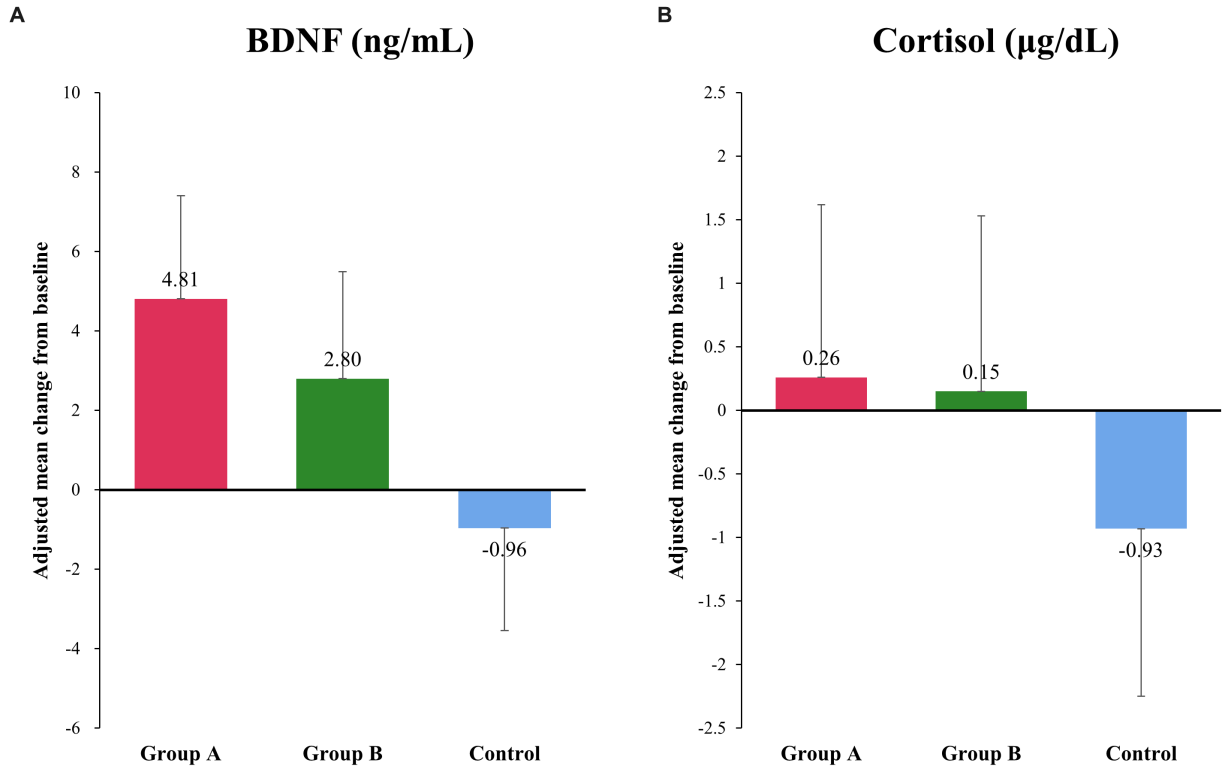

FIGURE 2
Changes in serum BDNF and plasma cortisol concentration. **(A)** There was an increase in the serum concentration of BDNF after interventions, whereas a decrease was observed in the control group, although the difference was not statistically significant. Adjusted mean (95% confidence interval) in µg/dL: group A, 4.81 (−0.44, 10.06); group B, 2.80 (−2.64, 8.23); and control group, −0.96 (−6.16, 4.24); $p = 0.288$. **(B)** There was no significant difference in the plasma cortisol level among different groups. Adjusted mean (95% confidence interval) in ng/mL: group A, 0.26 (−2.49, 3.02); group B, 0.15 (−2.67, 2.97); and control group, −0.93 (−3.6, 1.74); $p = 0.787$.

differences among the three groups at baseline ($p = 0.453$) (Figure 3D). However, beta diversity after intervention was significantly different among the three groups ($p = 0.033$) and between group A and the control group ($p = 0.013$) (Figure 3E). Comparison of the linear discriminant analysis effect size between group A and the control group after intervention showed that group A was more enriched with *Faecalibacterium* and *Bifidobacterium* than was the control group (Figure 3F). After intervention, group B presented more enriched with *Eubacterium* and *Clostridium* than the control group (Figure 3G).

The gut microbiome data before and after the intervention in each experimental group were compared to that of healthy control (Supplementary material 4). After an 8-week intervention period, group A's microbiota profile shifted toward that of the healthy control, while there were no significant changes observed in the microbiota profiles of group B and the control group (Supplementary materials 4A–E). UniFrac distances calculated between the healthy control group and each of the experimental groups also revealed that the distance was notably shorter in group A compared to the other groups (Supplementary material 4F). Moreover, *Faecalibacterium* was a genus that displayed a similar abundance between group A and the healthy control group but exhibited a significant difference in abundance when compared to the control group (Supplementary material 4G).

3.6. Subgroup analyses

Within MCI subgroup analyses, the results for RBANS total scale index scores and five subdomain index scores showed the similar pattern of significance as in the main analysis (Supplementary material 4). The linear mixed effects model showed a significant difference in changes in RBANS total scale index score among the three groups. The *post hoc* analysis showed that the total scale index scores improved more for group A than for group B ($p = 0.003$) and more for group A than for the control group ($p < 0.001$). The index score for the visual construction domain improved significantly in group A compared to the control group ($p = 0.001$). In the attention domain, the difference between group A and the control group was significant ($p = 0.038$). There was no significant group difference among mild dementia participants (Supplementary material 5).

Subgroup analysis for sex, showed a slightly different pattern in RBANS total scale and subdomain index scores. In the male group, changes in RBANS total scale index scores improved more for group A than for group B ($p = 0.003$) and more for group A than for the control group ($p < 0.001$), similar to the main analysis (Supplementary material 6). However, there was no significant group difference in subdomain index scores. In the female group, group A showed significant improvement in RBANS total scale index scores

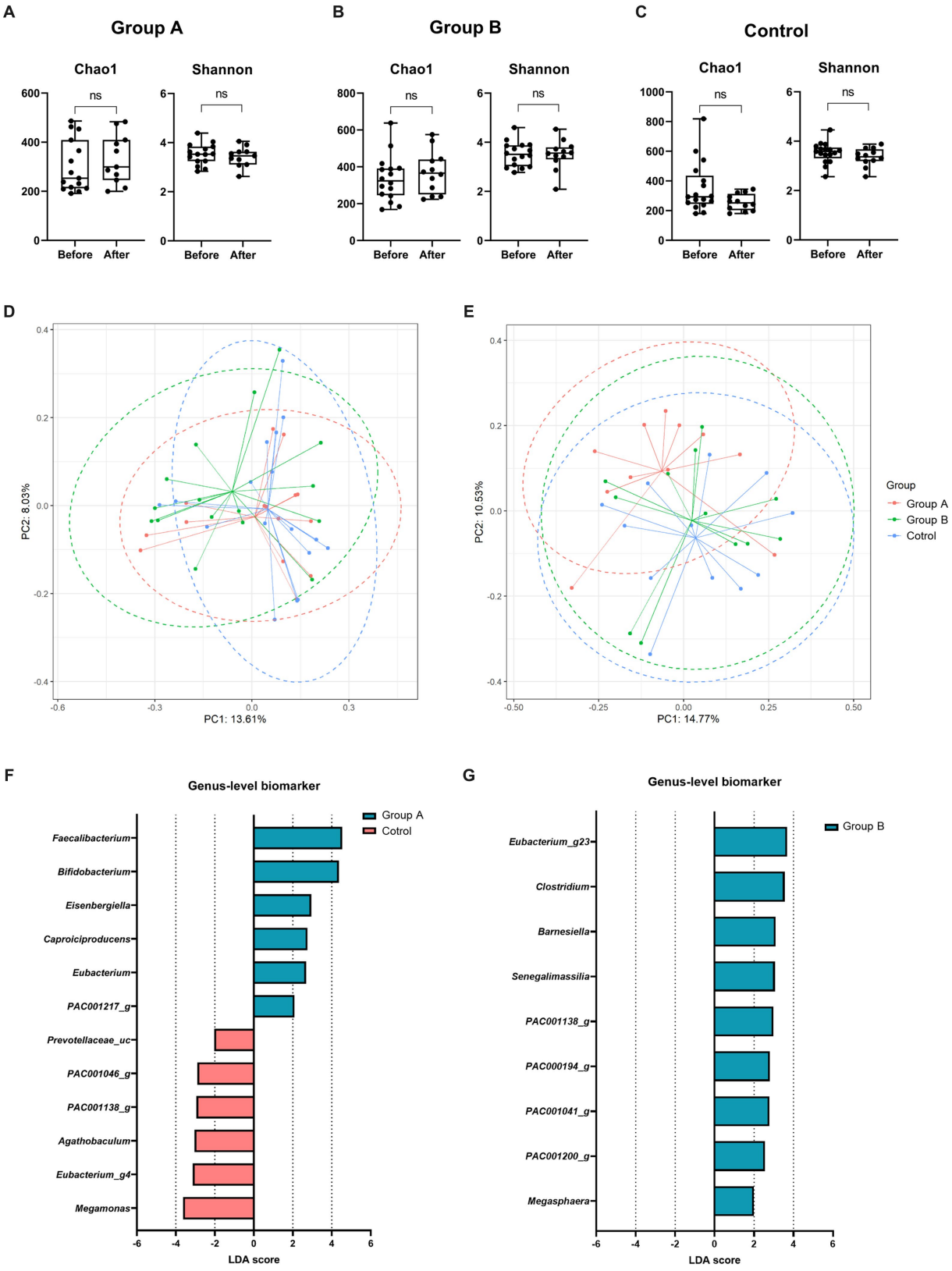

FIGURE 3
Gut microbiome analysis. There were no significant changes in alpha diversity in group A **(A)**, group B **(B)**, and the control group **(C)** before and after intervention. **(D)** The beta diversity at baseline showed no significant difference among the groups. **(E)** However, the beta diversity after intervention was significantly different between group A and the control group. **(F)** Linear discriminant analysis effect size analysis between group A and the control group showed that the genera *Faecalibacterium* and *Bifidobacterium* were more abundant in group A than in the control group after the intervention. **(G)** Group B were more enriched with Eubacterium and Clostridium than the control group, but the control group presented no characteristic genera. LDA, Linear discriminant analysis.

only compared to the control group, but not to group B (Supplementary material 7). Changes in visuoconstruction index scores of the female group were presented that group A improved significantly compared to the control group ($p = 0.003$). In addition, the attention index score showed a significant result that group A improved better than the control group ($p = 0.023$).

4. Discussion

To our knowledge, this is the first study to reveal the efficacy of a multidomain intervention with nutritional supplements on cognition and the gut microbiome in amyloid PET-proven early symptomatic AD patients. The RBANS total scale index scores improved significantly in patients with early symptomatic AD who received an 8-week multidomain intervention with nutritional supplements compared with patients who received nutritional supplements only or who received no intervention. Additionally, physical fitness was also significantly improved in the participants who received multidomain intervention with nutritional supplements.

Studies of multidomain interventions in patients with MCI have shown inconsistent results. The effect of multidomain interventions is difficult to decipher because of heterogeneity among the studies. Most trials that did not show the effectiveness of multidomain interventions combined only two main domains of interventions: exercise and cognitive training (Fiatarone Singh et al., 2014; Fogarty et al., 2016; Anderson-Hanley et al., 2018; Combourieu Donnezan et al., 2018; Shimada et al., 2018). In comparison, the multidomain intervention protocol of our study encompassed exercise, cognition, nutrition, and vascular risk-factor management, simultaneously providing a more comprehensive lifestyle modification to improve patient outcomes. The MAPT trial is similar to our study, as it also studied the effect of ready-to-eat nutritional supplements (omega-3 capsules) in addition to exercise and cognitive training. The subgroup analysis of patients with MCI presented positive effects; however, there was no cognitive improvement after their interventions (Andrieu et al., 2017). Thus, our study is the first trial that verifies the effectiveness of multidomain intervention with nutritional supplements on MCI and mild dementia, specifically in patients with proven Alzheimer's pathology.

According to a previous study, among participants with mild to moderate dementia and MMSE scores ranging from 9 to 28, the RBANS total scale index score correlated well with the variety of activities of daily living (Freilich and Hyer, 2007). Therefore, significant changes in RBANS scores, particularly in group A, may signify improvements in practical functionality as perceived by patients and caregivers. However, there were no definite group differences in changes of CDR-SB or K-IADL in our study. As such, future investigations should aim to target deeper into these practical aspects to provide a more comprehensive understanding of the impact of the multidomain intervention on patients' daily lives.

Group A showed favorable changes in attention subdomain index scores when compared to the control group. These findings align with the FINGER study, which reported enhancements in processing speed—a cognitive function closely associated with attention (Ngandu et al., 2015). This relationship is further supported by studies highlighting the effectiveness of computerized cognitive training in improving attention (Hill et al., 2017; Sherman et al., 2017), even in short-term interventions (Finn and McDonald, 2011; Hagovska and Olekszyova, 2016). Furthermore, our study underscores the positive impact of physical exercise on the attention domain (Yaguez et al., 2011). On the other hand, the best improvement of group A on visuoconstruction index score is consistent with the result of the SUPERBRAIN feasibility study that the facility-based multidomain intervention group improved on the visuoconstruction index score compared to the control group (Moon et al., 2021). However, this study showed an insignificant result in the delayed memory subdomain while the previous SUPERBRAIN study did. This difference could be explained by the different study design between both studies, and small sample size. The required sample size to evaluate the subdomains of the RBANS was found to be 13–64 participants based on the ANOVA model. Therefore, the interpretation of the subdomain index scores is limited, and a larger number of participants than in this study is required to assess significance with adequate power.

The difference between group B and the control group showed only borderline significance in our primary outcome. This is consistent with previous studies that revealed insignificant effect of providing nutritional supplements alone instead of combining with multidomain interventions (Shah et al., 2013; Soininen et al., 2017). Consequently, it is emphasized that significant effects can occur only when multidomain intervention is accompanied with nutritional supplements. However, since there was no experimental arm with the multidomain intervention alone in this study, it is not investigated whether the multidomain intervention with nutritional supplements is superior to that with the multidomain intervention alone. Therefore, further study is required to investigate the difference between the multidomain intervention with nutritional supplements and the multidomain intervention alone. Furthermore, because our studies were conducted in participants with early symptomatic AD, similar to participants in randomized controlled trials of newer disease-modifying therapies (Sims et al., 2023; van Dyck et al., 2023), future studies investigating the effects of combining multidomain interventions with disease-modifying therapy may further our understanding of AD treatment.

With cautious interpretation due to the small sample size for the RBANS subdomain index scores, this study showed borderline significance of superiority of group B over the control group for the visuoconstruction domain index score and total scale index score, while there was no difference in memory-function change between group B and the control group. In contrast, previous studies have shown that memory function improved more in patients who received nutritional supplements compared with those in control groups (Scheltens et al., 2010, 2012). This discrepancy with previous studies might be caused by the differences in the ingredients and proportions of different nutritional supplement products and the length of the intervention period.

The previous SUPERBRAIN trial revealed significant changes in biomarkers in the treatment group compared with the control group (Moon et al., 2021). However, in our study, the change in BDNF concentration among the three groups after intervention was not statistically significant. The reason might be that the number of exercise programs per week and the total number of sessions decreased from the previous study. Despite statistical insignificance, changes in BDNF concentration tended to increase in the treatment groups and decrease in the control group, which

suggests a possible multidomain intervention mechanism for cognitive improvement.

Meanwhile, cortisol levels revealed no such tendency among the groups, because awakening and blood-sampling time were not strictly controlled on the examination days. Changes in the exercise protocol are also one of the reasons for the insignificant result for cortisol levels. Furthermore, some studies have suggested that physical activity, a nonpharmacological intervention, alters the dynamics of cortisol secretion rather than the cortisol concentration at a specific time point (Tortosa-Martinez et al., 2015); therefore, more sophisticated study designs and considerations are required to draw convincing conclusions from cortisol data.

The 8-week-long intervention did not change the richness and diversity scales of the gut microbiome within the groups, but it significantly changed beta diversity between group A and the control group. Moreover, microbiota of group A shifted toward that of the external healthy population. Although there is interspecies variability within a genus, *Faecalibacterium* were more abundant in group A than in the control group, and that was also the genera that showed statistically similar abundance to the external healthy population. *Bifidobacterium* was also more abundant in group A than in the control group. These are genera that are generally known to produce aminobutyric acid. The production of aminobutyric acid by some bacteria is a possible mechanism for brain-protective effects (Strandwitz, 2018). In studies in mice, exercise increased butyrate-producing bacteria (Abraham et al., 2019), and *Bifidobacterium* was depleted in mice fed high-fat diets (Nam et al., 2017; Sah et al., 2017; Sanguinetti et al., 2018). In a human study, *Bifidobacterium* was depleted in older adults (Gavini et al., 2001) and in patients with AD dementia compared with a control group (Vogt et al., 2017). These studies possibly explain why patients diagnosed with early symptomatic AD in group A had more butyrate-producing bacteria than the control group who received no intervention. Moreover, no difference in beta diversity between group B and the control group suggests that the microbiota change does not occur after simple nutrition supplementation alone. As group A showed differences in the microbiota compared with the control group, it is clear that comprehensive lifestyle modifications, including nutritional guidance, exercise, and cognitive training, are more critical for microbiota change than a simple nutritional supplement.

A low adherence rate is a common limitation of multidomain lifestyle modification studies. A recent study revealed a positive correlation between the adherence rate to the intervention and improvement in cognition (Lam et al., 2015). The improvement in outcomes might be caused by the high adherence rates in our study (>90% in all groups). There are three possible reasons for these high adherence rates. First, there was a strategy to enroll participants on the waiting list while they were motivated. All participants were educated together about dementia prevention without knowing which group they would be assigned to so that control group participants were equally motivated to participate in the program. Subsequently, the participants were informed of their assigned group, and the control group participants were enrolled on the waitlist for the same program. This maintained the motivation of the control group and gave them the expectation of receiving the multidomain intervention program at the end of the study. Second, because the program was delivered in a two-person group or as individual sessions, it was possible for trained therapists to provide a more appropriate level of training content for a participant than in large group sessions. In addition, caregivers attended the sessions and assisted the participants. Finally, a short intervention period was crucial for achieving a high adherence rate.

One limitation of our study is the relatively short intervention period compared to some other multidomain intervention trials, which have ranged from 8 weeks to 6 years (Fiatarone Singh et al., 2014; Ngandu et al., 2015; van Charante et al., 2016; Andrieu et al., 2017; McMaster et al., 2020). This shorter duration was influenced by ethical considerations, as we were mindful of the delay in treatment for participants in the control group who were waitlisted. Additionally, the ongoing COVID-19 pandemic posed challenges in terms of resource utilization, healthcare facility availability, and time constraints, which are common factors limiting the feasibility of conducting long-term studies. To address this limitation, it is essential to establish a long-term cohort study to evaluate the conversion rate from MCI to probable dementia compared with the general population.

The original SUPERBRAIN feasibility study demonstrated the effectiveness of a home-based multidomain intervention (Moon et al., 2021). However, implementing a home-based intervention in our study presented certain challenges. Notably, the cognitive stages of our study participants differed from those in the original SUPERBRAIN study, as our participants were diagnosed with MCI or mild dementia, whereas the original study included individuals with better cognitive scores. Training participants to use tablet applications for home-based interventions, as done in the original SUPERBRAIN study, was relatively straightforward. However, even in that study, it took 8 weeks to train participants to use the application independently, alongside weekly group sessions held at the facilities. Given the cognitive challenges faced by our specific population, implementing a home-based intervention within an 8-week timeframe was deemed unsuitable for achieving effective cognitive outcomes. Therefore, we chose a facility-based intervention to ensure a more structured and supervised cognitive training approach for both participants and caregivers. Consequently, while our multidomain intervention is fundamentally based on the FINGER and SUPERBRAIN protocols, we designed a new protocol tailored to our distinct target population.

Another limitation of our study is the small sample size. Several previous studies conducted in Asia have used the RBANS as the primary outcome measure, with sample sizes ranging from 48 to 98 participants per experimental arm (Cheng et al., 2012; Kita et al., 2019; Ng et al., 2018, 2021). Notably, only one study from China reported a significant intervention effect on RBANS (Cheng et al., 2012), while the majority did not. It is important to highlight that the intervention employed in the Chinese study significantly differed from ours, as it did not encompass a multidomain approach and targeted healthy elderly individuals, which is distinct from the early symptomatic AD participants in our study.

Due to the scarcity of multidomain intervention studies specifically targeting early symptomatic AD, we faced challenges in determining the required sample size *a priori*. We computed our sample size based on a study that demonstrated a significant intervention effect on RBANS, the primary outcome measure (Calapai et al., 2017). The Cohen's f2 effect size for our primary outcome, the RBANS total scale index score, was calculated to be 0.53 (Selya et al., 2012), and its statistical power of 99.3%. Furthermore, our study adhered to the proposed criterion from a study assessing the RBANS anchor-based minimum clinically important difference (MCID) in

Chinese subjects, where a difference of 8 points was considered meaningful (Phillips et al., 2015). The adjusted mean of group A met this criterion, and the proportion of the participants meeting this criterion within the group was 60.0%. This confirms the effect of the multidomain intervention with nutritional supplements. Therefore, the main results of our study are statistically reliable, despite the limitation of small sample size.

In the subgroup analysis of the MCI group, the results for the RBANS index scores showed a pattern of significance similar to that observed in the main analysis. This is because the number of MCI participants in each experimental arm is equal to or greater than eleven, which is an adequate sample size to detect an effect on the RBANS. Subgroup analysis within the mild dementia group revealed that there was no significant difference in changes in RBANS total scale index scores among the three groups. The interpretation of this result must be constrained by the critical influence of the very small sample size within the early stage of dementia groups (group A: $n = 4$, group B: $n = 3$, control: $n = 5$). In another subgroup analysis exploring the impact of sex, it was observed that Group A yielded superior results compared to group B within the male subgroup while no such distinction was evident within the female group. Nevertheless, the interpretation of this result remains constrained by the small size of the subgroups.

In this study, our multidomain intervention with nutritional supplements demonstrated notable improvements in cognition, physical performance, and the gut microbiome when compared to patients who received nutritional supplements alone or those who received no intervention. While patients who received nutritional supplements alone showed a trend toward enhanced cognition compared to those who received no intervention, the multidomain approach emerged as the most effective.

These findings offer compelling support for the use of multidomain interventions with nutritional supplements in patients with early symptomatic AD. However, to gain a more profound understanding of the intervention's impact at specific disease stages and among different sexes, further research with larger sample sizes is warranted. Such endeavors will provide more definitive insights and contribute to advancing our knowledge of effective therapeutic strategies for this population.

Data availability statement

The 16S rRNA gene sequencing data presented in the study are deposited in the National Center for Biotechnology Information Sequence Read Archive, accession number PRJNA1025333.

Ethics statement

The studies involving humans were approved by Ewha Womans University, Seoul Hospital Institutional Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants, with the involvement of their legal guardians/next of kin.

Author contributions

EL: Data curation, Formal analysis, Writing – review & editing, Writing – original draft. GK: Data curation, Writing – review & editing. HP: Writing – review & editing, Conceptualization, Methodology. HK: Data curation, Writing – review & editing. YKP: Data curation, Methodology, Supervision, Writing – review & editing. HL: Formal analysis, Methodology, Writing – review & editing. CH: Methodology, Supervision, Writing – review & editing. SM: Methodology, Supervision, Writing – review & editing. SC: Conceptualization, Data curation, Formal analysis, Methodology, Supervision, Writing – review & editing. JJ: Conceptualization, Data curation, Formal analysis, Methodology, Supervision, Writing – review & editing. WK: Formal analysis, Visualization, Writing - review & editing. H-SO: Formal analysis, Visualization, Writing - review & editing. H-JY: Data curation, Formal analysis, Writing – review & editing.

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Conflict of interest

SM receives a research grant from Hyundai Pharmaceutical Co., Ltd. CH receives research support from Eisai Korea Inc. JJ receives research grants from Chong Kun Dang Pharmaceutical Corp., and consults for PeopleBio Co., Ltd. SM, CH, JJ, YKP, and SC are shareholders of Rowan Inc. SC consults for Hyundai Pharmaceutical Co., Ltd., and PeopleBio Co. Ltd. WK and H-SO were employed by CJ Bioscience Inc.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2023.1266955/full#supplementary-material

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Effects of remote combine exercise-music training on physical and cognitive performance in patients with Alzheimer's disease: a randomized controlled trial

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Introduction: This study aimed to investigate the effects of combined remote music and exercise training on the cognitive, psychological, and physical function of patients with Alzheimer's disease (AD).

Methods: Forty-one AD patients were randomly allocated to three groups, including control (C), training (T), and training with music (TM) groups. Participants were evaluated by cognitive and performance test batteries before and after the interventions. Both experimental groups performed 36 remote workouts in 3 months online via WhatsApp video call individually with the trainer. Training included simple and varied movements of all physical indicators. The number of sets began with two sets and progressively increased to one set every month, 5–10 repetitions per set. The overload was applied by reducing the break between sets every week. The TM group performed the same exercises while listening to Mozart and traditional Iranian songs.

Results: We observed a significant main, group, time, and interaction effect on Romberg (ηp^2:0.72), 30 s chair sit and stand (ηp^2:0.75), and walking on steppe test (ηp^2:0.63). Furthermore, there was a significant main time and interaction effect on push-ups (ηp^2:0.43), sit and reach (ηp^2:0.64), and MMSE (ηp^2:0.76). In all variables, two experimental groups demonstrated substantial improvements than the C group ($p < 0.01$). In addition, the TM group (27.8%) showed a significant improvement compared to the C group (–6.4%) and the T group (12.2%) in MMSE.

Conclusion: Combined remote training with listening to music as adjuvant treatment is an appropriate item to improve the cognitive and physical performance of Alzheimer's patients, especially during the COVID-19 pandemic.

KEYWORDS

music-therapy, combined training, muscle endurance, dementia, mental readiness

Introduction

Alzheimer's disease (AD) is the most common type of dementia; the primary symptoms include impairments in cognitive function such as recent memory, attention, language, visuospatial, and praxis. The patients also have difficulties in physical function and sleep quality. Although medications have limited these effects, they also have side effects, including nausea, anorexia, diarrhea, vomiting, and weight loss (DeLaGarza, 2003). Hence, non-pharmacological treatments such as exercise, social activity, mental challenges, and a healthy diet as prevention strategies with fewer side effects are recommended (Mendiola-Precoma et al., 2016; Nemoto and Suzuki, 2018).

Research has shown that exercise training effectively reduces the complications of all types of dementia (Santana-Sosa et al., 2008). In this regard, the positive benefits of resistance training on physical performance and limiting AD progression due to increased strength and muscle mass among old adults have been reported (Tracy et al., 1999; Bamman et al., 2003). On the other hand, aerobic training significantly improves activities of daily living, cardiorespiratory fitness, and a slower decline in cognitive function in patients with AD (Venturelli et al., 2011; Sobol et al., 2016). In general, a combination of strength and endurance training, combined training, is recommended for Alzheimer's patients to get the maximum benefits (Parvin et al., 2020). However, due to the low effectiveness of physical activity on cognitive function, adding a mental task to exercise training, known as dual-task training, has more significant effects on the mind and physical fitness of Alzheimer's patients (Dennis et al., 2009; Parvin et al., 2020). Researchers have shown that dual-task training has more positive effects, such as improving attention and accuracy, on Alzheimer's patients rather than the exercise alone (Åhman et al., 2019; Nam and Kim, 2021).

Music therapy is an important, low-cost, and effective way to maintain and improve cognitive function and social behavior in Alzheimer's patients (Raglio et al., 2014). Music therapy has no side effects, so patients and their caregivers can easily use it. Many studies have shown that music therapy can improve various cognitive and psychological aspects such as attention, memory, orientation, depression, and anxiety (Bruer et al., 2007; Ozdemir and Akdemir, 2009; Särkämö et al., 2014; Satoh et al., 2015). Individuals can exercise while music is playing or perform each one separately. A few research studies have been done on the combined effects of music therapy and exercise so far; in these studies, cognitive and exercise stimuli were not applied simultaneously. Recently, Higuti et al. (2021) reported listening to music and practicing physical exercise for 12 weeks; one session per week (25–30 min) did not significantly change functional or cognitive performance in institutionalized older adults with dementia (Higuti et al., 2021). In contrast, some studies that have used more frequency (twice a week) and duration (one hour) of exercise and music sessions reported improvements in cognitive, psychological, and motor abilities in patients with mild to moderate dementia (Satoh et al., 2014, 2017; Prinz et al., 2021). Therefore, a combination of music therapy and exercise as dual-task training can be an excellent option to improve AD patients' physical and cognitive fitness.

Listening to music in healthy human can modulate many physiological responses even during exercise (i.e., heart rate, catecholamines, muscle activation), which leads to improved performance (Ballmann, 2021). Furthermore, listening to music during exercise has positive impact on psychological (i.e., mood, motivation) and psychophysiological (i.e., rate of perceived exertion, arousal) status, which may have ergogenic potential. Moreover, research showed that music increases activity in some portions of the brain such as left inferior frontal gyrus and insular cortex activation that are important for physiological arousal, emotion, and perception (Bigliassi et al., 2018). So, listening to music during exercise could activate these brain regions and lead to an increase in cognitive processing speed and organization of movement (Bacon et al., 2012). Therefore, it seems that simultaneous exercise and music through neural activation and arousal have augmentation physiological and psychological effects to improve cognitive and physical performance.

Given that the physical effects of exercise training and the mental function of music therapy are more pronounced, we hypothesized that the combination of these two stimuli has a synergic impact on improving AD patients' physical and mental function. Due to the pandemic of COVID-19 infection, we conducted the study online with a video call for the safety of patients and their caregivers. Therefore, the present study aimed to investigate the effects of adding music to exercise training on the mental and physical fitness of Alzheimer's patients.

Materials and methods

Study design

A randomized clinical trial, with control and two parallel experimental groups and a single-blind design, was conducted on AD patients from May 2021 until August 2021. This study aimed to investigate the effects of 12 weeks of adding music therapy to exercise training remotely on the physical and cognitive performance of patients with AD. The participants and their caregivers attended a familiarization session 1 week before the study. They were informed about the benefits and potential risks of the study, signed a consent form and cognitive and performance tests were taken. The block randomization method (size 6) was applied, and the participants were assigned to three groups. Because of the COVID-19 pandemic, the training sessions were executed online. A neurologist performed the cognitive test, and the trainer took the performance tests. A CONSORT flow diagram of the present study is shown in Figure 1.

Participants

Patients with AD, who were eligible to participate in this Clinical Trials study, were recruited from the memory clinic of Roozbeh Hospital in Tehran, Iran. The inclusion criteria were AD patients aged 50–75 years with mild to moderate dementia and the ability to walk and perform exercise independently. A neurologist affirmed the diagnosis of dementia based on the Diagnostic and Statistical Manual

Abbreviations: AD, Alzheimer's disease; T, Training; TM, Training with music; DSM-5, Diagnostic and Statistical Manual of Mental Disorders; MMSE, Mini-Mental State Examination; ES, Effect size; SD, Standard deviation; SPSS, Statistical Package of Social Sciences; DEXA, Dual-energy X-ray; SPECT, Brain Single Photon Emission Computed Tomography; PET, Positron emission tomography.

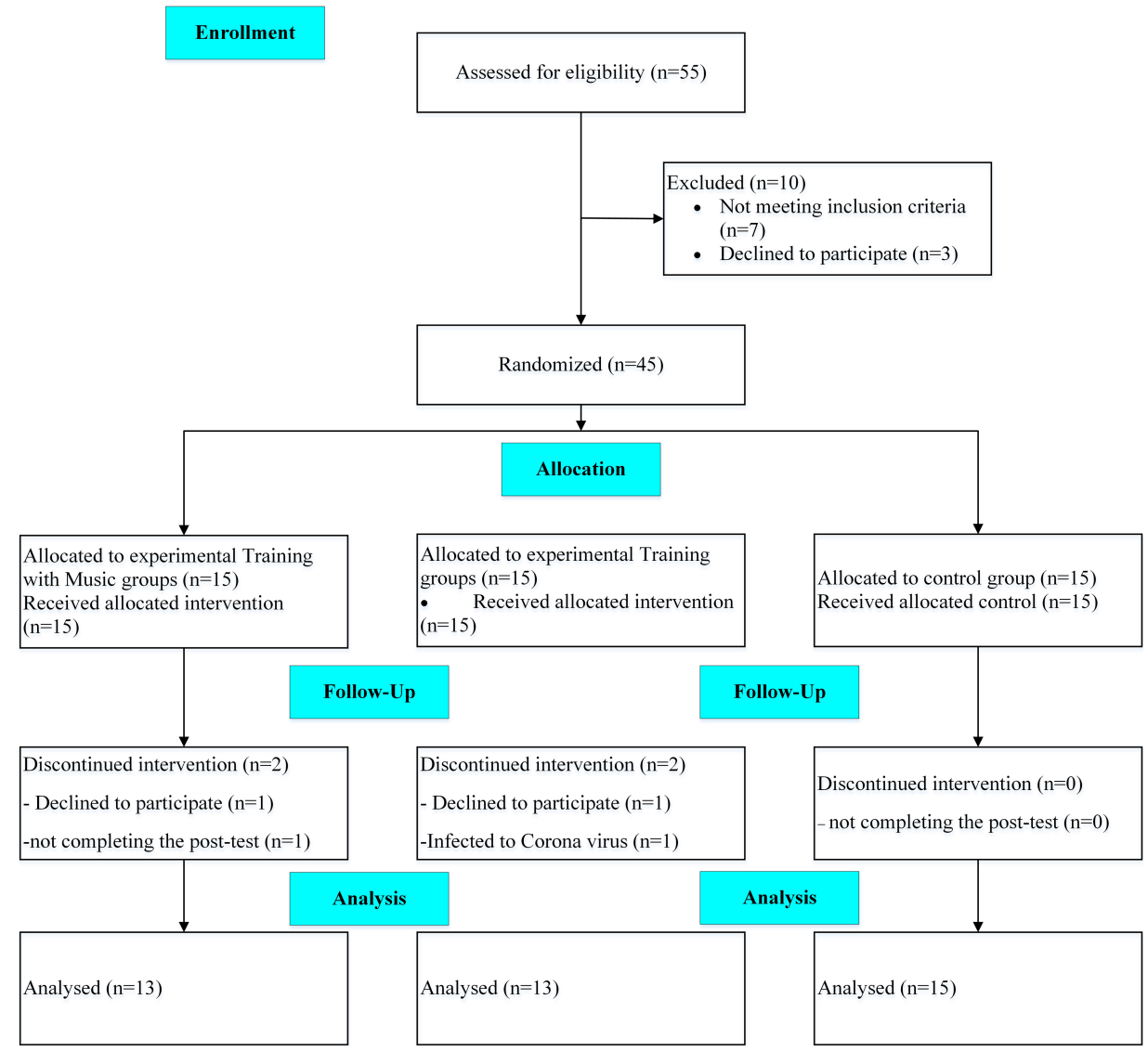

FIGURE 1
Schematic overview of study timeline (CONSORT flow diagram).

of Mental Disorders (DSM-5) criteria, low to moderate stages of dementia based on the FAST scale (3–6), and laboratory tests. The patients' medications were checked before beginning the study and were not changed in type or dosage during the intervention. In addition, patients with cardiac diseases (e.g., unstable angina and recent myocardial infarct) were not recruited. The exclusion criteria were the absence in more than three consecutive sessions, the unwillingness to continue training, the inability to perform exercises, not take post-tests, and the physician's decision to exclude the patients. A sample size calculation was conducted using G*Power Software version 3.1.9.6 (Faul et al., 2007) for repeated measure ANOVA, using a rejection criterion of 0.05 and 0.8 (1-beta) power, and large effect ($f = 0.5$), a minimum of 13 participants needed to each group.

Forty-five eligible patients volunteered to attend the study, but the data of 41 patients (age: 67.5 ± 8.2 years; height: 169.4 ± 6.8 cm, body mass: 75.8 ± 7.7 kg) was analyzed finally. A third person who was not in the research team, based on the cognitive test scores, randomly assigned participants into three groups ($n = 15$), including training (T), training with music (TM), and the control group (C). Two participants from each experimental group were either not interested in continuing the intervention, infected with the coronavirus, or did not complete the post-test.

Training protocol

The intervention lasted 3 months, 3 days per week (36 workouts). Each session was around 35–45 min, including 10 min of warm-up with dynamic movements, 20–35 min of main exercises, and 5 minutes of cool down with stretching movements. Because of the Coronavirus pandemic, all workouts were conducted online via WhatsApp video call individually with the trainer (researcher). The presence of a

caregiver in the training session was mandatory. The training group performed a combination of sitting and standing movements. The movements involved the whole body and large muscle groups. The main exercises are presented in Table 1. In each session, exercises were selected from all indicators of physical fitness. The break between sets started at 70 s, and gradually it reduced 10 s every two weeks until the tenth week eventually reduced by 5 s to reach 25 s. The number of sets began with two sets and progressively increased to one set every month, 5–10 repetitions per set depending on the difficulty of the movement and the patient's fitness. The trainer explained and demonstrated the activities to patients clearly. The TM group performed the same exercises while listening to the mix of Mozart's sonatas and traditional and instrumental Persian music (Johnson et al., 1998; Li et al., 2015). We used the examiner-choose music playlist based on expert cognitive neurologist opinion, including some sort of Mozart music Symphonia, and also traditional Iranian music by the patient's selection. Since familiarity with the music playlist could have positive effects on the patient's cognitive function and probably mood improvements, we preferred to utilize the mix of classical Mozart music with established impact on cognitive function and a more familiar music playlist with possible familiarity evidence on cognition function. The session started with Mozart's sonatas for 10–15 min, continued with Persian music, and then during the cool down, Mozart's sonatas were played. The patient's caregivers played music because of the greater clarity of the sound. Music was played throughout the exercise session. The overload was applied by reducing the break between sets every week (every three sessions). The training intensity was monitored using the Borg scale, a 10-point scale, in which we prescribed exercises in intensities of 4 to 6 on this scale. The C group did not receive any physical or cognitive intervention and continued their routine life; they participated in the pre and post-tests.

Measurements

All the following tests were taken before the implementation of the research protocol and 48 h after the last training session. Initially, anthropometric measurements were taken, followed by cognitive tests, and finally performance tests.

Anthropometric indices

Height and body mass were measured using a standard stadiometer (Seca 213, Germany) and a calibrated digital scale (Seca 769, Germany).

Cognitive tests

Cognitive functions were assessed by the Mini-Mental State Examination (MMSE). The MMSE is a short exam to evaluate the quality of consciousness and has high sensitivity and specificity in detecting dementia across different age groups. This questionnaire included six subsets: orientation, registration, attention, recall, language, and constructional praxis, with a total score of 30 points. A score below 23 indicates the possibility of the disorder (Hobson, 2015).

Performance tests

Physical performance tests were conducted in a written order with a 5 min interval. Before starting the testing, the participants had a 10 min warm-up, which included walking in place, chair sit-ups, wall push-ups, and light stretching. The Romberg, modified push-up, chair stand, sit and reach, and step tests were taken, respectively, to assess the patient's physical performance.

The Romberg test for assessing a standing balance or participant's ability to stand unassisted was performed on a firm and compliant support surface. Participants stood with both feet together without shoes, held their arms next to the body, or crossed in front of the body. Then, they were asked to close their eyes and keep their static balance. The time that the participants could stand with their eyes closed was recorded. The test was finished if participants opened their eyes, lost their balance by moving arms or feet, swayed their body, or began to fall and needed the examiner's intervention to maintain balance (Forbes and Cronovich, 2021). Participants performed this test twice, and the best time was recorded.

The modified push-up is a test for the assessment of the patient's shoulder endurance. In this test, the patients were asked to get push-ups positioned on their knees and do the push-up on their knees for 1 minute. The number of complete movements during 1 minute was counted.

We used the 30 s chair stand test to measure the subject's lower body muscle endurance. The test needs participants to sit on a chair, put their hand on the opposite shoulder, and cross at the wrists; then, from the sitting position, subjects stand completely up and back down as many times as possible within 30 s. Count the total number of complete chair stands. This test was taken twice, and the best result was recorded for each patient (Rikli and Jones, 2013).

The sit and reach test measured the lower back and hamstring's flexibility. The participants were asked to sit on the floor with their legs stretched out. The soles are placed flat against the box. Knees must

TABLE 1 Type of performed exercises.

Physical indicator	Kind of exercises
Balance	Keep balance on one foot, Heel-to-Toe
Coordination	Harmonious opening and closing of legs and arms, raise the opposite arm and leg simultaneously
Stretching	Reaching the fingertips to the toes while sitting on a chair, bringing the fingertips to toes while standing with straight knees
Upper body muscle endurance	Types of shoulder movements, shoulder press, biceps curl
Lower body muscle endurance exercises	Wall squat, raising feet simultaneously while sitting on a chair
Aerobic	Walking on the steppe, quick step

be locked and pressed flat to the floor. With the palms facing downwards and the hands-on top of each other, participants reached forward and tried to touch or pass their toes. The participants reach out and hold that position for at least one-two seconds while the distance is recorded. The level of the feet was considered as recording zero so that any measure that does not reach the toes is negative and any reach past the toes is positive.

A step test measured the patient's aerobic fitness. The participants stepped on and off the box (15–17 cm high) for two minutes, which was recorded by a chronometer. If patients start with the right or left foot, they should go down with the same leg with the "up," "up," "down," and "down" rhythm. The number of complete steps on and off the box was counted for statistical analysis.

Ethical aspect

All research procedures conducted in studies involving human participants were in accordance with the declaration of Helsinki. The study was approved by the Ethics Committee for Sport Sciences Research Institute of Iran (approval number: IR.SSRI.REC.1400.070). In addition, this research was registered in the Iranian Registry of Clinical Trials (IRCT) with registration number: IRCT20210726051993N1.

Statistical analysis

The Statistical Package of Social Sciences (SPSS, IBM, v19) was used to analyze row data. Data presented in mean ± standard deviation (SD). The normality distribution of the variables was done using the Shapiro–Wilk test. A repeated measure analysis of variance ANOVA with the time (T1 vs. T2) and group (C, MT, T) was performed to analyze the data. We calculated the effect size (ES) by the change score divided by the SD of the change score to examine the magnitude of differences while controlling for the influence of the sample size (Dankel and Loenneke, 2018), with 0.2 considered as a small ES, 0.5 as a moderate ES and >0.8 as a large ES. The significance level was considered at $p \leq 0.05$ for all statistical analyses.

Results

Cognitive performance

There was no significant difference between groups at the MMSE test at baseline ($p > 0.05$). The statistical analysis demonstrated there was no significant main group effect for MMSE ($F_{2,24} = 3.50$ $p = 0.054$, ηp^2:0.23), through a significant time ($F_{1,12} = 74.13$ $p = 0.001$, ηp^2:0.86) and interaction effect (group × time) ($F_{2,24} = 38.71$ $p = 0.001$, ηp^2:0.76) observed. The TM group (27.8%) demonstrated a significant improvement compared to the C group (−6.4%) ($p = 0.001$), and the T group (12.2%) ($p = 0.002$). In addition, there was a significant difference between the T group and the C group ($p = 0.001$). In details, we observed significant differences at orientation ($F_{2,24} = 9.74$ $p = 0.002$, ηp^2: 0.45), language ($F_{2,24} = 3.52$ $p = 0.047$, ηp^2: 0.23), memory ($F_{2,24} = 3.76$ $p = 0.042$, ηp^2:0.24) and delay recall ($F_{2,24} = 5.59$ $p = 0.017$, ηp^2:0.32) between groups. However, there were not any significant differences at registration ($F_{2,24} = 1.45$ $p = 0.257$, ηp^2: 0.11), visual-spatial ($F_{2,24} = 1.32$ $p = 0.287$, ηp^2:0.10), and comprehension ($F_{2,24} = 0.79$ $p = 0.412$, ηp^2: 0.06) following interventions between groups. For orientation and delay recall, there was a significant difference between the TM group and the other two groups ($p < 0.05$). Additionally, the scores obtained in the T group were significantly higher than in the C group in orientation ($p = 0.013$). The scores obtained in the TM group for language ($p = 0.014$) and memory ($p = 0.035$) were significantly higher than in the C group. Figure 2 displays the scores obtained from the MMSE test pre- and post-intervention.

Physical performance

There were no significant differences between groups at physical performance tests at baseline ($p > 0.05$). Table 2 presents the descriptive statistics of body mass and performance parameters, pre- and post-intervention. There was a significant main time effect ($F_{1,12} = 0.17.55$, $p = 0.001$, ηp^2:0.59), but no main group ($F_{2,24} = 0.25$ $p = 0.779$, ηp^2:0.02), and interaction effect ($F_{2.24} = 3.33$ $p = 0.053$, ηp^2:0.22) for body mass following intervention.

Overall, compared to the C group, both experimental groups demonstrated substantial improvements in all performance indices

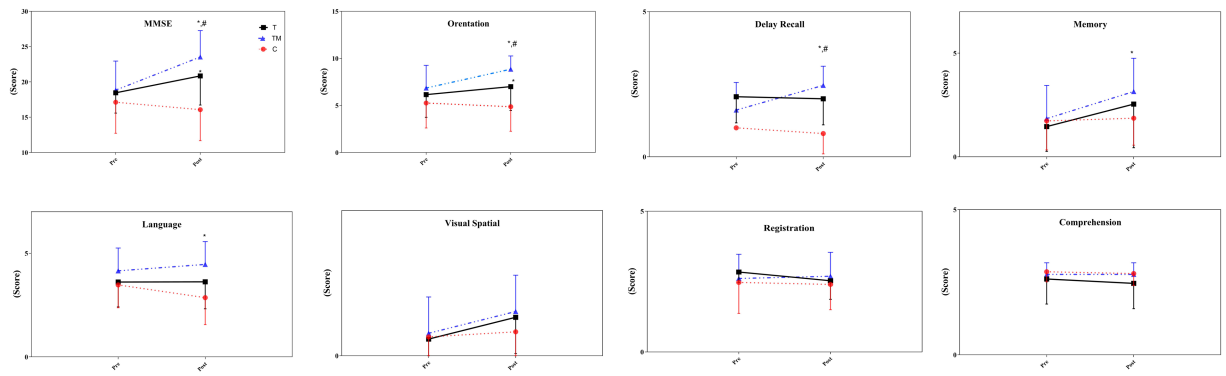

FIGURE 2
The scores of the MMSE test following the intervention. C, control group; T, training group; TM, training with the music group. *: significant difference with the C group; #: significant difference with the T group.

TABLE 2 The value of body mass and performance tests pre and after the intervention.

Variable	Group	Pre	Post	% change	Cohen's *d*	*p* between group
Body mass (kg)	C	75.94 ± 9.09	74.91 ± 8.81	−1.33	−1.23	Pre: 0.711 Post:0.062
	T	76.23 ± 5.24	75.96 ± 5.49	−0.37	−0.27	
	TM	74.09 ± 6.27	73.74 ± 6.06	−0.45	−0.41	
30 s stand-up (N)	C	7.47 ± 2.32	6.40 ± 2.29	−11.15	−0.82	Pre: 0.512 Post:0.001
	T	8.53 ± 3.36	13.31 ± 4.29	64.46*	2.09	
	TM	8.62 ± 3.12	14.23 ± 3.92	75.07*	2.13	
Push-ups (N)	C	3.80 ± 3.80	3.20 ± 3.55	−16.22	−0.91	Pre:0.269 Post: 0.001
	T	5.54 ± 5.23	12.00 ± 10.33	183.52*	1.03	
	TM	6.92 ± 5.96	12.54 ± 9.87	100.09*	1.25	
Romberg (s)	C	11.40 ± 5.78	10.00 ± 5.39	−11.41	−1.10	Pre: 0.265 Post:0.001
	T	15.54 ± 8.38	31.31 ± 11.10	54.40*	1.97	
	TM	13.92 ± 5.63	34.08 ± 12.01	90.32*	2.07	
Step walking for 2 min (N)	C	16.73 ± 9.91	14.73 ± 9.61	−14.36	−1.62	Pre:0.089 Post:0.001
	T	26.00 ± 13.83	38.31 ± 20.44	59.52*	1.22	
	TM	25.54 ± 12.31	39.46 ± 13.78	74.27*	1.93	
Sit and reach test (cm)	C	−3.40 ± 3.85	−3.67 ± 4.56	3.05	−0.19	Pre:0.442 Post: 0.001
	T	−5.15 ± 3.80	−1.31 ± 4.66	−69.33*	2.01	
	TM	−4.31 ± 3.01	−1.07 ± 4.29	−44.17*	1.29	

following 12 weeks of training protocols. We found no significant main group effect for push-ups ($F_{2,24} = 2.66$ $p = 0.091$, ηp^2:0.18), through a significant time ($F_{1,12} = 32.56$ $p = 0.001$, ηp^2:0.73) and interaction effect observed ($F_{2,24} = 9.20$ $p = 0.001$, ηp^2:0.43). The Bonferroni *post hoc* test showed the difference between the C group and both trained groups ($p < 0.01$). We observed a significant main group ($F_{2,24} = 9.99$ $p = 0.001$, ηp^2:0.45), time ($F_{1,12} = 103.55$ $p = 0.001$, ηp^2:0.90), and interaction effect ($F_{2,24} = 30.41$ $p = 0.001$, ηp^2:0.72) for Romberg test. Two experimental groups demonstrated significant improvement than the C group ($p < 0.01$). For 30 s chair sit and stand, there was a significant main group ($F_{2,24} = 6.18$ $p = 0.007$, ηp^2:0.34), time ($F_{1,12} = 79.86$ $p = 0.001$, ηp^2:0.87), and interaction effect ($F_{2,24} = 36.48$ $p = 0.001$, ηp^2:0.75). The difference was between the trained groups with the C group ($p < 0.01$). We found a significant main group ($F_{2,24} = 4.2$ $p = 0.027$, ηp^2:0.26), time ($F_{1,12} = 46.46$ $p = 0.001$, ηp^2:0.79), and interaction effect ($F_{2,24} = 20.35$ $p = 0.001$, ηp^2:0.63) for walking on steppe test. The Bonferroni *post hoc* test displayed two trained groups performed far better than the C group ($p < 0.01$). There was no significant main group effect for sit and reach test ($F_{2,24} = 0.06$ $p = 0.094$, ηp^2:0.01), through a significant time ($F_{1,12} = 33.24$ $p = 0.001$, ηp^2:0.74) and interaction effect observed ($F_{2,24} = 21.06$ $p = 0.001$, ηp^2:0.64). The Bonferroni *post hoc* test showed both experimental groups demonstrated further stretch than the C group ($p < 0.001$).

Discussion

The primary aim of this study was to examine the effectiveness of adding music as a cognitive activity to exercise at home on the cognitive and physical performance of Alzheimer's patients. The present study's findings indicated both trained groups demonstrated considerable improvements in all performance indicators and cognitive function than in the C group. However, the TM group showed much more significant improvement in cognitive function compared to the T group alone. The TM group demonstrated substantial improvements in orientation, delay recall, memory, and language. Therefore, the research findings show that adding cognitive stimuli such as music during exercise training has synergistic effects potentially through neural activation and arousal the on improving mental and physical performance to gain further benefits from physical training.

Although both the T (12.2%) and TM (27.8%) groups showed improvements in cognitive function, measured by the MMSE test, a significant improvement was observed in the TM group. It seems that performing exercises simultaneously with music has caused a further improvement in cognitive function by activating brain cells in remembering the music and remote memories. Given that there is an overlap between the areas of musical memory and the areas spared in AD, it was shown that listening to music can preserve these areas. In this regard, minimal cortical atrophy and minimally impaired glucose metabolism were observed despite a non-significant change in Aβ deposition (Jacobsen et al., 2015). In addition, music activates a broad network in the brain: bilateral temporal lobes, superior temporal regions, parahippocampal gyri, caudal anterior cingulate cortex, and ventral pre-supplementary motor areas (Satoh et al., 2006; Jacobsen et al., 2015). Moreover, the positive effect of music on cognition could be interpreted based on impacts on arousal and evoking autobiographical memory, which was demonstrated in previous studies. That could improve self-consciousness, global cognitive function, and especially behavioral symptoms of dementia. In detail, the TM group showed significant improvement in orientation, delay recall, memory, and language compared to the C group. Therefore,

simultaneously performing these two effective interventions by further perfusion and activating some areas of the mentioned brain could be effective in remembering events and maintaining cognitive performance. In contrast, Higuti et al. did not find any improvement in the cognitive function of patients after 12 weeks of exercise with music (Higuti et al., 2021). The methodological differences between our research and the former study may explain this contradiction. Our research was a dual-task in which music and exercise were performed simultaneously, but in Higuti's research, they were conducted separately. Overall, performing exercise and listening to music simultaneously by activating the brain and maintaining muscle fitness effectively improves cognitive function and quality of life in Alzheimer's patients.

Loss of muscle fitness due to muscle atrophy is a complication of AD that can lead to the inability to perform daily tasks, a poor psychological state, and ultimately a decline in quality of life (Burns et al., 2010; Lane et al., 2018). Our findings indicated that upper and lower body muscle endurance improved in both TM and T groups. Our training protocol involved many muscle endurance exercises for the upper and lower body, which were performed in several sets in all workouts; thus, expecting an improvement in muscle fitness was especially obvious in these patients whose physical fitness had considerably declined. Our finding has been supported by previous studies showing that a period of combined training, including resistance and aerobic exercises, significantly improved muscle strength and endurance in patients with cognitive impairment (Santana-Sosa et al., 2008; Langoni et al., 2019; Parvin et al., 2020). As there is a strong relationship between muscle atrophy and declined cognitive function (Burns et al., 2010), it was recommended that muscle maintenance exercises be included in AD patients' training programs. Therefore, combined training with enhancing the strength and muscular endurance of AD patients can promote patients' independence in performing routine activities and, to some extent, be effective in improving patients' mood and quality of life.

AD is also associated with reduced cardiovascular fitness (Lane et al., 2018) due to a sedentary lifestyle. Our findings show that both TM and T groups demonstrated an improvement in aerobic fitness, which was measured by walking on the steppe. Activities such as walking steps, quick going back and forth, and repetition of movements improve aerobic fitness. In this regard, Parvin et al. (2020) showed that a 12 week combined training period significantly improves aerobic fitness (Parvin et al., 2020). Interestingly, increased cardiorespiratory fitness is associated with reduced brain atrophy in AD patients (Burns et al., 2008). Thus, aerobic exercise is as essential as resistance training for Alzheimer's patients. The TM group showed a slightly better aerobic performance than the T group. Studies reported that the synchronization of music and exercise can result in improved running economy, efficiency, oxygen consumption and performance (Bacon et al., 2012; Terry et al., 2012). Therefore, exercising while listening to music, cardiovascular fitness can be improved through running economy.

One of the problems that Alzheimer's patients encounter is an imbalance resulting from loss of muscle strength and destruction of nerve cells. Both experimental groups enhanced their balance following the research protocol. Participants performed many balance exercises during the intervention; thus, continuous activation of the proprioceptive sense caused the patients' balance to develop. A previous study also confirmed that combined training had positive effects on the balance of Alzheimer's patients and reduced the risk of falls (Santana-Sosa et al., 2008). The most non-significant difference was seen in balance between two training groups. It's clear that cognitive processes, particularly attention are crucial when performing a balancing movement (Woollacott and Shumway-Cook, 2002). Hence, listening to music during exercise can activate the brain regions, involved in cognitive processing and organization of movement (Bacon et al., 2012); thus, this intervention can lead to the improvement of balance movements. In this regards, it has shown, listening to music improved postural balance in visually impaired adolescents (Maatoug et al., 2023).

Changes in body mass and composition need long-term manipulation of intake and expended calories. Although the current intervention lasted 3 months and is a good opportunity for changes in body weight, no significant change was observed following the interventions in all groups. In the present study, the amount of calories consumed was not calculated; however, it is evident that the calories expended in the exercise groups increased. Research has shown that Alzheimer's patients progressively lost their appetite due to hypo-perfusion to the right and left anterior cingulate and orbitofrontal cortices, ultimately leading to weight loss (Ismail et al., 2008). In the C group, we observed slightly more weight loss than in the two experimental groups, which indicates that exercise training has effectively restored patients' appetite.

We acknowledged that there were some limitations in our study. Firstly, we had limitations in using laboratory tools due to the coronavirus pandemic; we did not measure patients' body composition, which can be used to interpret the findings. Secondly, we also did not assess the changes in brain imaging after intervention due to the pandemic crisis. Hence, we propose evaluating the correlation between cognitive changes and alteration in brain structure by utilizing brain MRI and functional brain imaging such as brain Single Photon Emission Computed Tomography (SPECT) and Positron emission tomography (PET) scan and measuring body composition by dual energy X-ray (DEXA) in future studies. Additionally, we suggest that future studies evaluate the effects of the dual-task intervention on behavioral and psychological symptoms of dementia, sleep problems, and eventually the quality of life in dementia patients. In addition, given that familiar and unfamiliar music may have different effects on cognitive and performance indicators, it is recommended that researchers investigate this issue in a research. At last, in follow-up studies after 3–6 months could help us determine the constant effect of dual-task training on cognition.

Conclusion

In conclusion, our findings showed a combining remote training with music as appropriate non-pharmacological treatment is useful for improving the physical and cognitive function of Alzheimer's patients and could ultimately decrease the AD burden on society. Thus, we recommend that neurologists include dual-task training (training with music) in the adjunctive treatment of Alzheimer's patients, along with pharmacological therapies.

Data availability statement

The datasets presented in this article are not readily available because the datasets generated and analysed during the current study are available from the corresponding author on reasonable request. Requests to access the datasets should be directed to amani_sadegh@khu.ac.ir.

Ethics statement

The studies involving humans were approved by Sport Sciences Research Institute of Iran. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

GS: Data curation, Methodology, Writing – original draft. FM: Conceptualization, Supervision, Writing – review & editing. MN: Conceptualization, Writing – review & editing, Formal analysis. SA-S: Conceptualization, Formal analysis, Writing – review & editing, Supervision. KS: Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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From theory to practice: translating the concept of cognitive resilience to novel therapeutic targets that maintain cognition in aging adults

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While the concept of cognitive resilience is well-established it has not been defined in a way that can be measured. This has been an impediment to studying its underlying biology and to developing instruments for its clinical assessment. This perspective highlights recent work that has quantified the expression of cortical proteins associated with cognitive resilience, thus facilitating studies of its complex underlying biology and the full range of its clinical effects in aging adults. These initial studies provide empirical support for the conceptualization of resilience as a continuum. Like other conventional risk factors, some individuals manifest higher-than-average cognitive resilience and other individuals manifest lower-than-average cognitive resilience. These novel approaches for advancing studies of cognitive resilience can be generalized to other aging phenotypes and can set the stage for the development of clinical tools that might have the potential to measure other mechanisms of resilience in aging adults. These advances also have the potential to catalyze a complementary therapeutic approach that focuses on augmenting resilience via lifestyle changes or therapies targeting its underlying molecular mechanisms to maintain cognition and brain health even in the presence of untreatable stressors like brain pathologies that accumulate in aging adults.

KEYWORDS

cognitive resilience, cognitive aging, cognitive decline, neuropathology, molecular mechanisms

Introduction

Aging is characterized by continuous changes in cognitive abilities that in many older adults can become prominent enough to warrant a diagnosis of mild cognitive impairment or Alzheimer's disease (AD) dementia. Aging is also characterized by underlying and insidious accumulation of multiple brain pathologies and

TABLE 1 List of current terminologies and definitions from prevailing frameworks on cognitive reserve and resilience.

Framework	Term	Definition
Reserve and Resilience Framework (Blanchard et al., 1996)	Cognitive reserve	Better-than-expected cognitive performance given the degree of brain aging, injury, or disease.
	Brain reserve	The neurobiological status of the brain at any point in time, e.g., neocortical size.
	Brain maintenance	The preservation of brain morphology, i.e., absence of neuropathologic changes.
Resilience and Resistance Framework (Arenaza-Urquijo and Vemuri, 2018)	Brain resilience	Better-than-expected cognitive performance in the presence of Alzheimer's disease pathology. (This is similar to *cognitive reserve*).
	Brain resistance	The absence or lower-than-expect levels of pathology (This is similar to *brain maintenance*)
Scaffolding Theory of Aging and Cognition (Reuter-Lorenz and Park, 2014)	Compensatory scaffolding	The effects of neural processes that reduce the negative impact of brain aging on cognition.
National Institutes of Aging and the American Geriatrics Society (Abadir et al., 2023)	Resilience	A desirable outcome after exposure to a stressor that is expected to diminish the outcome.
Trans National Institutes of Health Resilience Working Group (Office of Dietary Supplements NIoH, Trans-NIH Resilience Working Group, 2023)	Resilience	Any system's (individual, community, environment) capacity to resist, recover, grow, or adapt in response to a challenge or stressor.

degeneration of neural structures crucial for cognition. Yet, not all individuals with evidence of accumulated brain pathologies and neurodegenerative changes manifest cognitive impairment or decline. Up to a third of individuals in the Religious Orders Study (ROS) and Rush Memory and Aging Project (MAP) cohorts (described in further detail below), who meet the criteria for a diagnosis of pathologic AD at autopsy do not manifest clinical signs of impaired cognition prior to death (Bennett et al., 2006a,b). Other reports have shown similar results (Crystal et al., 1988; Katzman et al., 1988; Snowdon, 1997). These studies led to the hypothesis that individuals who remain cognitively intact despite the presence of significant neuropathologic AD burden harbor resilience factors that offset the negative cognitive effects of accumulating brain pathologies (Mortimer, 1997; Cummings et al., 1998; Stern, 2002). While early clinical-pathologic studies (Crystal et al., 1988; Katzman et al., 1988; Snowdon, 1997), and later, neuroimaging studies (Reuter-Lorenz, 2002; Stern et al., 2003; Stern, 2017), provided further evidence supporting the cognitive resilience hypothesis, a lack of consensus on how the construct is operationalized has also prevailed.

The concept of cognitive resilience has been difficult to operationalize

Cognitive resilience has been broadly conceptualized as the ability to maintain function despite physiologic or pathologic, stressors (Luthar et al., 2000; Wagnild and Collins, 2009; Windle, 2011; Fletcher and Sarkar, 2013; Jain et al., 2014; Whitson et al., 2016). Some individuals function better (or worse) than average vis-a-vis specific stressors. Prevailing perspectives have proposed various operational definitions to distinguish among different forms of resilience (Stern, 2009, 2012; Cabeza et al., 2018; Stern et al., 2019, 2020), yet they have only focused on protective factors that afford a beneficial effect on an individual's function. Table 1 provides a list of current terminologies and definitions from prevailing frameworks (Reuter-Lorenz and Park, 2014; Arenaza-Urquijo and Vemuri, 2018; Stern et al., 2020; Abadir et al., 2023; Office of Dietary Supplements NIoH, Trans-NIH Resilience Working Group, 2023). Most of these terms are related, and the literature is ripe with studies teasing out proxies of reserve and applying various brain modalities to study what makes individuals (more) resilient to disease (Nyberg et al., 2012; Habeck et al., 2017; Anatürk et al., 2021; Vaqué-Alcázar et al., 2021; Gazes et al., 2023; Neth et al., 2023). Thus, while a wide range of potential reasons for why some individuals function better than average have been suggested, explanations on why other individuals might function worse than average have not been addressed. These overarching definitions acknowledge the multidimensionality of resilience and give value to various approaches to elucidate the mechanisms of resilience; however, the concept of resilience has remained a challenge to translate it into a tool that quantifies resilience on a person-specific level with aims to identify individuals with high or low resilience.

This perspective will first give a brief overview of our prior clinical-pathologic work that has laid the foundations of our more recent work using genomic data to elucidate the neurobiological mechanisms of resilience. This work has led to approaches that seek to translate our findings into a qualifiable tool that can be used to measure the identified resilience mechanisms on a person-specific level. We treat cognitive resilience like most risk factors that lie on a wide continuum ranging from beneficial to detrimental, hence a population's levels of resilience may span from low to average to high, again like any continuous risk factor. This approach allows us to utilize (and eventually quantify) the full spectrum of functioning (better, *or worse* than expected) given the exposure (neuropathologic burden), thus offering a more intuitive approach than *a priori* categories of yes/no resilience. We discuss in some detail how we approach the study of cognitive resilience with the aim of filling outstanding gaps in currently proposed frameworks.

Our team initiated clinical-pathologic cohort studies to investigate cognitive resilience

The Religious Orders Study (ROS) and Rush Memory and Aging Project (MAP) began in 1994 and 1997, respectively, (together referred to as ROSMAP) to study aging and Alzheimer's disease. The MAP was initiated as a complementary cohort study and extension of ROS, with the aims of identifying the structural basis of neural reserve, and of elucidating what determines its capacity. While ROS participants are Catholic nuns, priests, and brothers from more than 40 US groups, MAP participants are recruited from retirement communities and subsidized senior housing facilities throughout Chicago and Eastern Illinois. Participants are over the age of 65, enroll without known dementia, agree to annual clinical evaluations, cognitive testing, and blood draws, and agree to organ donation (Bennett et al., 2005, 2012, 2018). Both studies are ongoing.

Since the inception of these studies, we have conceptualized resilience via two basic mechanisms: one that degrades resilience and one that maintains it. Over the past two decades, we have provided evidence for both. First, we have shown that mechanisms that degrade resilience are not confined to AD pathology but include multiple pathologies including cerebral infarctions and Lewy bodies (Schneider et al., 2007a,b). Over the years our findings have also indicated that there are yet undiscovered neurobiological mechanisms that interact and damage neural networks that reduces the brain's ability to tolerate these insults. For instance, psychosocial risk factors, such as chronic distress, loneliness, and higher reports of depressive symptomatology, have been associated with higher odds of dementia but were not associated with pathologic AD, Lewy bodies, or infarcts (Wilson et al., 2003, 2006, 2007a,b), indicating that other mechanisms that degrade resilience via these risk factors await discovery.

We have also shown that several psychosocial factors reduce the likelihood of clinical expression of brain pathologies by increasing or maintaining resilience mechanisms. For instance, we have reported on protective factors, such as education (Bennett et al., 2003), participation in cognitive activities (Wilson et al., 2002), social network size (Bennett et al., 2006c), cognitive processing (Boyle et al., 2008), purpose in life (Boyle et al., 2012), and physical activity (Buchman et al., 2019) that contribute to resilience by modifying the association between neuropathology and cognitive decline, i.e., these factors reduce the untoward effects of pathology on cognition. These findings are in line with the hypothesis that compensatory mechanisms in the nervous system might work more efficiently to circumvent insults, thus allowing the brain to maintain function despite the accumulation of pathology.

Building on over two decades of foundational work, we aim to fill in current conceptual gaps by (i) conceptualizing resilience as a continuum ranging from detrimental to beneficial, (ii) integrating genomic data to expand the search for further biological drivers of resilience, and (iii) quantifying our proteomic findings to maximize the utility of the resilience concept.

Conceptualizing resilience as a continuum aligns it with many other risk factors

The dichotomous approach to the study of cognitive aging (dementia/no dementia, AD pathology/no AD pathology) has prevailed despite challenges to this approach presented by decades of epidemiological work (Morris, 2005; Howieson et al., 2008; Schneider et al., 2009; Sperling et al., 2011; Wilson et al., 2011; Bennett et al., 2012). Similarly, most studies have examined dichotomous resilience (resilient/not resilient) (Stern et al., 2023). Yet, if we regress out the negative effects of pathology, we can isolate cognitive decline due to pathologies from decline due to other (yet unknown) mechanisms.

This residual approach, better operationalized as a positive (or negative) deviation from the regression line, reflects the average effect of the stressor (pathology) on the rate of cognitive decline. Each individual deviation from each observed outcome gives residuals of cognitive decline, ranging from negative (less resilience) to positive residuals (more resilience). Consequently, some individuals decline at slower rates than expected, while others decline at faster rates. We can see the raw trajectories and model-derived predicted slopes of cognitive decline before (Figures 1A,B) and after (Figures 1C,D) we regress out pathology. Any third factor that is associated with the residuals is a measure of either more or less resilience.

We previously identified a host of "third" factors associated with residual cognitive decline, that can be termed resilience factors. For instance, we found that higher daily physical activity, measured with a wrist-worn sensor, was associated with slower cognitive decline, and lower daily physical activity was associated with faster cognitive decline, even after we regressed out the negative effects of brain pathologies (Buchman et al., 2019). These data provide empiric evidence that daily physical activity may afford cognitive resilience unrelated to brain pathologies (Figures 2A,B).

We have also used biological markers, such as genes and proteins, to identify resilience mechanisms. For instance, Neuritin 1 (NRN1) is associated with slower cognitive decline independent of the effects of neuropathology (Yu et al., 2020; Zammit et al., 2023; Figures 2C,D). NRN1 is a neurotrophic factor, and a hub protein in a module associated with synaptic biology, and which plays an important role in synaptic function and plasticity (Naeve et al., 1997; Ng et al., 2023). Initially discovered as a neuronal activity-dependent synaptic gene product in the dente gyrus of the rat brain (Nedivi et al., 1993), NRN1 promotes axon regeneration by inducing neuritogenesis, arborization, and axonal elongation in the peripheral and central nervous systems (Shimada and Yamagata, 2013; Zhou and Zhou, 2014). The role of NRN1 in the formation of axonal arbors and dendritic branching in regulating neurodevelopment has been extensively reported. It has been associated with cognitive resilience in multiple studies in that higher abundance is associated with slower cognitive decline (Wingo et al., 2019; Yu et al., 2020; Hurst et al., 2023; Zammit et al., 2023). It has also been directly associated with indices of AD pathology (Yu et al., 2020; Hurst et al., 2023) in that individuals with higher abundance of NRN1 have less AD pathology. Lastly, there is also evidence that NRN1 mediates the association between cognitive resilience and AD pathology (Hurst et al., 2023). Collective evidence supports the promise of NRN1 as a therapeutic target to enhance synaptic resilience mechanisms in preclinical AD (An et al., 2014; Choi et al., 2014; Hurst et al., 2023; Ng et al., 2023).

Conceptualizing cognitive resilience as a biologic continuum extends current frameworks (Stern et al., 2020, 2023) by going beyond the ability to maintain better-than-expected cognitive function in the presence of brain pathologies to encompass the full spectrum of cognitive resilience. This allows us to identify a larger range of potential modifiable resilience behaviors or lifestyles that

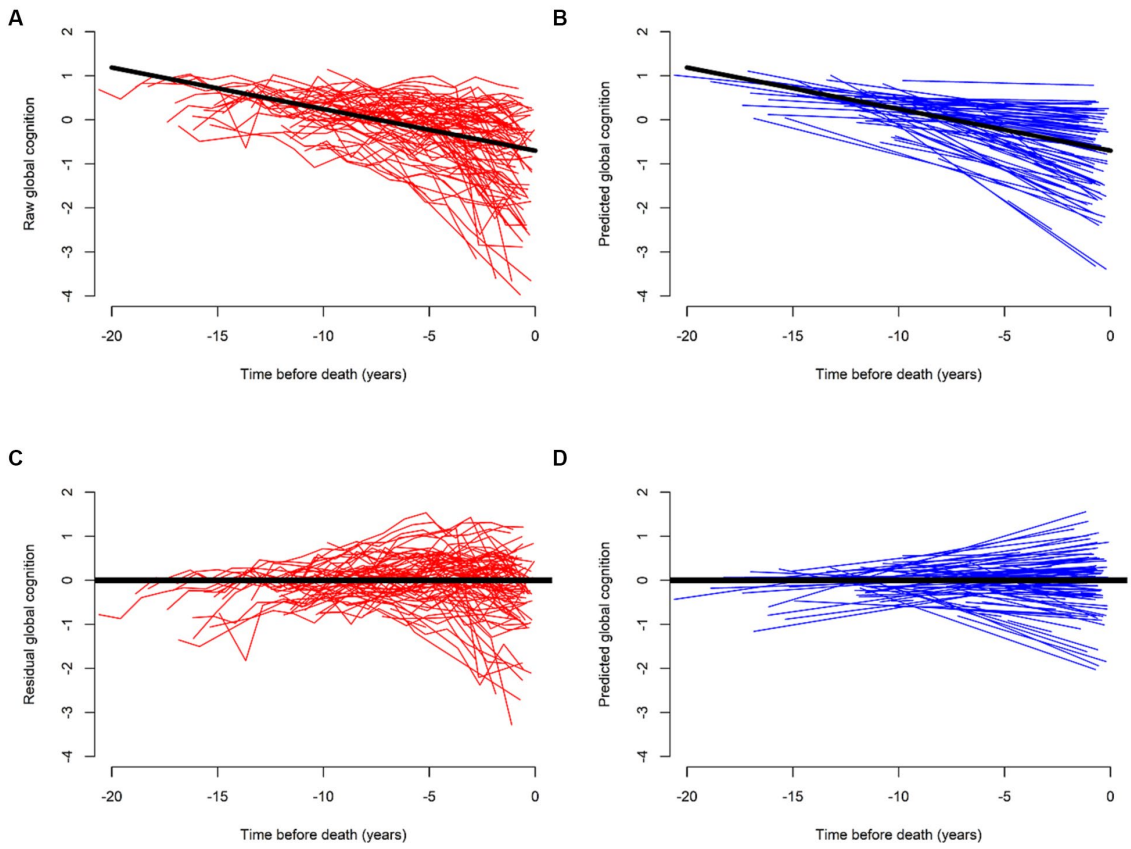

FIGURE 1
Trajectories of cognitive decline before (red) and after (blue) regressing out the effects of common brain pathologies. **(A,C)** Illustrate raw and **(B,D)** model-derived trajectories of cognitive decline for 562 participants. **(A,B)** Illustrate their trajectories without terms for brain pathologies. (**C,D)** Show reduced steepness of the slopes of cognitive decline as compared to **(A,B)**. This flattening, or improvement highlights the residual of cognitive decline after we regress out the effects of brain pathologies. Further modeling of residual cognitive decline with proteome can identify cognitive resilience proteins associated with cognitive decline that are unrelated to brain pathologies. We used data from ROS and MAP participants to generate this figure specifically for this perspective.

are either associated with slower, or faster rates of cognitive decline, independent of brain pathologies (Bennett et al., 2006c; Wilson et al., 2006, 2007a, 2013, 2014; Boyle et al., 2008, 2012; Buchman et al., 2019). This broader conceptualization of resilience provides more statistical power and more granularity than a dichotomous approach (Yu et al., 2020; Zammit et al., 2022). Further work is needed to identify which resilience lifestyle factors can be modified, or whether combinations of different behaviors can serve as a clinical signature or biomarker, identifying vulnerable older adults with lower-than-average resilience.

While the approach has also been criticized mainly due to the possibility that the residual measure might be correlated with the outcome (Elman et al., 2022), such a scenario would allow us to hypothesize possible unexplained variance between the error and the outcome. It might also be indicative of uncaptured non-linear decline. Despite critiques, the residual approach seems to capture clinical meaningful information about aging, cognitive decline, and the risk of dementia (Bocancea et al., 2021). Alternative solutions to the residual approach have been proposed (Elman et al., 2022), such as testing for effect-modification; however, we use these alternative approaches as validation steps, as we discuss further below. Analytic implementation of the residual method to resilience are likely to continue evolving with technological advancements in statistical modeling.

Identifying biological mechanisms underlying cognitive resilience provides potential therapeutic targets

Discovering genes and proteins widely distributed in the central nervous system, that are likely candidates for the molecular mechanisms underlying cognitive resilience is a crucial first step for drug discovery studies for resilience therapies. Over the past decade, our group and others have applied our operationalization of resilience to different streams of genomic data to advance our understanding of its underlying biology (Wilson et al., 2013; Buchman et al., 2016; Mostafavi et al., 2018; Yu et al., 2018, 2020; Wingo et al., 2019). For instance, in prior work utilizing proteomic data (Wingo et al., 2019), 38 hub proteins associated with cognitive stability after adjusting for pathology were identified; proteins associated with more stability were enriched for higher synaptic function and more mitochondrial activity, while those associated with less stability (more rapid decline) were enriched for inflammatory response, apotosis, and endothelial

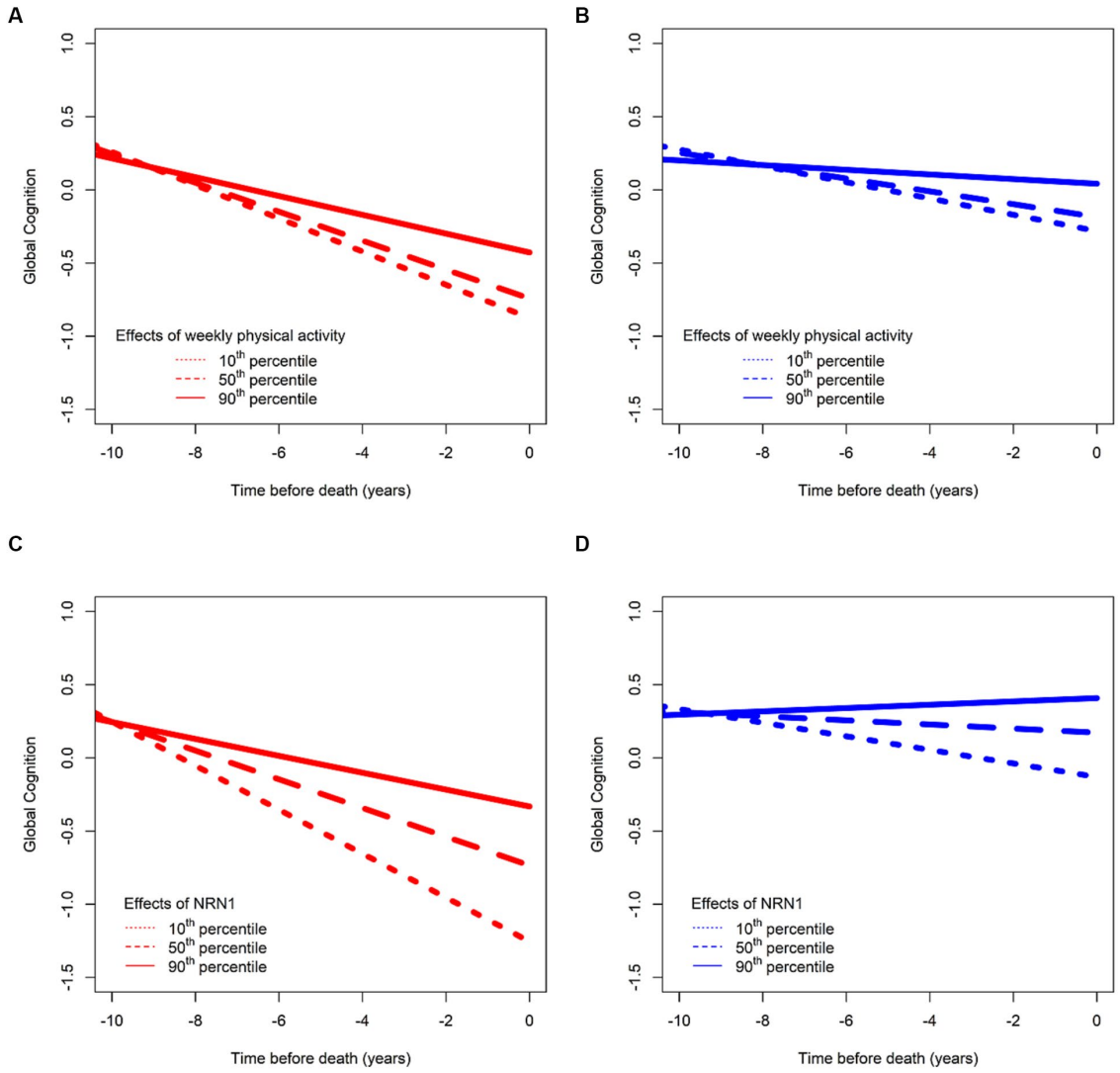

FIGURE 2
Effects of two risk factors on cognitive decline before (in red) and after (in blue) regressing out effects of common brain pathologies. Consistent with the concept that resilience is a continuous measure like other clinical risk factors, we illustrate here associations between total daily physical activities and cognitive decline in **(A,B)**. **(A)** The residual of cognitive function by regressing out age, sex, and education (depicted in red) for an average participant whose total daily physical activity is in the 10th (short dashed line), 50th (long dashed line), and 90th (solid line) percentiles and in **(B)** after further regressing out neuropathological indices (depicted in blue) for the same participant with total daily physical activity being in the 10th (short dashed line), 50th (long dashed line), and 90th (solid line) percentiles, with more activity being associated with higher cognition, and lower activity being associated with lower cognition. Similarly, like clinical risk factors, such as physical activity, we also illustrate the association between a biological resilience factor as a continuum (the protein NRN1) and its associations with cognitive decline after regressing out age, sex, and education **(C)** and after further regressing out neuropathological indices **(D)**, with a higher level of the proteins being associated with slower cognitive decline. We used data from ROS and MAP participants to generate this figure specifically for this perspective.

function in glial cells. Co-expression network analysis of these hub proteins showed that largest modules with strongly expressed proteins relating to more cognitive stability were enriched for synaptic abundance and mitochondrial activity higher cognitive stability, while modules containing expressed proteins associated with less stability were enriched for apotosis, myelination, and inflammatory response. Overall, these findings lend support for subsequent work in ROSMAP cohorts that has aimed to identify cortical resilience proteins and explicate their underlying mechanisms.

In a recent proteome-wide study we examined the association of over 8,000 proteins from the dorsal lateral prefrontal cortex. We regressed out the effects of 10 ADRD pathologies on the slope of global cognitive decline. We identified 8 proteins (NRN1, ACTN4, EPHX4, RPH3A, SGTB, CPLX1, SH3GL1, UBA1) that remained associated with cognitive resilience (Yu et al., 2020). Consistent with the idea that resilience is a continuum, higher levels of 7 of these cognitive resilience proteins and a lower level of UBA1 were associated with a slower rate of cognitive decline. More recently we extended these results in a larger sample size and identified 47 proteins that are either commonly or specifically associated with five different cognitive abilities (Zammit et al., 2023). Supplementary Table S1 shows the full list of identified proteins. Gene ontology enrichment analyses showed that the majority of the resilience proteins associated with slower cognitive decline were enriched for mitochondrial and synaptic

plasticity, which is supportive of prior work in other smaller cohorts which found similar pathways for proteins that are higher-abundance in cognitive stability independent of AD pathologic indices (Wingo et al., 2019). In addition, this work also provided evidence for both shared and distinct biological pathways associated with resilience in specific cognitive abilities. For instance, proteins associated with higher resilience in episodic memory were enriched for mitochondrial translation, while proteins associated with higher resilience in working memory were enriched in the prevention of the translation of mRNA into potentially harmful proteins (Zammit et al., 2023). Mitochondria are organelles that under the form of ATP molecules provide cellular energy for almost all processes from cell survival to death; in neurons, mitochondria are crucial for regulating and maintaining synaptic transmission, plasticity and neurotransmitter synthesis. Messenger RNAs on the other hand, are single-stranded molecules of RNA that are involved in the process of synthesizing proteins in the cytoplasm; they play a fundamental role in regulation of gene expression. Both enrichment of mitochondrial translation and regulation of mRNA translation have been implicated in AD (Liang et al., 2008; Reddy and Beal, 2008; Wingo et al., 2019; Ghosh et al., 2020; Rybak-Wolf and Plass, 2021); however, their differential role in specific cognitive abilities is largely unexplored and an area for potential future research.

More recently, we extended our proteomic studies of resilience to glycoproteomics. The study of glycoproteomics expands the potential to identify the mechanisms underlying cognitive resilience. A glycopeptiform is a protein that has one or more glycans attached to it. The addition of glycans to a protein is the most common post-translational modification in the brain. Glycan composition and its location on a protein can affect protein structure and function. Our recent glycoproteome-wide study of the DLPFC identified 8 glycopeptiforms associated with cognitive resilience; higher levels of four glycopeptiforms were associated with slower rates of cognitive decline and higher levels of another four were associated with a faster rate of cognitive decline (currently under review). These latter findings remained significant when controlling for the parent proteins. These findings suggest that glycopeptiforms derived from post-translational protein modification have a separate association with cognitive resilience after controlling for the parent protein. These results lend support that our residual approach can be extended to studies of other streams of genomic data to identify additional mechanisms underlying cognitive resilience in older adults.

Resilience mechanisms can be quantified on a person-specific level

To leverage the potential therapeutic benefits of novel interventions or lifestyle changes that may afford resilience it will be necessary to develop instruments that can quantify some of the mechanisms driving resilience in the community or outpatient clinic settings so healthcare professionals can identify adults at risk of cognitive impairment to guide appropriate interventions. Efforts leveraging omics reviewed above highlight the need for an approach that can aggregate the varied effects of many molecular mechanisms, such as cortical proteins, likely to underlie cognitive resilience. In other clinical areas, risk scores have been used to aggregate the additive risks of multiple genes or clinical risk factors (Wolf et al., 1991; Desikan et al., 2017).

We have assessed the feasibility of developing a resilience index based on many resilience proteins that might be able to classify adults with higher- or lower-than-average resilience. We used a quantitative targeted protein pipeline (i.e., selective reaction monitoring) which enables large-scale, lower-cost measurement of 226 specific proteins, and leveraged data from 1,192 older decedents. We modeled cognitive decline using a global composite score and controlled for the effects of neuropathologic indices. We identified 52 proteins that were associated with residual cognitive decline, i.e., independent of the effects of neuropathologic indices. While 31 proteins were associated with less decline (more resilience), 21 were associated with steeper decline (less resilience) (Supplementary Figure S1A). A full list of the proteins can be found in Supplementary Table S2. We then aggregated the expression levels of these resilience proteins into a person-specific cognitive resilience index, allowing us to not only quantify resilience based on the expression of these proteins on a person-specific level but also to study it as a continuum, as discussed above (Supplementary Figure S1B). A higher level of the index was associated with a lower burden of postmortem AD pathology and was also associated with a 30% reduction in the detrimental effects of AD pathology on dementia proximate to death.

The cognitive resilience index constructed from many proteins was not specific for cognitive resilience and was also associated with other non-cognitive aging phenotypes including less decline in motor function and less severe parkinsonism. Supplementary Figure S2 highlights that while most of the proteins used to construct the cognitive resilience index are specific for cognitive resilience, about 30% of the proteins included in the cognitive resilience index also provide resilience to motor phenotypes. This emphasizes that resilience proteins can be pleiotropic and provide resilience for multiple phenotypes. This may explain the broad range of health benefits afforded by resilience factors.

Using varied analytic approaches, these studies have identified three potential molecular mechanisms that can provide cognitive resilience. First, proteins can be associated with clinical traits independent of brain pathologies (identified using the residual approach). Second, proteins can interact with brain pathologies to attenuate or modify their negative association with clinical traits (using effect-modification). Third, proteins can directly affect the level of ADRD pathologies (also referred to as resistance in some studies; Bocancea et al., 2021). Our results for the constructed resilience index are summarized in Figure 3. These results suggest the feasibility of aggregating molecular drivers of resilience into a continuous index for the development of a clinical instrument that may be able to identify older adults at risk, who might benefit from resilience therapies to maintain cognition and other important aging traits. As the index was developed from omics obtained in decedents, this work will need to be translated into an index that can be employed in living adults to maintain cognition and brain health. While translational work is challenging, we recently developed AD imputation models, specifically trained to predict postmortem AD pathology in living adults by using clinical information up to 8 years before death (Yang et al., 2023). Such work can be extended to the resilience space. We also linked pathology and omic data to brain imaging and are currently extending that approach to the resilience space (Yu et al., 2017; Gaiteri et al., 2019; Makkinejad et al., 2021). Finally, we recently generated subpopulations with brain omic data and projected that to monocyte RNAseq data (Iturria-Medina et al., 2022). Overall, this is a challenge which we and

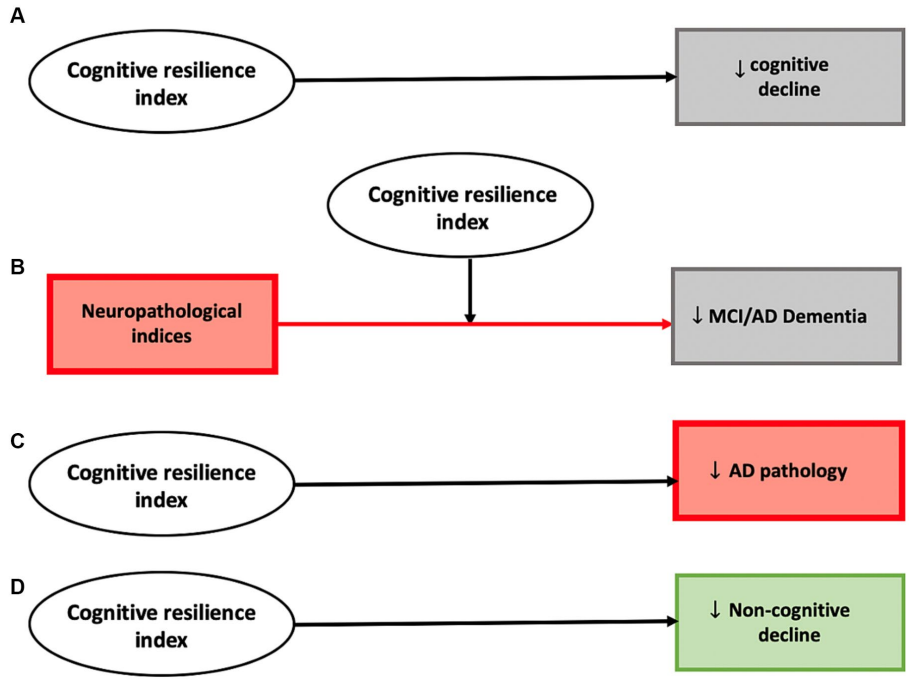

FIGURE 3
Analyses employing the constructed cognitive resilience index highlights several potential mechanisms through which cortical proteins can provide cognitive resilience. A higher cognitive resilience index derived from proteomic data demonstrated evidence for a direct negative association with cognitive decline **(A)**, modified the association between neuropathological indices and cognitive phenotypes including diagnoses of mild cognitive impairment and AD dementia **(B)**, was negatively associated with pathologic AD **(C)**, and was also negatively associated with decline in non-cognitive phenotypes (motor function and parkinsonism) **(D)**.

others are trying to tackle to make brain omic data actionable in living humans.

Resilience therapies may offer a novel approach to maintaining cognition in older adults

Advances in our understanding of brain pathologies have been crucial to the great strides that have been made over the past several decades in our understanding of the underlying biology of late-life cognitive impairment. Yet, despite these advances, nearly all brain pathologies remain untreatable. The studies reviewed above highlight the rapid advances in operationalizing the concept of resilience and explicating its underlying biology. Yet, more importantly, these advances may pave the way for new therapeutic options for late-life cognitive and physical impairments despite the lack of currently available treatments for nearly all brain pathologies.

Recent work suggests that the genetic architecture of resilience is distinct from that of AD dementia related to brain pathologies (Dumitrescu et al., 2020). Considering resilience, instead of brain pathologies, as a therapeutic target, offers a novel paradigm for maintaining cognition and brain health in aging adults via modifiable resilience behaviors and new resilience therapies. Using resilience as a therapeutic target may support cognition even in the presence of the negative cognitive effects of accumulating brain pathologies that are currently untreatable. Moreover, targeting resilience may even have a greater impact on cognitive outcomes than interventions targeting specific pathologies. Indeed, even if therapies are developed for a specific pathology (Mintun et al., 2021; van Dyck et al., 2023), the beneficial effect from treating a single pathology might be minor given the large number of combinations of person-specific burden of mixed-brain pathologies observed in aging brains (Boyle et al., 2018, 2021).

Given the challenges of highly heterogeneous neuropathologic stress and its varied negative effects on cognitive decline and brain health across individuals, it seems more plausible and advantageous to redirect efforts to potential therapeutic interventions unrelated to accumulating pathologies. Hence, advancing the initial studies done to date with further mechanistic and drug discovery studies has potential to catalyze the development of interventions focusing on resilience behaviors or novel drugs that can be deployed to maintain cognition and other vital aging phenotypes even in the presence of aging brains that accumulate untreatable mixed brain pathologies.

Extending the successful approaches employed in these initial studies to a wider range of phenotypes and to more brain regions and tissues outside the brain that support the distributed networks underlying non-cognitive aging phenotypes will expand the therapeutic toolkit available for resilience therapies and eventually lead to personalized and targeted resilience treatments.

Conclusion

Conceptualizing resilience as a continuum aligns it with many other conventional risk factors. This conceptualization has been crucial in quantifying, and operationalizing studies of resilience using

varied analytical approaches that regress out the negative cognitive effects of brain pathologies. Studies analyzing novel streams of genomic data have isolated cognitive resilience unrelated to brain pathologies to identify genes and proteins that degrade or enhance resilience. These varied molecular mechanisms lend additional empirical support for considering resilience as a continuum. All individuals may have some degree of resilience. Some individuals may have more genes and proteins that enhance resilience, yielding higher-than-average function, and some adults may have more genes and proteins that degrade resilience producing vulnerability and lower-than-average resilience. While there are thousands of genes and proteins in the human brain, the molecular mechanisms identified in recent resilience studies provide high-value therapeutic targets for further mechanistic and drug discovery studies that can catalyze new resilience therapies that maintain cognition and brain health in aging adults even in the presence of untreatable brain pathologies.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by the Rush Institutional Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

AZ: Writing – original draft. DB: Writing – review & editing. AB: Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2023.1303912/full#supplementary-material

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The association between closed-eye unipedal standing and the risk of cognitive impairment in the elderly: a 7-year community-based cohort study in Wuhan, China

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Objectives: The prevention of cognitive impairment in the elderly is one of the public health priority areas. However, the relationship between closed-eye unipedal standing and cognitive impairment remains unclear.

Methods: This study was conducted on a group of elderly individuals from a community, using a prospective cohort study design. Participants were monitored for 7 years and were diagnosed with new-onset cognitive impairment. Logistic regression models and restricted cubic spline (RCS) were used to investigate the relationship between closed-eye unipedal standing and cognitive impairment. Stratified analysis by baseline characteristics were also performed.

Results: At baseline, 1,652 people aged 65 years or older were enrolled. Ultimately, 880 participants completed the follow-up and 155 (17.61%) of them satisfied the diagnostic criteria for cognitive impairment at follow-up. Compared to the closed-eye unipedal standing low group as the reference, the middle (OR = 0.601, 95% CI: 0.396–0.911) and high (OR = 0.508, 95% CI: 0.329–0.785) groups had significantly lower cognitive impairment risks. RCS analysis indicated a linear relationship ($P_{non-linear}$ = 0.177), with a reduced risk of developing cognitive impairment when the duration of closed-eye unipedal standing was exceeded ~2.920 s. Stratified analysis showed that for female, aged 70 years or younger, with 3 or more years of education, without lack of exercise and without falls within 1 year subgroup, the elderly in the high group of closed-eye unipedal standing had significantly reduced cognitive impairment risks.

Conclusion: Among the elderly population, closed-eye unipedal standing duration was linearly and negatively associated with the cognitive impairment risk. The closed-eye unipedal standing duration might be a predictive index for cognitive impairment in the elderly.

KEYWORDS

cognitive impairment, closed-eye unipedal standing, cohort study, restricted cubic spline, the elderly

1 Introduction

Cognitive impairment is characterized by a decline in one or more cognitive abilities due to various causes, such as reduced language skills, memory loss or even severe dementia, and other psychiatric disorders (Koder, 1998; American Psychiatric Association, 2013; Hu et al., 2021). In China, more than 360,000 people are diagnosed with cognitive impairment each year (Pu et al., 2023), and it is estimated that the total number of people with cognitive impairment in China will reach up to 48.68 million by 2060 (Prince et al., 2016). With the extension of the population's life expectancy, the number of individuals experiencing cognitive impairment has dramatically increased. The prevalence of mild cognitive impairment among Chinese individuals aged 60 years or older is ∼14.71%. Furthermore, the annual transition rate from cognitive impairment to dementia is reported to be in the range of 10–30%, which is much higher than that in the elderly individuals with normal cognitive function (1–3%) (Jia et al., 2020). The prevention of cognitive impairment in the elderly is one of the public health priority areas.

The existing evidence for the elderly indicates that physical inactivity is a specific potential variable risk factor that can promote the development of cognitive impairment (Sabia et al., 2017; Livingston et al., 2020). Approximately 3% of cognitive impairment can be prevented by increased physical activity (Li, 2013; Lourenco et al., 2018; Livingston et al., 2020). Given the current dearth of effective treatments for cognitive impairment, identifying potential risk factors for cognitive impairment and dementia, especially those that can be modified such as physical activity, is an effective way to prevent cognitive decline.

In the absence of any visual reference, closed-eye unipedal standing relies solely on the balance receptors in the vestibular organ of the brain and the coordinated movement of the muscles throughout the body to maintain the center of gravity with a single foot supported (Springer et al., 2007). The duration of closed-eye unipedal standing is an important indicator of physical fitness for the elderly (Büchel et al., 2021). During closed-eye unipedal standing, the combined action of the vestibular system and proprioceptors plays a crucial role. The vestibular system is responsible for sensing acceleration and angular changes in the head to maintain balance (Henry and Baudry, 2019). Additionally, the proprioceptors provide important inputs for balance control by sensing information about the body's joint angles, muscle tone, and skin contact (Martínez-Amat et al., 2013). The prefrontal cortex of the brain is involved in regulating attention, somatic movements, and executive functions. Recent studies have shown that single-leg standing can activate the prefrontal cortex to improve cognitive performance (Sugihara et al., 2021). In addition, Morenilla et al. (2020) concluded that balance or cognitive performance decreased in older adults when a cognitive task was performed simultaneously with a postural control task (i.e., dual-task paradigm). Vellas et al. (1997) found that participants with abnormal balance in single-leg standing also scored worse on subjective health status, humor, and neurocognitive function. These evidences imply that common areas of the brain may be used for postural control and cognition. Without the aid of visual sense, closed-eye unipedal standing can accurately measure the relationship between postural control and cognitive function. It is rational to hypothesize that the duration of closed-eye unipedal standing might be a predictive index of cognitive impairment.

Therefore, we conducted a community-based cohort study among the elderly to investigate the relationship between closed-eye unipedal standing and the risk of cognitive impairment by tracking participants over a 7-year period. Optimizing the duration of closed-eye unipedal standing to prevent cognitive impairment may help in obtaining the maximum benefit.

2 Methods

2.1 Study population

Our study was a community-based prospective cohort study fousing on elderly individuals aged ≥ 65 years. In October 2015, a total of 2,101 participants were interviewed in Wuhan, Hubei Province, Central China, using a multistage stratified random sampling method. First, seven districts were randomly selected from the 17 districts in Wuhan City. Then, in each district, three to five communities were randomly recruited. In each community, 60–100 participants were randomly recruited through the Elderly Health Management Information System in Wuhan City, Hubei Province. The study staff, consisting of community doctors and nurses, were trained to use a uniform questionnaire and standardized survey terminology to collect baseline and follow-up data. At baseline, all participants self-reported their demographic characteristics and medical history (gender, age, height, weight, smoking status, years of education, and cardiovascular and cerebrovascular disease), and were required to complete the closed-eye unipedal standing test and the Mini-Mental State Examination (MMSE) test. The exclusion criteria included participants who (1) lost the ability to live on one's own, (2) were unable to complete the closed-eye unipedal standing test, (3) had been previously diagnosed by doctor with cognitive impairment or dementia, (4) failed to complete the MMSE test, or the baseline MMSE test suggested cognitive impairment, and (5) had other disorders that may affect cognitive function or closed-eye unipedal standing (e.g., epilepsy, lumbar disorders, diabetes neuropathy, Parkinson's disease, intracranial trauma, or surgery). Finally, 1,652 participants were included in our baseline study (Figure 1).

Studies involving participants were reviewed and approved by the institutional review board of Wuhan University of Science and Technology (Reference Number: 2023120). All participants provided written informed consent for their participation. The study was conducted in accordance with the Declaration of Helsinki guidelines.

2.2 Follow-up

The follow-up survey was conducted 7 years after the baseline in March 2023 in the same manner as the baseline examination. With 592 lost to follow-up and 180 deaths, 880 participants were finally included in this study. The mortality data were obtained

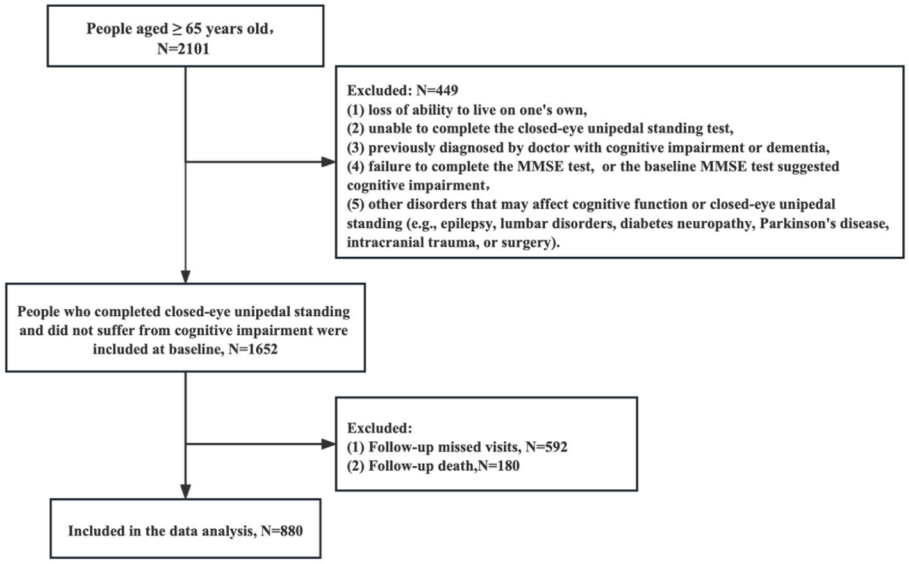

FIGURE 1
A flow chart of participant selection for this study.

from the Wuhan Death Surveillance System. Missing visitors were defined as those whose whereabouts were not known after at least three home searches, telephone contacts, or contact with community workers.

2.3 Cognitive assessment

The MMSE test was used to screen cognitive impairment at baseline and follow-up (Pangman et al., 2000; Arevalo-Rodriguez et al., 2015). The Chinese version of the MMSE assessment was administered by trained community doctors and nurses. The MMSE measures the level of cognition in the following aspects: (1) Temporal and spatial orientation: 10 points; (2) Immediate memory: 3 points; (3) Recall: 3 points; (4) Attention: 5 points; (5) Language: 8 points; (6) Visual space: 1 point. The MMSE scores range from 0 to 30, with higher scores indicating higher levels of cognition. In the Chinese population, cognitive impairment was defined as an MMSE score $\leq$ 17 for those with no education, $\leq$20 for those with 1–6 years of education, or $\leq$24 for those with $\geq$7 years of education (Guo et al., 1988; Jia et al., 2021).

2.4 Closed-eye unipedal standing test

The closed-eye unipedal standing can test a participant's balance strength (Yoshimoto et al., 2016; Büchel et al., 2021). Using a standard stopwatch, participants were allowed to stand naturally or with their arms crossed and eyes closed, standing on one foot with the customary foot and the other leg bent at the knee with the foot off the ground so that the lower leg rested against the knee of the standing leg. The timer was set when the off-ground foot leaves the ground, and the meter was stopped when the off-ground foot hits the ground or the standing foot moves, and the time of standing on one foot with eyes closed was calculated (Rikli and Jones, 2012). Finally, the test was conducted three times, and the average of the three tests was calculated.

2.5 Definition of covariates

Covariates consisted of participant's baseline demographic characteristics (age, gender, education, height, weight), health status (hypertension, hyperlipidemia, diabetes, cerebrovascular accident, coronary artery disease, eye and ear disease), and health-related behaviors (smoking status and physical exercise) at baseline. Hypertension, hyperlipidemia, diabetes, cerebrovascular accidents, and coronary artery disease were determined by the question (Do you have a chronic disease diagnosed by a doctor?). Eye and ear diseases were determined by self-reported data and were dichotomous variables. Lack of physical exercise was defined as engaging in moderate-intensity exercise less than three times per week, with each session lasting <30 min. Smoking was defined as having smoked within the past month, and falls were defined as having fallen within the last 1 year.

2.6 Statistical analysis

All analyses were conducted using R (Version 4.2.1) and SPSS (version 26.0) software. Continuous variables were described as mean $\pm$ standard deviations (SDs). Categorical variables were expressed by counts and percentages. The elderly were divided into the following three groups according to the tertiles (33.33 and 66.67% digits) of the duration of closed-eye unipedal standing: <2 s, low group (lowest tertile); 2–4 s, middle group (middle tertile); and $\geq$4 s, high group (highest tertile). One-way ANOVA

TABLE 1 Baseline based on closed-eye unipedal standing participant characteristics.

Characteristics	All (n = 1,652)	Closed-eye unipedal standing			P
		Low group (n = 652)	Middle group (n = 528)	High group (n = 472)	
MMSE Score in 2015	26.89 ± 2.78	26.03 ± 3.10	27.30 ± 2.46	27.64 ± 2.30	**<0.001**
Age (years)	72.09 ± 4.81	73.25 ± 5.48	71.38 ± 4.12	71.30 ± 4.17	**<0.001**
Male (n, %)	902 (54.60)	331 (50.77)	298 (56.44)	273 (57.84)	**0.037**
Education (years)	3.61 ± 2.80	3.27 ± 2.84	3.70 ± 2.73	3.97 ± 2.79	**<0.001**
Height (cm)	161.19 ± 8.01	160.23 ± 7.97	161.90 ± 7.95	161.73 ± 8.02	**<0.001**
Weight (kg)	63.95 ± 10.72	63.50 ± 10.73	64.07 ± 10.63	64.43 ± 10.81	0.336
BMI (kg/m^2)	24.58 ± 3.59	24.72 ± 3.75	24.40 ± 3.40	24.60 ± 3.59	0.299
Waist circumference (cm)	87.91 ± 9.84	89.14 ± 10.27	87.66 ± 9.02	86.49 ± 9.93	**<0.001**
Hip circumference (cm)	96.82 ± 8.49	97.10 ± 8.73	97.03 ± 7.77	96.19 ± 8.90	0.162
Diabetes, yes (n, %)	746 (45.16)	266 (40.80)	248 (46.97)	232 (49.15)	**0.013**
Hypertension, yes (n, %)	260 (15.74)	75 (11.50)	92 (17.42)	93 (19.70)	**<0.001**
Hyperlipidemia, yes (n, %)	213 (12.89)	104 (15.95)	61 (11.55)	48 (10.17)	**0.009**
Cerebrovascular accident, yes (n, %)	233 (14.10)	100 (15.34)	68 (12.88)	65 (13.77)	0.469
Coronary artery disease, yes (n, %)	71 (4.30)	38 (5.83)	22 (4.17)	11 (2.33)	**0.017**
Eye and ear diseases, yes (n, %)	526 (31.84)	231 (35.43)	164 (31.06)	131 (27.75)	**0.022**
Smoking, no (n, %)	1,331 (80.57)	537 (82.36)	410 (77.65)	384 (81.36)	0.111
Falls within 1 year, yes (n, %)	164 (9.93)	75 (11.50)	54 (10.23)	35 (7.41)	0.149
Lack of exercise, yes (n, %)	353 (21.37)	181 (27.76)	106 (20.08)	66 (13.98)	**<0.001**

The bold values indicated $P < 0.05$.

and chi-squared tests were used for comparing the differences among these three groups.

Logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) to evaluate the relationship between closed-eye unipedal standing tertiles and cognitive impairment risks (Zhang and Yu, 1998). To rule out the influence of confounding factors, three models were used: unadjusted; adjusted model 1 (adjusted for age, gender, and years of education), and adjusted model 2 (adjusted for age, gender, years of education, lack of exercise, smoking, and diseases such as hypertension, hyperlipidemia, diabetes, cerebrovascular accident, and coronary artery disease). Meanwhile, we used the restricted cubic spline (RCS) method to flexibly model the potential non-linear relationship between the continuous closed-eye unipedal standing duration and the cognitive impairment risk. We set three knots for the RCS analysis considering the sample size, curve smoothing, and reduced precision due to overfitting. The stratified analysis by baseline characteristics (age, gender, education level, whether lack of exercise or not, and whether falls within a year) were also performed. In this study, multicollinearity statistics (tolerance and variance inflation factors) were computed for each logistic regression model and $P < 0.05$ was considered statistically significant.

3 Results

3.1 Basic characteristics of participants

Among the 1,652 participants without cognitive impairment at baseline, the mean age was 72.09 ± 4.81 years, and the mean MMSE score was 26.89 ± 2.78. As presented in Table 1, the average of MMSE scores, age, years of education, height and waist circumference, as well as the distribution of gender, hypertension, hyperlipidemia, diabetes, coronary artery disease, eye and ear disease, and whether they lacked exercise, were significantly different among the low, middle, and high closed-eye unipedal standing groups ($P < 0.05$).

TABLE 2 Participant characteristics based on cognitive impairment at follow-up.

Characteristics	All ($n = 880$)	Cognitive impairment ($n = 155$)	Normal cognition ($n = 725$)	P
Age (years)	78.34 ± 4.21	79.26 ± 4.67	78.14 ± 4.09	**<0.001**
Male (n, %)	465 (52.84)	73 (47.10)	392 (54.07)	0.114
Education (years)	3.76 ± 2.79	4.59 ± 3.20	3.60 ± 2.67	**<0.001**
Height (cm)	161.25 ± 7.93	159.05 ± 8.68	161.73 ± 7.68	**<0.001**
Weight (kg)	64.13 ± 10.61	62.49 ± 9.97	64.48 ± 10.73	**0.027**
BMI (kg/m^2)	24.64 ± 3.66	24.73 ± 3.78	24.62 ± 3.63	0.754
Waist circumference (cm)	87.71 ± 9.73	87.47 ± 9.72	87.77 ± 9.74	0.730
Hip circumference (cm)	96.66 ± 8.35	96.59 ± 8.26	96.68 ± 8.37	0.908
Diabetes, yes (n, %)	394 (44.77)	75 (48.39)	319 (44.00)	0.319
Hypertension, yes (n, %)	145 (16.48)	25 (16.13)	120 (16.55)	0.898
Hyperlipidemia, yes (n, %)	109 (12.39)	24 (15.48)	85 (11.72)	0.197
Cerebrovascular accident, yes (n, %)	109 (12.39)	15 (9.68)	94 (12.97)	0.259
Coronary artery disease, yes (n, %)	29 (3.30)	4 (2.58)	25 (3.45)	0.583
Eye and ear diseases, yes (n, %)	269 (30.57)	44 (28.39)	225 (31.03)	0.516
Smoking, no (n, %)	715 (81.25)	127 (81.93)	588 (76.97)	0.810
Falls within 1 year, yes (n, %)	83 (9.43)	10 (6.45)	73 (10.07)	0.225
Lack of exercise, yes (n, %)	197 (22.39)	47 (30.32)	150 (20.69)	**<0.001**
Closed-eye unipedal standing				
Low group (n, %)	344 (39.09)	79 (50.97)	265 (36.55)	**0.003**
Middle group (n, %)	270 (30.68)	41 (26.45)	229 (31.59)	
High group (n, %)	266 (30.23)	35 (22.58)	231 (31.86)	

The bold values indicated $P < 0.05$.

3.2 Basic characteristics of participants between the cognitive impairment group and the normal group

After 7 years of follow-up, 880 elderlies were included. Among them, 155 (17.61%) participants satisfied the diagnostic criteria for cognitive impairment. As presented in Table 2, the cognitive impairment group was older, had higher education level, and lower height and weight than the normal cognitive group ($P < 0.05$). Significant differences were found between the two groups in terms of lack of exercise (30.32 vs. 20.69%, $P < 0.001$). The elderly in the low closed-eye unipedal standing tertile had a higher prevalence of cognitive impairment compared to the middle and high groups ($P < 0.01$).

3.3 The relationship between closed-eye unipedal standing and cognitive impairment

The scatterplot between participants' closed-eye unipedal standing time and MMSE scores showed a non-linear relationship, as shown in Supplementary Figure 1. Considering the low group as the reference group, the cognitive impairment risks in the middle (OR = 0.601, 95% CI: 0.396–0.911) and high (OR = 0.508, 95% CI: 0.329–0.785) groups were significantly lower. After adjusting for covariates, results were similar to those before adjustment (Table 3).

To flexibly model and visualize the relationship between continuous closed-eye unipedal standing and the risk of cognitive impairment, we further performed the regression analysis using RCS. The results were consistent with the overall results. Within a short period of closed-eye unipedal standing of ~2.920 s, there was no protective effect on reducing the risk of cognitive impairment in older adults, and the risk of cognitive impairment gradually decreased as the duration of closed-eye unipedal standing increased ($P_{non-linear} = 0.177$) (Figure 2).

3.4 Stratified analysis of the association between closed-eye unipedal standing and cognitive impairment

Figure 3 illustrates the stratified analysis of the association between closed-eye unipedal standing groups and cognitive impairment risk by gender, age, years of education, whether lack of exercise or not and whether falls within 1 year. The results showed that for women, ≤70 years old, with ≥ 3 years of education, without lack of exercise and without falls within 1

TABLE 3 Association between closed-eye unipedal standing and cognitive impairment.

	B	S. E	Wald	*P*	OR	95% CI for OR	
						Lower	Upper
Unadjusted							
Low group	Ref				Ref		
Middle group	−0.510	0.213	5.753	**0.016**	0.601	0.396	0.911
High group	−0.677	0.222	9.285	**0.002**	0.508	0.329	0.785
Model 1							
Low group	Ref				Ref		
Middle group	−0.493	0.227	4.716	**0.030**	0.611	0.391	0.953
High group	−0.639	0.234	7.475	**0.006**	0.528	0.334	0.834
Model 2							
Low group	Ref				Ref		
Middle group	−0.452	0.231	3.828	**0.050**	0.636	0.404	1.000
High group	−0.600	0.240	6.255	**0.019**	0.568	0.354	0.911

Model 1: adjusted for age, gender, and education.
Model 2: adjusted for age, gender, education, height, weight, diabetes, hypertension, hyperlipidemia, cerebrovascular accident, coronary artery disease, smoking, falls within 1 year, and lack of exercise.
The bold values indicated $P < 0.05$.

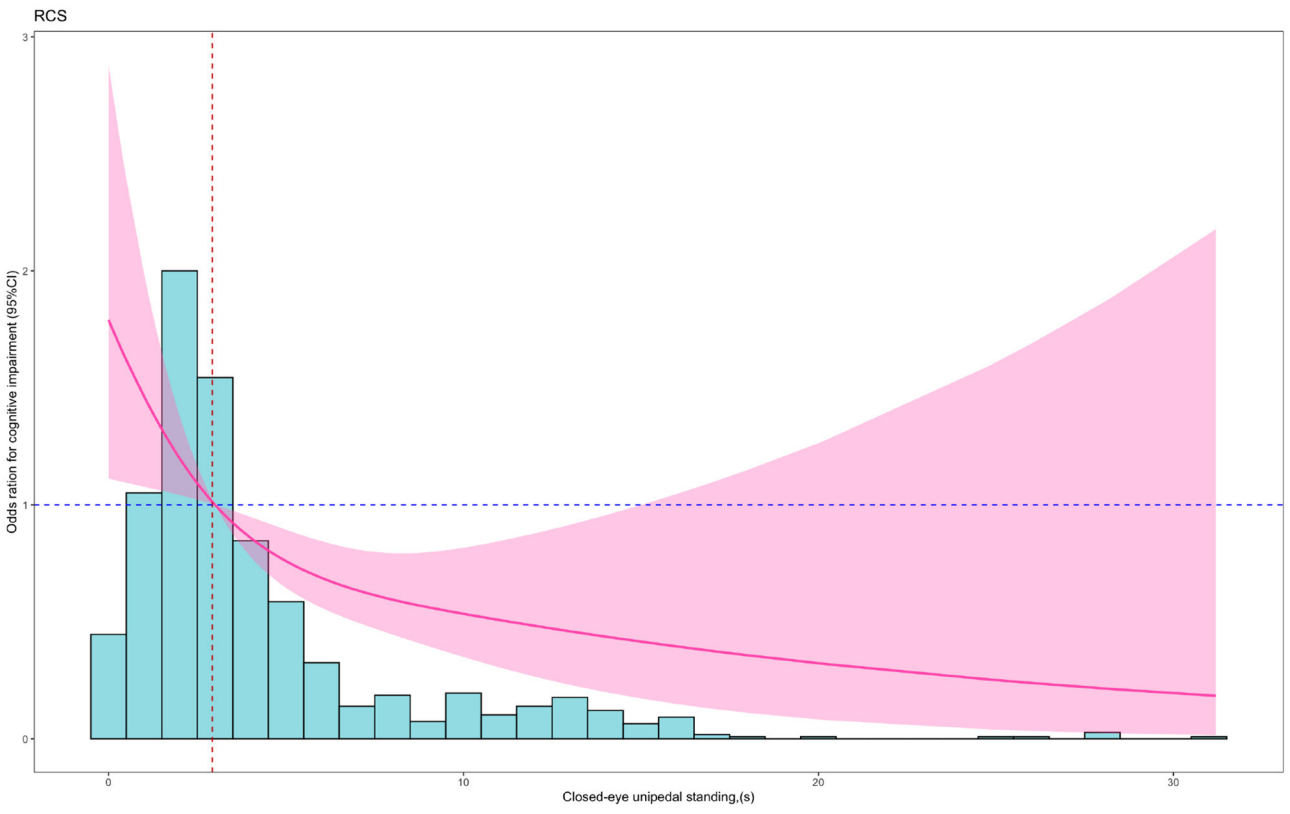

FIGURE 2
RCS plot of the association between closed-eye unipedal standing and cognitive impairment. Red solid lines showed the odds ratios, and red shading showed the 95% confidence interval. The analysis was adjusted for age, sex, education, height, weight, diabetes, hypertension, hyperlipidemia, cerebral stroke, coronary artery disease, and lack of exercise.

year subgroup, the participants with the high group of closed-eye unipedal standing exhibited a significant decrease in the cognitive impairment risk. However, there were no statistically significant associations between the middle group of closed-eye unipedal standing and cognitive impairment risk in any of the different subgroups.

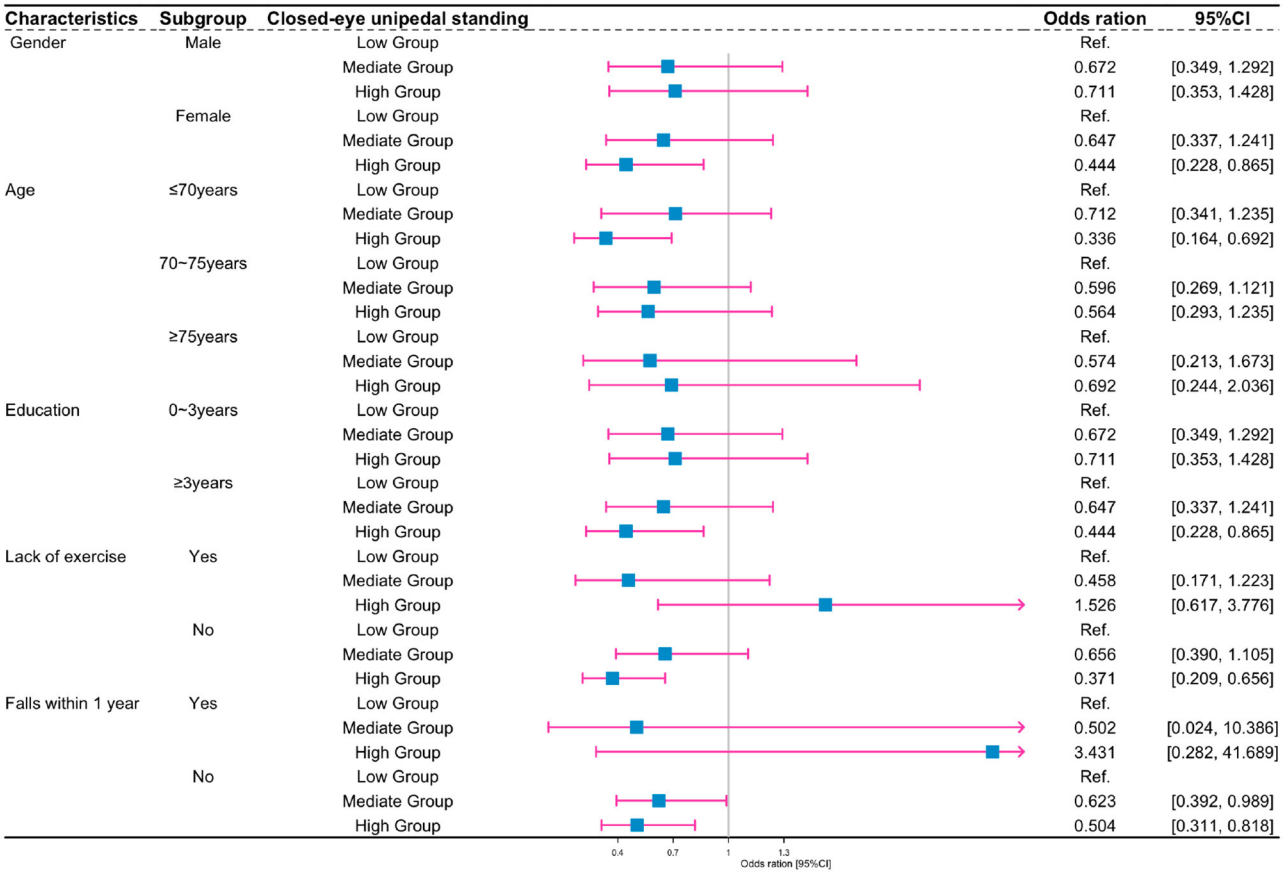

FIGURE 3
Subgroup analysis of the association between closed-eye unipedal standing and cognitive impairment according to participant characteristics. **Gender group:** adjusted for age, education, height, weight, diabetes, hypertension, hyperlipidemia, cerebrovascular accident, coronary artery disease, smoking, falls within 1 year, and lack of exercise. **Age group:** adjusted for gender, education, height, weight, diabetes, hypertension, hyperlipidemia, cerebrovascular accident, coronary artery disease, smoking, falls within 1 year, and lack of exercise. **Education group:** adjusted for age, gender, height, weight, diabetes, hypertension, hyperlipidemia, cerebrovascular accident, coronary artery disease, smoking, falls within 1 year, and lack of exercise. **Lack-of-exercise group:** adjusted for age, gender, education, height, weight, diabetes, hypertension, hyperlipidemia, cerebrovascular accident, coronary artery disease, smoking, and falls within 1 year. **Falls-within-1-year group:** adjusted for age, gender, education, height, weight, diabetes, hypertension, hyperlipidemia, cerebrovascular accident, coronary artery disease, smoking, and lack of exercise.

4 Discussion

To the best of our knowledge, the relationship between closed-eye unipedal standing and the risk of cognitive impairment was explored for the first time in the Chinese elderly population. By following up on participants for 7 years, we found that the cognitive impairment risks in middle and high closed-eye unipedal standing groups were significantly lower. Furthermore, the results of the RCS analysis indicated that, when the duration exceeded ~2.920 s, the risk of cognitive impairment in the elderly decreased with increasing duration of closed-eye unipedal standing. These relationships remained significant after adjusting for confounders.

After 7 years of follow-up, the follow-up rate of the elderly was only 53.27%, which might limit the extrapolation and accuracy of our results. The reasons for missing follow-up included elderly individuals relocating with their offspring, death, or unwillingness to visit the hospital or accept the doctor's visit due to coronavirus disease (COVID-19), and so on. Finally, the incidence rate of cognitive impairment in the elderly was 17.61%. In the Chinese Longitudinal Healthy Longevity Survey (CLHLS), Zhang et al. (2022) found that, after 3 years of follow-up, 14.4% were diagnosed with cognitive impairment, which is lower than that observed in this study, possibly because the diagnostic criteria for cognitive impairment (MMSE scores <24) were different and the follow-up interval years were shorter.

During closed-eye unipedal standing, cooperative work of multiple physiological systems is essential. Among these, the neurological system relies on intrinsic sensations, such as proprioceptors and the vestibular system, to visualize the position and movement of the body. Simultaneously, the muscle system and articulations perform an essential role in maintaining the body's stability by adjusting muscle tensions (Serra-Añó et al., 2015; Afschrift et al., 2021). Existing evidence suggests that controlling body posture can improve cognitive performance by stimulating the corresponding functional areas of the brain (Henry and Baudry, 2019). It can be speculated that closed-eye unipedal standing may

be much difficult for people with cognitive impairment. This is because they might struggle to effectively perceive their body's position and posture, thereby facing difficulties in making timely adjustments to maintain balance.

Our results showed that, when compared with the low tertile group, the risk of cognitive impairment was 0.601 and 0.508 times higher in the middle and high closed-eye unipedal standing tertile groups, respectively. The RCS results also indicated that higher closed-eye unipedal standing duration was protective against the risk of cognitive impairment in older adults. In spite of reaching a certain duration, the CI included 1, which might be due to a potentially insufficient sample size combined with other confounding factors, such as dietary habits. Similarly, many researchers, such as Rolland et al. (2009) and Tabara et al. (2015), have shown that the single-leg balance standing test can predict cognitive decline in the elderly, possibly due to parietal and hippocampal dysfunction which can lead to memory loss and visual orientation deficits. Sugihara, on the other hand, revealed that activation of the left and right prefrontal cortex was observed during one-legged standing in the absence of a cognitive function task; however, this activation was altered in aging, cognitive impairment, and Parkinson's syndrome subjects (Sugihara et al., 2021). Hence, the closed-eye unipedal standing duration might be a predictive index for cognitive impairment in the elderly.

Furthermore, the histogram in our study showed that the majority of the elderly performed the closed-eye unipedal standing at a lower level. Previous studies have concluded that intensive practice of closed-eye unipedal standing may help activate and improve areas of the brain associated with balance and spatial cognition, thereby facilitating connections and information transfer between neurons (Bustillo-Casero et al., 2017; Papegaaij et al., 2017). Involving the elderly in exercise to improve balance and lower limb muscle strength to prolong closed-eye unipedal standing may be helpful to delay the development of cognitive impairment. Hence, the closed-eye unipedal standing, being a simple and adaptable method, can serve as a predictive index for cognitive impairment in the elderly. Additionally, it might also be considered an intervention method to prevent cognitive dysfunction. Further intervention studies are necessary to confirm this hypothesis.

The stratified analysis showed that, after adjusting for confounders, the risk of cognitive impairment in the female elderly was much lower than the male elderly. It is possible that the female elderly individuals are more prone to mood swings, insomnia, irritability and anxiety, which may affect the brain functions to a certain extent (Livingston et al., 2020). In addition, consistent with the previous findings by Ahn and Kim (2023) and Nagata et al. (2023), closed-eye unipedal standing reduces the risk of cognitive impairment in the elderly in the exercise group but not in the lack of exercise group. With increasing age, certain elderly people lose their ability to balance, along with degenerative changes in the brain tissue, such as amyloidosis and demyelination in nerve cells (Lourenco et al., 2018; Omura et al., 2020; Yang et al., 2023). Furthermore, decreased levels of the acetylcholine mediator contribute to reduced brain function, which in turn leads to the possibility that closed-eye unipedal standing may have a lesser impact on the risk of cognitive impairment in people over 75 years of age.

5 Limitations

While this study has important theoretical and practical implications, it also has certain limitations and points to areas for further exploration in the future. First, the rate of loss to follow-up was relatively high. The follow-up assessment was conducted only once. The evolution of the mean cognitive impairment scores over time could not be depicted. Second, the recruited participants were homogeneously aged and sourced from diverse geographical regions within Wuhan City. The definition of cognitive impairment depended only on MMSE scores. Due to sample size limitations, the influence of baseline MMSE scores on the effect of closed-eye unipedal standing duration on the risk of cognitive impairment was not completely excluded. These limitations potentially limited the generalizability of the findings to the broader elderly Chinese population. Finally, the study did not account for all the potential confounding factors, such as diet, sleep, and so on. In the future, we will continue to conduct further rigorous prospective and intervention studies to reveal the relationship and mechanisms between closed-eye unipedal standing and cognitive impairment.

6 Conclusion

Our results showed that, closed-eye unipedal standing in the elderly was linearly and negatively associated with cognitive impairment. The risk of developing cognitive impairment was decreased when the duration of closed-eye unipedal standing exceeded approximately 2.920 s. The closed-eye unipedal standing duration might be a predictive index for cognitive impairment in the elderly. Further intervention studies are necessary to confirm the protective effects and mechanisms of closed-eye unipedal standing on cognitive impairment in the elderly.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Institutional Review Board of Wuhan University of Science Technology (Number: 2023120). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

SW: Conceptualization, Data curation, Formal analysis, Investigation, Software, Writing – original draft, Writing – review

& editing. PG: Writing – original draft, Writing – review & editing. CH: Software, Writing – review & editing. YZ: Data curation, Writing – review & editing. BX: Investigation, Writing – review & editing. JZ: Data curation, Writing – review & editing. FZ: Data curation, Writing – review & editing. XX: Conceptualization, Writing – review & editing. YG: Data curation, Writing – original draft. MY: Conceptualization, Investigation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2024.1308151/full#supplementary-material

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Repetitive transcranial magnetic stimulation regulates effective connectivity patterns of brain networks in the spectrum of preclinical Alzheimer's disease

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Objectives: Subjective cognitive decline (SCD) and amnestic mild cognitive impairment (aMCI) are considered as the spectrum of preclinical Alzheimer's disease (AD), with abnormal brain network connectivity as the main neuroimaging feature. Repetitive transcranial magnetic stimulation (rTMS) has been proven to be an effective non-invasive technique for addressing neuropsychiatric disorders. This study aims to explore the potential of targeted rTMS to regulate effective connectivity within the default mode network (DMN) and the executive control network (CEN), thereby improving cognitive function.

Methods: This study included 86 healthy controls (HCs), 72 SCDs, and 86 aMCIs. Among them, 10 SCDs and 11 aMCIs received a 2-week rTMS course of 5-day, once-daily. Cross-sectional analysis with the spectral dynamic causal model (spDCM) was used to analyze the DMN and CEN effective connectivity patterns of the three groups. Afterwards, longitudinal analysis was conducted on the changes in effective connectivity patterns and cognitive function before and after rTMS for SCD and aMCI, and the correlation between them was analyzed.

Results: Cross-sectional analysis showed different effective connectivity patterns in the DMN and CEN among the three groups. Longitudinal analysis showed that the effective connectivity pattern of the SCD had changed, accompanied by improvements in episodic memory. Correlation analysis indicated a negative relationship between effective connectivity from the left angular gyrus (ANG) to the anterior cingulate gyrus and the ANG.R to the right middle frontal gyrus, with visuospatial and executive function, respectively. In patients with aMCI, episodic memory and executive function improved, while the effective connectivity pattern remained unchanged.

Conclusion: This study demonstrates that PCUN-targeted rTMS in SCD regulates the abnormal effective connectivity patterns in DMN and CEN, thereby improving cognition function. Conversely, in aMCI, the mechanism of improvement may differ. Our findings further suggest that rTMS is more effective in preventing or delaying disease progression in the earlier stages of the AD spectrum.

Clinical Trial Registration: http://www.chictr.org.cn, ChiCTR2000034533.

KEYWORDS

subjective cognitive decline, amnestic mild cognitive impairment, repetitive transcranial magnetic stimulation, dynamic causal model, effective connectivity

1 Background

Amnestic mild cognitive impairment (aMCI) is a pre-dementia syndrome marked by declining objective cognitive function declines, while daily life functionality remains intact (Winblad et al., 2004). Subjective Cognitive Decline (SCD) refers to an individual's subjective perception of cognitive decline in the absence of objective impairment on cognitive assessments, and is considered a potential prodromal manifestation of MCI (Rabin et al., 2017). A growing body of research indicates that SCD and aMCI continue to impair brain function and structure and accelerate the progression of Alzheimer's disease (AD) to varying degrees (Mishra et al., 2018; Xue et al., 2019). These observations underscore the notion SCD and aMCI can be considered precursors to AD, sharing underlying therapeutic mechanisms while existing in different pathological states at different stages of the disease (Xue et al., 2019). Given the profound impact of severe cognitive deterioration on an individual's daily life, it is essential to prevent or delay pathological cognitive decline and determine effective treatment options for the spectrum of preclinical AD.

To date, pharmacological interventions have demonstrated limited efficacy in treating AD, necessitating the exploration of other treatments (Livingston et al., 2017). Repetitive transcranial magnetic stimulation (rTMS) is the most widely researched non-invasive brain stimulation technique that has been applied to a variety of psychiatric disorders (Sabbagh et al., 2020). The research indicates that low-frequency rTMS can reduce excitability in the target cortical area, while high-frequency rTMS can enhance excitability in the target cortical area (Maeda et al., 2000). rTMS involves the application of coils to the scalp to modulate underlying brain activity by generating a magnetic field that surrounds cortical neurons, using a strong but brief electromagnetic pulse (George and Aston-Jones, 2010). Previous studies on neuromodulation have confirmed the ability of rTMS acting on the dorsolateral prefrontal cortex (DLPFC) to enhance overall cognitive function and improve clinical performance (Cotelli et al., 2011; Bagattini et al., 2020). Several recent studies have underscored the potential of rTMS targeted at the precuneus (PCUN) to enhance memory and attenuate cognitive decline in preclinical AD (Chen et al., 2017, 2021). The PCUN is a key brain region in AD that undergoes pathological changes 10–20 years before the manifestation of clinical symptoms (Bateman et al., 2012). These alterations include decreased cerebral blood flow (CBF), amyloid deposits, cortical thickness, and functional connectivity (FC) (Ikonomovic et al., 2011; Chen et al., 2017; Thomas et al., 2019). Therefore, it is reasonable to believe that the PCUN is a vulnerable region within the spectrum of preclinical AD, rendering it an ideal target for therapeutic intervention.

Current studies on the spectrum of preclinical AD using functional magnetic resonance imaging (fMRI) mainly focus on the dynamics of brain networks. The default mode network (DMN) and the executive control network (CEN) are the two core brain networks (Chen et al., 2013). The DMN is mainly located in the ventromedial prefrontal cortex and the posterior cingulate cortex. It plays an important role in the self-reference psychological process and social functioning, exhibiting increased activity in internally oriented behaviors (Broyd et al., 2009). In contrast, the CEN is mainly located in the DLPFC and plays an important role in the active maintenance and operation of working memory information, showing increased activity in externally directed behaviors (Bressler and Menon, 2010). The FC is an important tool for studying brain networks, measuring internal fluctuations in blood oxygenation level-dependent signals in different brain regions and analyzing the cooperation between different brain regions during rest or task execution (Zhu et al., 2021). Numerous studies have shown changes in the FC of the DMN and CEN, accompanied by changes in cognitive function (Xu et al., 2020; Yuan et al., 2021).

Recent research on the impact of rTMS on brain networks has mostly focused on the changes in FC within these networks (Cotelli et al., 2011; Pilato et al., 2012). However, FC is based on the correlation between the time series of brain regions, thus lacking the ability to provide the directionality of inter-regional brain interactions; hence, it does not represent real "connectivity" (Friston et al., 2003). Therefore, FC cannot accurately map specific changes in brain networks or provide an in-depth understanding of changes in brain activity.

Effective connectivity is mostly model-based, and it partially addresses the limitations of traditional data analysis by elucidating the causal effects among brain regions and emphasizing the direction of action of these interactions. Among all the effective connectivity methods, the dynamic causal model (DCM) shows superior performance in neuronal coupling modeling (Friston, 2009). Initially designed for task-state fMRI, DCM was subsequently adapted by Friston et al. (2003) to estimate effective connectivity from resting-state fMRI time series under the smoothness assumption of cross spectra, resulting in the formulation of the spectral dynamic causal model (spDCM). SpDCM constructs a reliable model of coupling neuron states and generates complex cross spectra to measure directional neural effects (Friston et al., 2014). Relevant studies have shown changes in the effective connectivity of brain networks in the spectrum of preclinical AD, and these changes have shown correlations with cognitive function, revealing the potential neural processes in the course of the disease (Chand et al., 2017, 2018). However, it remains unclear whether rTMS interventions can regulate the effective connectivity of brain networks and thus improve cognition.

Therefore, we aimed to validate the hypothesis that PCUN-targeted rTMS could improve cognitive function in the spectrum of preclinical AD by regulating the effective connectivity patterns within brain networks. First, we performed a cross-sectional analysis using spDCM to evaluate the causal interactions within the DMN and CEN

and compared the effective connectivity patterns observed in patients with SCD, aMCI, and healthy controls (HCs) to investigate potential pathological changes in the effective connectivity patterns of brain networks in the spectrum of preclinical AD. In addition, we introduced a PCUN-targeted rTMS intervention, assuming that this treatment might change the effective connectivity patterns of the DMN and CEN networks, thereby improving cognitive function.

2 Methods and materials

2.1 Subjects

The data utilized in this study were obtained from our internal database, Nanjing Brain Hospital-Alzheimer's Disease Spectrum Neuroimaging Project 2 (NBH-ADsnp2) (Nanjing, China), which is continuously updated. For information on NBH-ADsnp2, see Supplementary material. A total of 256 subjects (89 with HC, 75 with SCD, and 92 with aMCI) were initially enrolled in this study. However, 12 participants (3 with HC, 3 with SCD, and 6 with aMCI) with excessive head movements (cumulative translation or rotation >3.0 mm or 3.0°) were excluded from the analysis. Thus, a total of 244 subjects (86 with HC, 72 with SCD, and 86 with aMCI) were finally included in the study. Of these, 10 patients diagnosed with SCD and 11 patients diagnosed with aMCI underwent follow-up rTMS intervention, fMRI, and clinical cognitive data acquisition. The specific inclusion and exclusion criteria for the subjects are described in Supplementary material S1.

2.2 Ethics approval statement

This study was approved by the Human Participants Ethics Committee of the Affiliated Brain Hospital of Nanjing Medical University (No. 2018-KY010-01 and No. 2020-KY010-02). Written informed consent was obtained from all subjects prior to enrolment.

2.3 Neuropsychological assessments

A standardized clinical interview and comprehensive neuropsychological assessment were conducted in this study. The comprehensive neuropsychological assessment was divided into four cognitive domains: episodic memory (AVLT, LMT, and CFT-20-min-DR), information processing speed (DSST, TMT-A, Stoop-A, and Stoop-B), visuospatial function (CFT and CDT), and executive function (TMT-B, Stoop-C, DST-backward, VFT, and Semantic Similarity). Detailed information for each neuropsychological assessment can be found in Supplementary material S2.

2.4 MRI data acquisition

All magnetic resonance imaging (MRI) data were acquired at the Affiliated Brain Hospital of Nanjing Medical University using a 3.0 Tesla Verio Siemens scanner equipped with an 8-channel head coil. Resting-state functional images were acquired when participants were instructed to rest with their eyes open, to not fall asleep, and to not think of anything in particular. The gradient-echo echo-planar imaging (GRE-EPI) sequence included 240 volumes. The parameters were: repetition time (TR) = 2,000 ms, echo time (TE) = 30 ms, number of slices = 36, thickness = 4.0 mm, gap = 0 mm, matrix = 64× 64, flip angle (FA) = 90°, field of view (FOV) = 220 mm × 220 mm, acquisition bandwidth = 100 kHz, and voxel size = 3.4 × 3.4 × 4 mm^3.

High-resolution T1-weighted images were acquired by 3D magnetization-prepared rapid gradient-echo (MPRAGE) sequence. The parameters were: TR = 1,900 ms, TE = 2.48 ms, inversion time (TI) = 900 ms, number of slices = 176, thickness = 1.0 mm, gap = 0.5 mm, matrix = 256 × 256, FA = 9°, FOV = 256 mm × 256 mm, and voxel size = 1 × 1 × 1 mm^3.

2.5 fMRI data preprocessing

All fMRI data were preprocessed using MATLAB 2013b and DPABI software (Yan et al., 2016). As a preliminary step, the first 10 volumes were discarded to reduce the instability of the MRI signal. Subsequently, slice timing correction and head motion correction were performed (Power et al., 2012; Van Dijk et al., 2012). Interscan motion was assessed with translation/rotation, and an exclusion criterion (>3 mm translation and/or > 3° rotation in each direction) was set. The functional image of each subject was aligned with their respective structural image. Next, to spatially normalize the fMRI data, the T1 images were segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) using the Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) algorithm. Then, the functional images were normalized by DARTEL to the MNI space (resampling voxel size, 3 × 3 × 3 mm^3). Finally, spatial smoothing was applied using a Gaussian kernel with a full-width at half maximum of 6 mm^3 to reduce spatial noise. Independent component analysis (ICA) was performed on the pre-processed data. To maintain the independence of the data during the ICA and capture the intrinsic independent components for more accurate analysis results, we refrained from performing covariate removal during the data preprocessing stage.

2.6 Group independent component analysis and regions of interest

The number of independent components in ICA analysis is typically not fixed and depends on the research question and data characteristics. In this study, we employed the informix algorithm available in the Group ICA toolbox[1] to decompose the data into 27 independent components. Subsequently, these components were subjected to spatial correlation analysis against the corresponding network templates provided by Smith et al. (2009) and Xue et al. (2021). According to the results of the correlation calculation, the independent components were sorted, and the components that showed the highest alignment with the DMN and CEN templates were selected for further analysis.

1 http://icatb.sourceforge.net/

After selecting the independent components of the DMN and CEN, we used the XjView toolbox[2] to obtain the peak coordinates of the core regions of the DMN and CEN. Based on the obtained core peak coordinates, a total of 13 ROIs were defined as spheres with a radius of 6 mm in this study. The eight ROIs of the DMN were: the PCUN, bilateral ANG, ACG, left MFG, left middle temporal gyrus (MTG), and bilateral inferior occipital gyrus (IOG). The five ROIs of the CEN were: the right ANG, left inferior parietal lobule (IPL), left MTG, and bilateral MFG.

2.7 Spectral dynamic causal modeling

Using SPM,[3] we established a general linear model (GLM) for each subject and regressed the extracted CSF, WM signals, and motion parameters as covariates to adjust the GLM. Due to its extensive validation and widespread use, the Jenkinson motion parameters have been considered a standardized and accurate method for precise measurement of head motion. Therefore, we chose to include the Jenkinson motion parameters as covariates in our analysis. Subsequently, a sphere model was established for the selected ROIs, and a GM mask was used to assist in extracting the time series from each ROI. Next, an 8×8 fully connected model for DMN networks and a 5×5 fully connected model for CEN networks were established respectively, and cross spectra were used for parameter estimation. We were modeling on the resting-state fMRI data. No exogenous input was included in the model. After parameter estimation was completed, all possible models were defined. Bayesian estimation was applied to obtain the corresponding posterior probabilities for each model. The optimal model was finally obtained, along with its effective connectivity patterns.

2.8 rTMS protocol

This study used a Magstim Rapid2 magnetic stimulator connected to a 70-mm figure-8-shaped coil with two coils cross-tipped at the Pz site of the electroencephalogram system 10–20, targeting the PCUN region. The stimulus intensity was set to 100% of the resting-state motor threshold (MT). MT was determined by applying rTMS to the left PCUN (located approximately above the central sulcus) and shifting it by 0.5 cm along the scalp to the left motor cortical area (M1) (Koch et al., 2018). At the same time, the opposite side (right) was monitored to ensure relaxation of the first dorsal interosseous muscle. At least 5 of the 10 experiments produced a minimum intensity value of 50 μV motor evoked potential (MEP). We identified the interpupillary point as the anatomical landmark on the scalp and matched it with the corresponding marker on the headgear, establishing a correspondence between them. Subsequently, based on the calibrated headgear device, we determined the target region of the PCUN.

A total of 10 patients with SCD and 11 patients with aMCI underwent a total of 25 sessions of rTMS. Continuous stimulation for 40 times, each lasting 4 s, followed by an interval of 56 s. This sequence was repeated for 25 rounds, resulting in a total of 1,000 pulses, and lasting for 25 min. Each subject received this treatment once a day, five days a week (Monday to Friday), for a duration of two weeks per course of treatment. The entire procedure was repeated for a total of four weeks, equivalent to two treatment courses (Chen et al., 2021; Yuan et al., 2023). Subsequently, imaging data acquisition and neuropsychological evaluation were performed for each subject.

2.9 Statistical analyses

The Statistical Package for the Social Sciences (SPSS) software version 22.0 (IBM, Armonk, NY, United States) was used for statistical analyses. The analysis of variance (ANOVA), paired *t*-test, and the chi-square test were conducted to compare the demographic and neurocognitive data among groups, namely the HCs, and patients with SCD, aMCI, and SCD and aMCI before rTMS and after rTMS. Bonferroni correction was used for *post hoc* comparisons. A p-value < 0.05 indicated statistically significant differences.

For the 8×8 fully connected model built in the DMN network and the 5×5 fully connected model built in the CEN network, the effective connectivity values for all subjects were obtained. These values were subjected to statistical testing using one-sample *t*-test ($p < 0.05$) to find effective connectivity links that significantly deviated from zero within the DMN and CEN networks for each of the three groups of subjects. Next, ANOVA was used to compare the effective connectivity patterns among the HC, SCD, and aMCI groups ($p < 0.05$, uncorrected) to identify any differences in the effective connectivity between the groups. Then, after controlling for the effects of age, gender, and level of education, correlation analyses were conducted between changes in effective connectivity and cognitive function to reveal their relationships ($p < 0.05$).

After conducting rTMS intervention in 10 patients with SCD and 11 patients with aMCI, paired *t*-tests were used to compare the changes in effective connectivity before and after rTMS treatment in the SCD and aMCI groups ($p < 0.05$, uncorrected). Similarly, correlation analyses were conducted to explore associations between changes in effective connectivity and cognitive changes before and after rTMS intervention ($p < 0.05$).

3 Results

3.1 Demographic and neurocognitive characteristics

The demographic and neurocognitive information of all subjects is detailed in Tables 1, 2. Detailed raw scores of individual neuropsychological tests for all subjects and the *p*-values of demographics and clinical measures across different groups in Supplementary Tables S1–S3. We found no significant difference in age and gender among the three groups of patients, whereas the educational level of patients with aMCI was significantly lower compared to HCs. In addition, the aMCI group showed a decline in episodic memory, information processing speed, executive function, and visuospatial function, compared to the HC and SCD groups. After receiving rTMS intervention, the SCD group showed improved

2 http://www.alivelearn.net/xjview

3 http://www.fil.ion.ucl.ac.uk/spm/software/spm12/

TABLE 1 Demographics and clinical measures of HC and patients with SCD, and aMCI.

Characteristics	HC	SCD	aMCI	*F*-values(χ^2)	*p*-values
	n = 86	*n* = 72	*n* = 86		
Age (years)	63.35(7.010)	65.28(7.527)	65.24(7.521)	1.861	0.158
Gender (male/female)	32/54	17/55	29/57	3.520	0.172
Education level (years)	12.35(2.683)	11.73(2.696)	11.04(2.845)[b]	4.886	0.008**
Composite *Z* scores of each cognitive domain					
Episodic memory	0.24(0.61)	0.28(0.59)	−0.48(0.63)[bc]	41.266	0.000***
Information processing speed	0.23(0.74)	0.17(0.70)	−0.37(0.68)[bc]	18.568	0.000***
Executive function	0.25(0.48)	0.19(0.47)	−0.41(0.50)[bc]	49.080	0.000***
Visuospatial function	0.15(0.72)	0.13(0.68)	−0.26(0.88)[bc]	7.797	0.001***

Data are presented as mean (standard deviation, SD). HC, healthy controls; SCD, subjective cognitive decline; aMCI, amnestic mild cognitive impairment. *Significant differences were found among HC, SCD, and aMCI subjects. *$p \leq 0.05$, ** $p \leq 0.01$, ***$p \leq 0.001$. Most *p*-values were obtained using ANOVA, except for gender (chi-square test). Comparisons of each paired group were conducted to further reveal the source of ANOVA difference (b: aMCI vs. HC; c: aMCI vs. SCD). Bonferroni correction was applied for multiple group comparisons. This study utilized the composite *Z* scores to determine the level of each cognitive domain.

TABLE 2 Demographics and clinical measures of SCD and aMCI before rTMS and after rTMS.

Characteristics	Before rTMS SCD	After rTMS SCD	*T*-values (χ^2)	*p*-values	Before rTMS aMCI	After rTMS aMCI	*T*-values (χ^2)	*p*-values
	n = 10	*n* = 10			*n* = 11	*n* = 11		
Age (years)	66.00(7.874)	67.00(7.513)	−2.2535	0.032*	65.82(7.534)	66.45(7.647)	−1.750	0.111
Gender (male/female)	3/7	3/7	0.000	1.000	2/9	2/9	0.000	1.000
Education level (years)	11.40(3.273)	11.40(3.273)	0.000	1.000	12.55(3.197)	12.55(3.197)	0.000	1.000
Composite *Z* scores of each cognitive domain								
Episodic memory	−0.27(1.70)	1.53(1.36)	−3.252	0.010**	−1.52(2.14)	0.38(1.96)	−2.808	0.019*
Information processing speed	0.76(2.73)	1.42(3.30)	−1.175	0.270	−1.52(3.14)	−0.47(2.96)	−2.131	0.059
Executive function	0.80(3.11)	1.64(3.85)	−1.323	0.218	−2.17(2.05)	−0.05(2.86)	−2.987	0.014*
Visuospatial function	0.71(1.56)	0.18(1.96)	0.801	0.444	−0.80(1.89)	−0.01(1.35)	−1.235	0.245

Data are presented as mean (standard deviation, SD). SCD, subjective cognitive decline; aMCI, amnestic mild cognitive impairment. *Significant differences were found between before rTMS and after rTMS. *$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$. Most *p*-values were obtained using paired *T*-tests, except for gender (chi-square test). This study utilized the composite *Z* scores to determine the level of each cognitive domain.

episodic memory, and the aMCI group showed improved episodic memory and executive function.

3.2 Group ICA and ROIs

Among the 27 independent components, the 25th and 18th components exhibited the highest correlations with the DMN and CEN brain network templates, respectively. Figure 1A shows the spatial pattern of the DMN and Figure 1B shows the spatial pattern of the CEN. The whole-brain detail maps of DMN and CEN are presented in Supplementary Figure S1. The coordinates of the ROIs of the DMN and CEN, determined using the XjView toolbox, are shown in Table 3 and spatial locations are shown in Figure 2.

3.3 Effective connectivity patterns of three groups

The effective connectivity patterns for the DMN and CEN for the three groups obtained through a one-sample *t*-test based on the effective connectivity strength values are shown in Figure 3. The DMN and CEN of all three groups exhibited varying degrees of excitatory or inhibitory connectivity within their respective networks.

3.4 Differences in effective connectivity of three groups

Figures 4, 5 and Table 4 show the differences in effective connectivity among the three groups. In the DMN, compared to the HC group, the inhibitory connectivity from PCUN to ANG.R switched to excitatory connectivity, the inhibitory connectivity from PCUN to MFG.L decreased, and the excitatory connectivity from ACG to PCUN decreased in the SCD group. Meanwhile, excitatory connectivity from MTG.L to ANG.R and MFG.L increased in the aMCI group. Compared to the SCD group, the excitatory connectivity from MFG. L to MTG.L decreased, while that from MTG.L to ANG.R increased in the aMCI group. In the CEN, compared to the HC group, excitatory connectivity from IPL.L to ANG.R and MFG.R increased in the SCD group, while that from IPL.L to IPL.L decreased, and excitatory connectivity from MFG.R to IPL.L and MTG.L decreased.

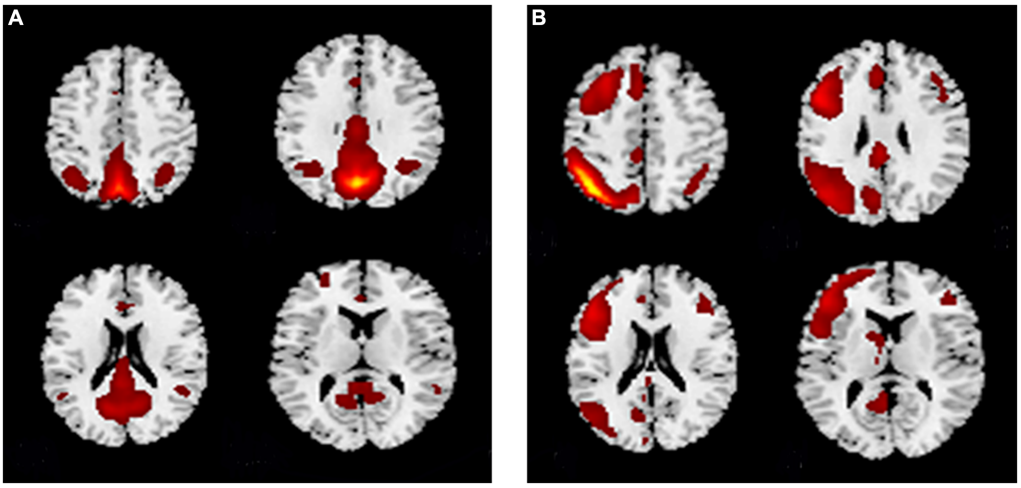

FIGURE 1
The spatial pattern of the **(A)** DMN and **(B)** CEN. **(A)** The spatial pattern of the DMN. **(B)** The spatial pattern of the CEN. DMN, default mode network; CEN, central executive network.

TABLE 3 ROIs for DCM analyses.

Anatomical region	MNI coordinate		
	X	*Y*	*Z*
Default mode network			
PCUN	−3	−72	30
ANG.L	−36	−60	39
ANG.R	42	−57	42
ACG	−6	27	27
MFG.L	−27	51	9
MTG.L	−54	−18	−18
IOG.L	−24	−93	−9
IOG.R	36	−78	−18
Central executive network			
ANG.R	39	−60	45
IPL.L	−36	−57	42
MTG.L	−57	−48	−15
MFG.L	−45	42	3
MFG.R	45	36	21

MNI, Montreal neurological institute; PCUN, precuneus; ANG, angular gyrus; ACG, anterior cingulate gyrus; MFG, middle frontal gyrus; MTG, middle temporal gyrus; IOG, inferior occipital gyrus; IPL, inferior parietal lobule; L, left; R, right.

Conversely, in the aMCI group, excitatory connectivity from MFG.L to MFG.L decreased in the CEN. Compared to the SCD group, the aMCI group showed increased excitatory connectivity from MFG.R to IPL.L, MTG.L, and MFG.L.

3.5 Change of effective connectivity after rTMS

After the rTMS intervention, notable alterations in effective connectivity were observed. In the SCD group, within the DMN network, excitatory connectivity from ANG.L to PCUN was elevated, and inhibitory connectivity from ANG.L to ACG, MFG.L, and IOG.L to ANG.L was transformed into excitatory connectivity. Within the CEN network, the excitatory connectivity from ANG.R to MFG. R was transformed into inhibitory connectivity. However, we did not observe significant changes in effective connectivity in the aMCI group. The specific changes in effective connectivity are shown in Figure 6 and Table 5.

3.6 Correlation analysis with neuropsychological scores

Correlation analyses were performed to explore the associations between regions with significantly altered effective connectivity and cognitive domains ($p < 0.05$), and age, gender, and educational level were considered as covariates. The results showed that in both SCD and aMCI groups, the effective connectivity between the DMN networks MFG.L and MTG.L was positively correlated with episodic memory ($r = 0.200$, $p = 0.012$). Moreover, the effective connectivity of the CEN network IPL.L to ANG.R was negatively correlated with visuospatial function in the HC and SCD groups ($r = -0.163$, $p = 0.044$). After the rTMS intervention, the effective connectivity from ANG.L to ACG in the DMN network was negatively correlated with visuospatial function in the SCD group ($r = -0.547$, $p = 0.023$). Meanwhile, the effective connectivity from ANG.R to MFG.R in the CEN network was negatively correlated with executive function in the SCD group ($r = -0.509$, $p = 0.037$; Figure 7).

4 Discussion

This study aimed to investigate the regulation and effect of PCUN-targeted rTMS intervention on effective connectivity and cognitive function within brain networks. Our investigation presents two main findings. First, we found that within the DMN and CEN, the spectrum of preclinical AD had different causal patterns, indicating effective connectivity within the brain networks associated with various

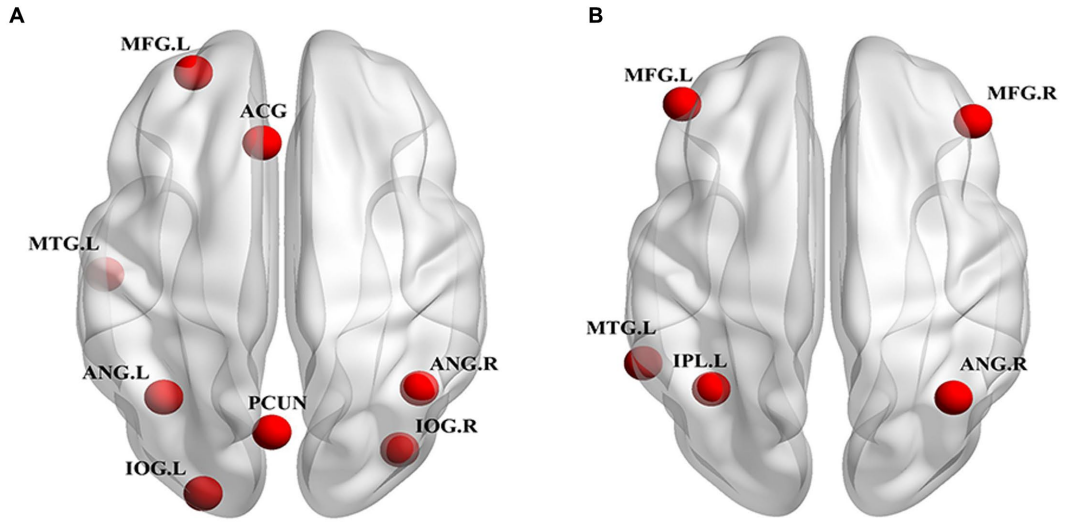

FIGURE 2
Spatial location of ROIs for DCM analyses. **(A)** DMN ROIs: PCUN, bilateral ANG, ACG, MFG.L, MTG.L, bilateral IOG. **(B)** CEN ROIs: ANG.R, IPL.L, MTG.L, bilateral MFG. ROI, region of interest; DCM, dynamic causal model; DMN, default mode network; CEN, central executive network; PCUN, precuneus; ANG, angular gyrus; ACG, anterior cingulate gyrus; MFG, middle frontal gyrus; MTG, middle temporal gyrus; IOG, inferior occipital gyrus; ANG, angular gyrus; IPL, inferior parietal lobule; L, left; R, right.

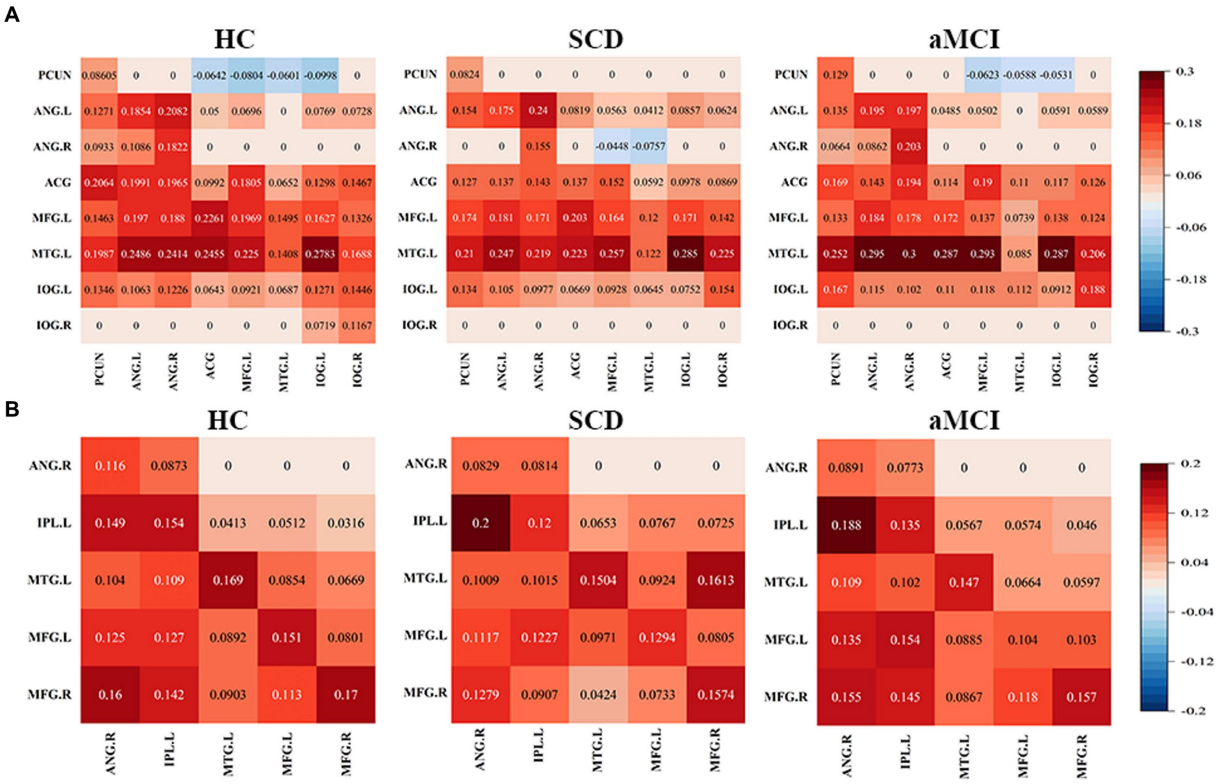

FIGURE 3
Mean values in effective connectivity for HC, patients with SCD and aMCI. **(A)** DMN effective connectivity patterns of HCs, SCD and aMCI. **(B)** CEN effective connectivity patterns of HCs, SCD and aMCI. HC, healthy controls; SCD, subjective cognitive decline; aMCI, amnestic mild cognitive impairment; DMN, default mode network; CEN, central executive network; PCUN, precuneus; ANG, angular gyrus; ACG, anterior cingulate gyrus; MFG, middle frontal gyrus; MTG, middle temporal gyrus; IOG, inferior occipital gyrus; IPL, inferior parietal lobule; L, left; R, right.

pathological states in the spectrum of preclinical AD. Secondly, after the rTMS intervention, the spectrum of preclinical AD showed changes in effective connectivity, accompanied by improvements in cognitive function. Therefore, this study showed that the rTMS intervention targeting the PCUN can modulate the effective connectivity patterns of the brain network in the spectrum of preclinical AD and improve cognitive function. Thus, the PCUN can be considered an ideal target for rTMS intervention.

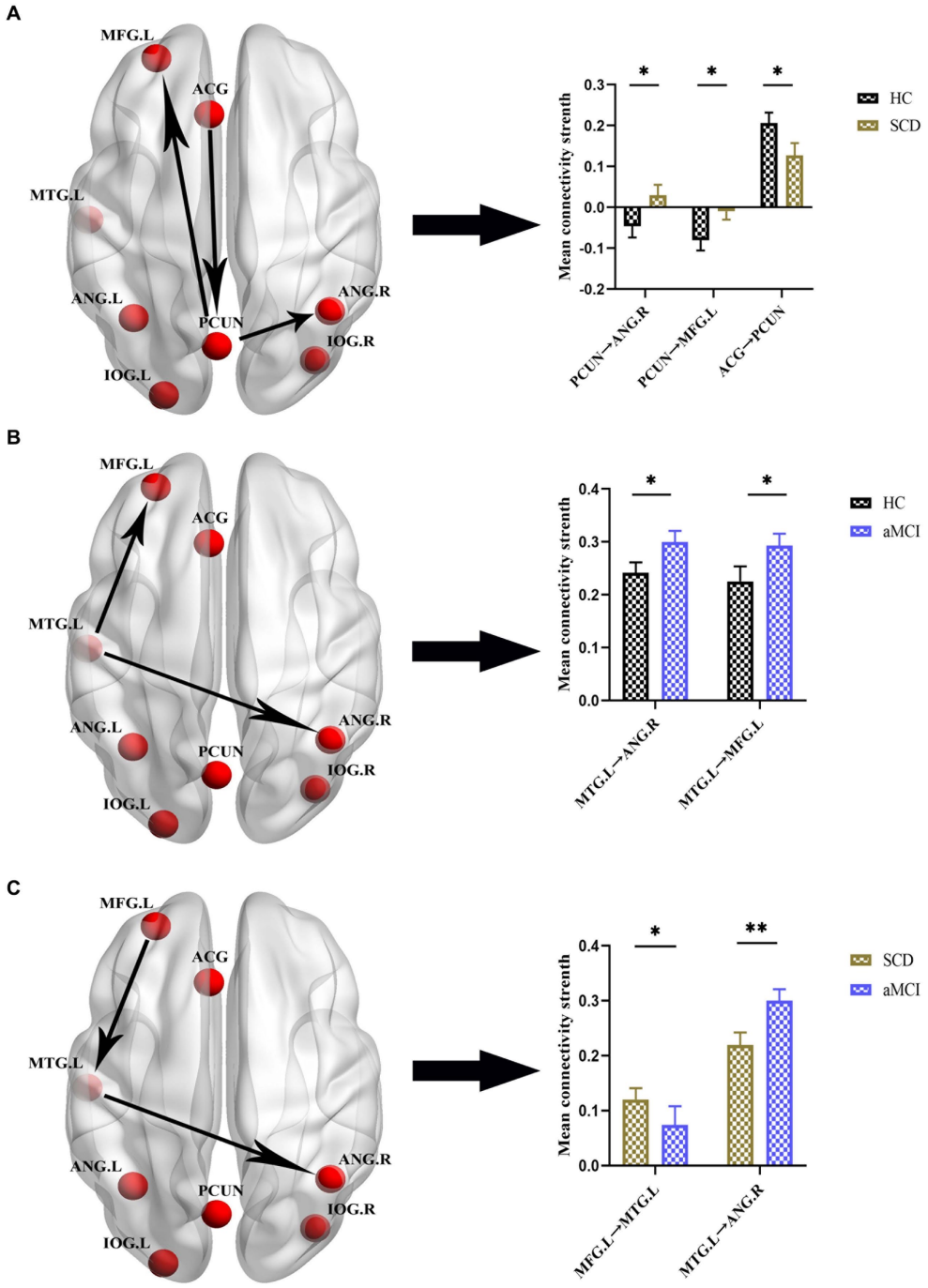

FIGURE 4
Group differences in effective connectivity HC, patients with SCD, and aMCI in DMN. **(A)** Differences in effective connectivity in patients with SCD compared to HC. A bar chart indicating the quantitative comparison of effective connectivity between these regions. **(B)** Differences in effective connectivity in patients with aMCI compared to HC. A bar chart indicating the quantitative comparison of effective connectivity between these regions. **(C)** Differences in effective connectivity in patients with aMCI compared to SCD. A bar chart indicating the quantitative comparison of effective connectivity between these regions. *Significant different (*$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$); error bar, standard error of the mean (SEM). HC, healthy controls; SCD, subjective cognitive decline; aMCI, amnestic mild cognitive impairment; DMN, default mode network; PCUN, precuneus; ANG, angular gyrus; ACG, anterior cingulate gyrus; MFG, middle frontal gyrus; MTG, middle temporal gyrus; L, left; R, right.

4.1 Altered DMN and CEN effective connectivity patterns in patients with SCD and aMCI

The DMN is considered the first large-scale system to be compromised in the progression of AD. Studies on the strength of FC between important nodes of DMN in patients with SCD showed de-coupling of DMN nodes (Dillen et al., 2017). In addition, DMN, a key hub in the spectrum of preclinical AD, is thought to be more susceptible to amyloid-beta deposition and glucose hypometabolism (Mutlu et al., 2017). Using fMRI and diffusion-weighted imaging (DWI), Zhou et al. found abnormal structural and functional

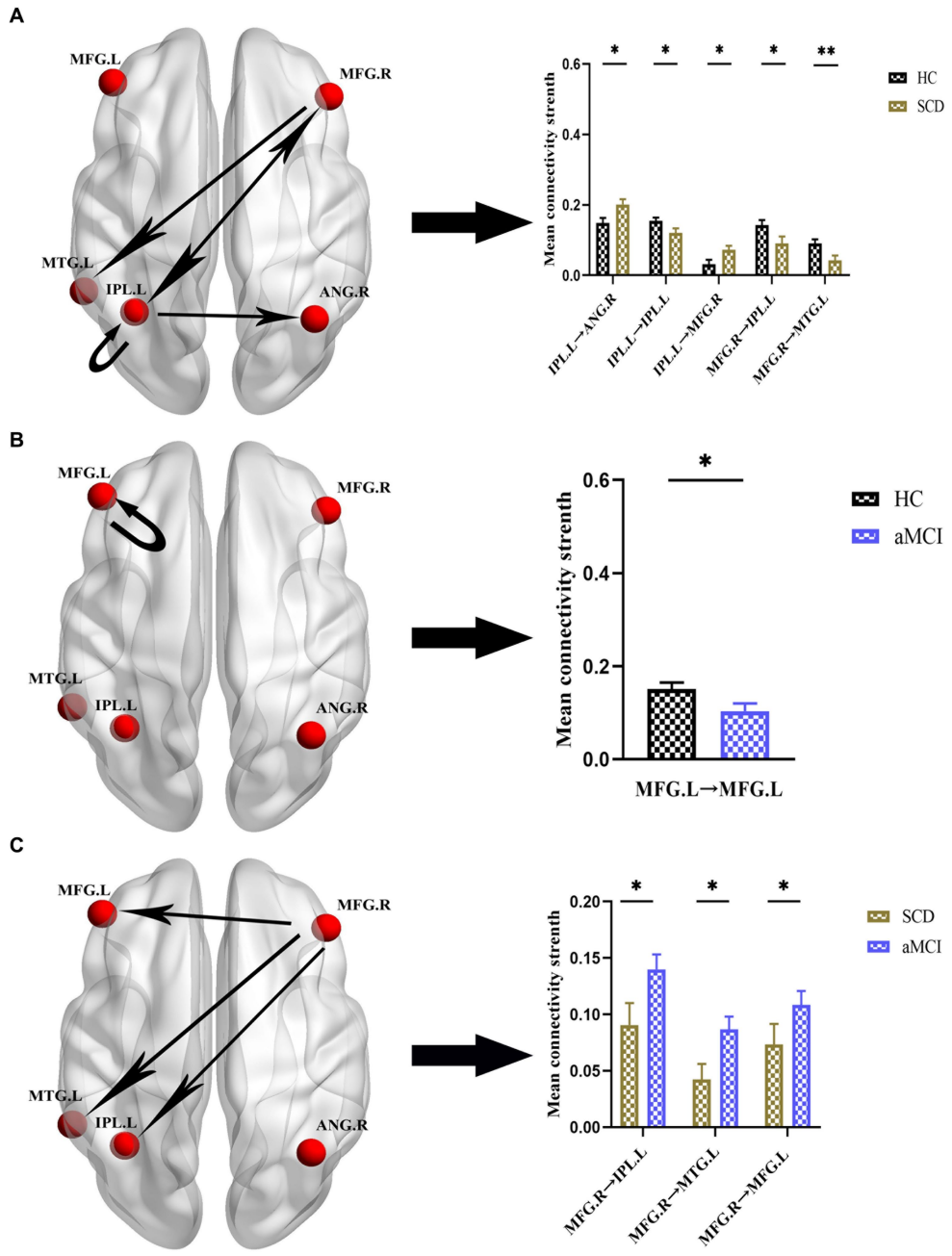

FIGURE 5
Group differences in effective connectivity HC, patients with SCD, and aMCI in CEN. **(A)** Differences in effective connectivity in patients with SCD compared to HC. A bar chart indicating the quantitative comparison of effective connectivity between these regions. **(B)** Differences in effective connectivity in patients with aMCI compared to HC. A bar chart indicating the quantitative comparison of effective connectivity between these regions. **(C)** Differences in effective connectivity in patients with aMCI compared to SCD. A bar chart indicating the quantitative comparison of effective connectivity between these regions. *Significant different (*$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$); error bar, standard error of the mean (SEM). HC, healthy controls; SCD, subjective cognitive decline; aMCI, amnestic mild cognitive impairment; CEN, central executive network; IPL, inferior parietal lobule; ANG, angular gyrus; MFG, middle frontal gyrus; MTG, middle temporal gyrus; L, left; R, right.

connectivity within the DMN in patients with MCI, demonstrating a significant association with cognitive decline (Zhou et al., 2022). The above studies indicate that in the spectrum of preclinical AD, the DMN exhibits altered functional, structural, and metabolic changes. Consistent with these findings, the present study stated that the effective connectivity pattern of the DMN is altered in the spectrum of preclinical AD. In patients with SCD, we observed a decrease in effective connectivity from the ACG to the PCUN and an increase in effective connectivity from the PCUN to the ANG.R and MFG.L. This suggests that during the SCD phase, the PCUN, a core node of the DMN, can compensate for the increased activity to maintain normal levels of cognition despite the presence of partially impaired brain area function. Similarly, in patients with MCI, the effective connectivity from MTG.L to ANG.R and MFG.L was elevated. This is consistent

TABLE 4 Effective connectivity parameters differences across three groups.

Brain regions	Mean strength		*F*-values
Default mode network			
HC vs. SCD	HC	SCD	
PCUN→ANG.R	−0.0462 ± 0.2565	0.0294 ± 0.2187	0.044
PCUN→MFG.L	−0.0804 ± 0.2328	−0.0097 ± 0.1729	0.035
ACG → PCUN	0.2064 ± 0.2360	0.1271 ± 0.2566	0.036
HC vs. aMCI	HC	aMCI	
MTG.L → ANG.R	0.2414 ± 0.1837	0.3000 ± 0.1932	0.045
MTG.L → MFG.L	0.2250 ± 0.2654	0.2933 ± 0.2065	0.045
SCD vs. aMCI	SCD	aMCI	
MFG.L → MTG.L	0.1203 ± 0.1749	0.0739 ± 0.3164	0.033
MTG.L → ANG.R	0.2190 ± 0.1952	0.3000 ± 0.1932	0.008
Central executive network			
HC vs. SCD	HC	SCD	
IPL.L → ANG.R	0.1488 ± 0.1312	0.2014 ± 0.1258	0.012
IPL.L → IPL.L	0.1540 ± 0.0884	0.1200 ± 0.1134	0.035
IPL.L → MFG.R	0.0316 ± 0.1162	0.0725 ± 0.0975	0.017
MFG.R → IPL.L	0.1424 ± 0.1342	0.0907 ± 0.1653	0.026
MFG.R → MTG.L	0.0903 ± 0.1085	0.0424 ± 0.1163	0.007
HC vs. aMCI	HC	aMCI	
MFG.L → MFG.L	0.1509 ± 0.1301	0.1038 ± 0.1514	0.028
SCD vs. aMCI	SCD	aMCI	
MFG.R → IPL.L	0.0907 ± 0.1653	0.1446 ± 0.1357	0.020
MFG.R → MTG.L	0.0424 ± 0.1163	0.0867 ± 0.1063	0.012
MFG.R → MFG.L	0.0733 ± 0.1552	0.1177 ± 0.1346	0.027

Data are presented as mean (standard deviation, SD). HC, healthy controls; SCD, subjective cognitive decline; aMCI, amnestic mild cognitive impairment; PCUN, precuneus; ANG, angular gyrus; MFG, middle frontal gyrus; ACG, anterior cingulate gyrus; MTG, middle temporal gyrus; IPL, inferior parietal lobule; L, left; R, right.

with a recent study that highlights increased neural activity in the frontotemporal region as the disease progresses to resist neurotoxic effects (Gour et al., 2011). We also found that the effective connectivity from MFG.L to MTG.L decreased was positively correlated with the decline in memory in the SCD and aMCI groups. This suggests that MFG. L is damaged during the disease process and is closely related to cognitive abilities, and the degree of damage may predict the decline in memory. Therefore, altered effective connectivity patterns observed in the DMN in the spectrum of preclinical AD can be considered important neuroimaging evidence.

Neuroimaging studies have shown the existence of the brain network degeneration hypothesis in the AD spectrum (Mutlu et al., 2017). An arterial spin labeling perfusion and fMRI study confirmed that decreases in CBF and amplitude low-frequency fluctuation (ALFF) indicate disruption of the CEN (Zheng et al., 2019). Liao et al. demonstrated abnormal interhemispheric CEN network connectivity in patients with MCI using voxel-mirrored homotopic connectivity (Liao et al., 2018). In addition, Granger causality analysis confirmed that progressive MCI cases exhibit different patterns of effective CEN connectivity, potentially serving as a biomarker for predicting the progression of AD (Cai et al., 2017). Similarly, this study used spDCM to demonstrate altered effective connectivity patterns in the CEN in patients with SCD and aMCI. In patients with SCD, effective connectivity from IPL.L to ANG was increased and that to IPL.L and MFG.R was decreased. In contrast, patients with aMCI showed decreased self-connection within MFG.L. This is consistent with the study by Wu et al. (2014), which showed a concurrent decrease in the functional connectivity of the CEN. Decreased effective connectivity is suggestive of damage to brain regions, whereas increased effective connectivity may reflect a maladaptive compensatory mechanism. This implies a transition from a healthy neuroplastic compensation mechanism to maladaptive processes within damaged brain regions, triggered by factors such as GM atrophy and hypoperfusion (Mesulam, 2006). The research findings suggest that IPL, as a multimodal and heterogeneous brain region, plays a crucial role in the CEN (Uddin et al., 2011). Therefore, based on our partial correlation results, it can be inferred that the increased effective connectivity of IPL reflects its compensatory mechanism. However, this mechanism may vary in its impact on different brain networks, thereby exhibiting a negative association with visual function. Elevated and decreased within-network effective connectivity in the DMN and CEN networks have been observed in both SCD and aMCI patients, possibly reflecting complex brain regulation following cognitive impairment. This may involve intricate interactions within and between multiple brain networks, warranting further in-depth investigations in future research. These insights offer novel perspectives on the pathogenesis and neuroimaging of the spectrum of preclinical AD.

4.2 Changes in effective connectivity patterns and cognition after rTMS in patients with SCD

After undergoing two courses of rTMS treatment, notable changes were observed in the effective connectivity patterns of the DMN and CEN in patients with SCD, including improvements in episodic memory. Specifically, the effective connectivity of the ANG.L to the PCUN, ACG, MFG.L, and IOG.L in the DMN increased, and the previously excitatory effective connectivity from ANG.R to MFG.R in the CEN transformed into inhibitory connectivity. ANG plays an important role in the development, progression, and transition of the spectrum of AD (Hu et al., 2022). Cai et al. (2020) documented a decrease in ANG FC in patients with SCD. Furthermore, decreased CBF in ANG was observed in patients with MCI who eventually progressed to AD (Hirao et al., 2005). IOG is mainly related to vision, and a study reported an increase in fALFF values in patients with SCD (Sun et al., 2016). It has been suggested that local stimulation of rTMS acting on a target site can be transmitted via synapses to interconnected nodes, facilitating regulation within brain regions and networks (Chen et al., 2021). Anatomical and functional studies on the PCUN have shown that is a complex cortical and subcortical structure characterized by extensive connectivity (Cavanna and Trimble, 2006). Therefore, we hypothesize that local stimulation of rTMS targeting the PCUN is transmitted synaptically to susceptible brain regions connected to it, thereby modulating the DMN and CEN networks and causing changes in effective connectivity patterns.

A previous meta-analysis has shown that episodic memory requires the involvement of multi-brain networks (Liang et al., 2022).

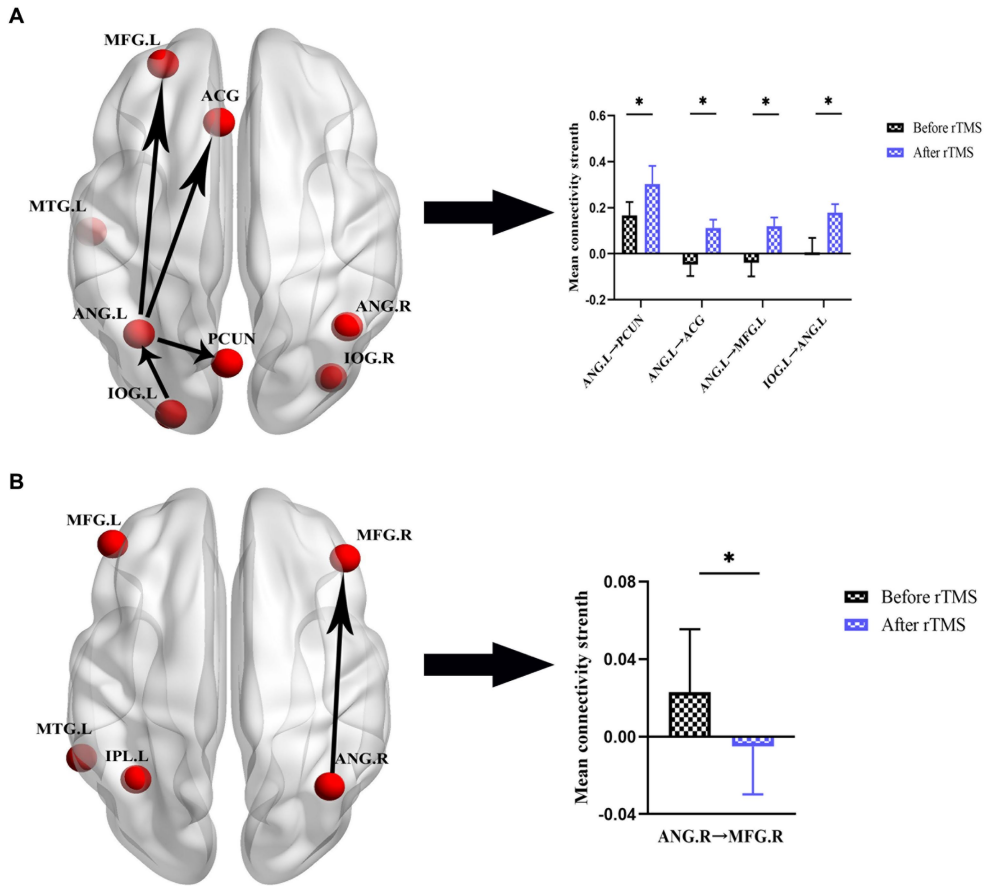

FIGURE 6
Effective connectivity changes in DMN and CEN before and after rTMS in patients with SCD. **(A)** Effective connectivity changes in DMN. A bar chart indicating the quantitative comparison of effective connectivity between these regions. **(B)** Effective connectivity changes in CEN. A bar chart indicating the quantitative comparison of effective connectivity between these regions. *Significant different (*$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$); error bar, standard error of the mean (SEM). DMN, default mode network; CEN, central executive network; SCD, subjective cognitive decline; rTMS, repetitive transcranial magnetic stimulation; ANG, angular gyrus; PCUN, precuneus; ACG, anterior cingulate gyrus; MFG, middle frontal gyrus; IOG, inferior occipital gyrus; L, left; R, right.

DMN and CEN, as the two core networks for maintaining cognition, also play an important role in episodic memory. A long-term memory model has shown that the PCUN is involved in both the encoding and retrieval of episodic memory (Daselaar, 2009). PCUN-targeted rTMS improves episodic memory (Chen et al., 2021). The ANG is widely recognized as a pivotal interface, playing a crucial role in the processes of episodic simulation and episodic memory (Thakral et al., 2017). The application of facilitatory TMS to the ANG has been linked to improvements in episodic memory performance (Nilakantan et al., 2017). Furthermore, the IOG predominantly processes visual information and is closely associated with visuospatial and executive functions (Bilo et al., 2013). Cognitive-behavioral investigations have provided evidence highlighting the significant contribution of visual attention in the retrieval of episodic memories (Guerin et al., 2012). According to the results of partial correlation analysis, alterations in effective connectivity of the ANG were found to exhibit a negative correlation with visuospatial and executive functions. This finding suggests the presence of a complex regulatory mechanism involving interplay among various brain regions, which may contribute to the suppression or disruption of visuospatial and executive functions, while not necessarily indicating a significant decline in functionality. Thus, we propose that in patients with SCD, PCUN-targeted rTMS regulates the effective connectivity patterns within the DMN and CEN networks. This modulation activates brain regions integral to episodic memory function and promotes functional integration, thereby improving episodic memory. In summary, we believe that SCD is an ideal stage for rTMS interventions aimed to improve cognition by regulating effective connectivity patterns.

4.3 Cognitive changes after rTMS intervention in patients with aMCI

The present study showed noteworthy improvements in episodic memory and executive function in patients with aMCI after PCUN-targeted rTMS. However, we did not observe changes in the effective connectivity patterns of the DMN and CEN. Episodic memory is the ability to encode, retain, and retrieve information related to personal events and experiences that occurred at a specific time and place. Decreased episodic memory function is a central feature of aMCI (Bai et al., 2016). Meanwhile, executive functions include complex attention, working memory, verbal and visual organization, planning,

TABLE 5 Effective connectivity parameters change of SCD and aMCI before rTMS and after rTMS.

Brain regions	Mean strength		*T*-values
Default mode network			
SCD	Before	After	
ANG.L → PCUN	0.1667 ± 0.1838	0.3033 ± 0.2471	0.044
ANG.L → ACG	−0.0479 ± 0.1560	0.1123 ± 0.1148	0.035
ANG.L → MFG.L	−0.0393 ± 0.1895	0.1202 ± 0.1195	0.034
IOG.L → ANG.L	−0.0220 ± 0.2295	0.1782 ± 0.1183	0.029
aMCI			
None			
Central executive network			
SCD	Before	After	
ANG.R → MFG.R	0.0230 ± 0.1025	−0.0300 ± 0.0829	0.031
aMCI			
None			

Data are presented as mean (standard deviation, SD). SCD, subjective cognitive decline; aMCI, amnestic mild cognitive impairment; ANG, angular gyrus; PCUN, precuneus; ACG, anterior cingulate gyrus; MFG, middle frontal gyrus; IOG, inferior occipital gyrus; L, left; R, right.

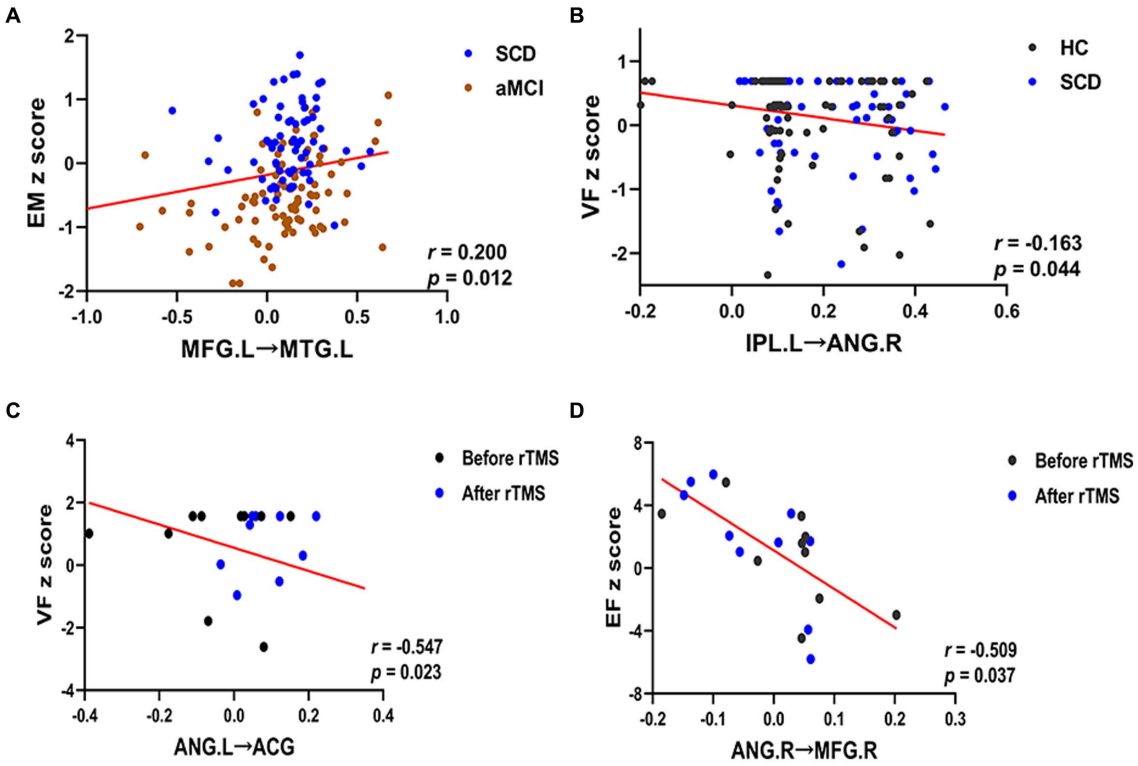

FIGURE 7
Relationship between altered effective connectivity and cognitive function in HC, SCD, aMCI, before rTMS and after rTMS. **(A)** Relationship between effective connectivity of the MFG.L to MTG.L and episodic memory in patients with SCD and aMCI in the DMN. **(B)** Relationship between effective connectivity of the IPL.L to ANG.R and visuospatial function in patients with HC and SCD in the CEN. **(C)** Relationship between effective connectivity of the ANG.L to ACG and visuospatial function in patients with the SCD before and after rTMS in the DMN. **(D)** Relationship between effective connectivity of the ANG.R to MFG.R and executive function in patients with the SCD before and after rTMS in the CEN. HC, healthy controls; SCD, subjective cognitive decline; aMCI, amnestic mild cognitive impairment; rTMS, repetitive transcranial magnetic stimulation; DMN, default mode network; CEN, central executive network; EM, episodic memory; VF, visuospatial function; EF, executive function. MFG, middle frontal gyrus; MTG, middle temporal gyrus; IPL, inferior parietal lobule; ANG, angular gyrus; ACG, anterior cingulate gyrus; L, left; R, right.

sound judgment, and reasoning capacities. Executive dysfunction has been shown to predict the progression of aMCI to AD (Tabert et al., 2002).

A study using high-frequency rTMS showed sustained improvements in episodic memory in patients with MCI (Drumond Marra et al., 2015). Some studies have also shown the potential of

rTMS to improve attention and psychomotor speed in patients with MCI and AD (Anderkova et al., 2015). A recent systematic review including studies on rTMS intervention in patients with MCI and AD showed that rTMS can improve and restore impaired cognitive function (Chou et al., 2020). These findings are consistent with the current study, which showed improved cognitive function in patients with aMCI after rTMS treatment.

However, unlike patients with SCD, we did not observe any changes in the effective connectivity patterns of the DMN and CEN in patients with aMCI. There may be a possibility that the differential response to rTMS intervention in SCD and aMCI patients could be attributed to the distinct baseline effective functional connectivity and varying degrees of impairment. Moreover, these discrepancies may be attributed to the differential mechanisms by which rTMS influences SCD and aMCI. Despite both being prodromal stages of Alzheimer's disease, rTMS exerts its effects through distinct modalities in these conditions. In SCD patients, rTMS ameliorates cognitive function by modulating the effective connectivity patterns of diverse cerebral networks. Conversely, in the case of aMCI patients, rTMS may operate via alternative pathways. A previous study showed that correction of disruptions in the structure of the hippocampus and its connectivity with MTG can causally enhance episodic memory in aMCI (Chen et al., 2022). It has also been shown that rTMS can increase the expression of brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF), thereby increasing synaptic neuroplasticity and thus improving cognition (Zhang et al., 2015). Cristina et al. proposed that rTMS improves cognition by promoting the compensatory recruitment potential of other neural networks (Solé-Padullés et al., 2006). Therefore, we propose that rTMS is a promising non-invasive technique for enhancing cognitive function in SCD and aMCI patients. Specifically, rTMS achieves this by modulating the effective connectivity patterns of cerebral networks in SCD patients, while the mechanisms underlying its effects on aMCI patients remain to be further investigated in future studies. Based on our findings, we propose that rTMS can better improve cognitive function in patients with SCD by modulating effective connectivity within the brain network.

4.4 Limitations

The main limitation of this study is the relatively small sample size. However, to ensure the accuracy of the experiment, all subjects met the diagnostic criteria and were strictly grouped. In addition, we should establish a more comprehensive definition of the preclinical spectrum of AD to facilitate more extensive research (Zhou, 2021). Furthermore, this study currently lacks a sham rTMS group for control comparison. However, we are actively recruiting more participants and utilizing a more advanced stereotactic neuronavigation system to monitor coil positioning for target localization. This will enable us to conduct more comprehensive and in-depth research in the future, and further advancing our understanding in this area. Despite these limitations, to our knowledge, this is the first study to target the efficacy of rTMS at the level of effective connectivity in brain networks, and we once again demonstrate the effectiveness of rTMS therapy targeting PCUN.

5 Conclusion

This study demonstrates that SCD and aMCI are changed in the effective connectivity patterns of DMN and CEN as the spectrum of preclinical AD. In addition, after two courses of PCUN-targeted rTMS treatment, the effective connectivity of the spectrum of preclinical AD was modulated, accompanied by cognitive improvement. These results prove that PCUN can be used as an effective target for rTMS, acting on the spectrum of preclinical AD, especially in the SCD stage, which can delay or reverse the disease process. This provides new insights into the pathogenesis and clinical treatment of the spectrum of preclinical AD.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Human Participants Ethics Committee of the Affiliated Brain Hospital of Nanjing Medical University (Nos. 2018-KY010-01 and 2020-KY010-02). Written informed consent was obtained from all subjects prior to enrolment. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

XuL: Formal analysis, Methodology, Writing – original draft. CXu: Methodology, Writing – original draft. DZ: Data curation, Methodology, Writing – original draft. QY: Data curation, Writing – original draft. WQ: Formal analysis, Writing – original draft. YR: Investigation, Writing – original draft. SC: Software, Writing – original draft. YS: Validation, Writing – original draft. HW: Data curation, Writing – original draft. XiL: Funding acquisition, Writing – original draft. CXi: Project administration, Writing – review & editing. JC: Funding acquisition, Project administration, Resources, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2024.1343926/full#supplementary-material

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Higher remnant cholesterol is associated with an increased risk of amnestic mild cognitive impairment: a community-based cross-sectional study

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Background and aims: Amnestic mild cognitive impairment (aMCI) is the most common subtype of MCI, which carries a significantly high risk of transitioning to Alzheimer's disease. Recently, increasing attention has been given to remnant cholesterol (RC), a non-traditional and previously overlooked risk factor. The aim of this study was to explore the association between plasma RC levels and aMCI.

Methods: Data were obtained from Brain Health Cognitive Management Team in Wuhan (https://hbtcm.66nao.com/admin/). A total of 1,007 community-dwelling elders were recruited for this project. Based on ten tools including general demographic data, cognitive screening and some exclusion scales, these participants were divided into the aMCI ($n = 401$) and normal cognitive groups ($n = 606$). Physical examinations were conducted on all participants, with clinical indicators such as blood pressure, blood sugar, and blood lipids collected.

Results: The aMCI group had significantly higher RC levels compared to the normal cognitive group (0.64 ± 0.431 vs. 0.52 ± 0.447 mmol/L, $p < 0.05$). Binary logistics regression revealed that occupation ($P<0.001$, OR = 0.533, 95%CI: 0.423–0.673) and RC ($p = 0.014$, OR = 1.477, 95% CI:1.081–2.018) were associated factors for aMCI. Partial correlation analysis, after controlling for occupation, showed a significant negative correlation between RC levels and MoCA scores ($r = 0.059$, $p = 0.046$), as well as Naming scores ($r = 0.070$, $p = 0.026$). ROC curve analysis demonstrated that RC levels had an independent predictive efficacy in predicting aMCI (AUC = 0.580, 95%CI: 0.544 ~ 0.615, $P < 0.001$).

Conclusion: Higher RC levels were identified as an independent indicator for aMCI, particularly in the naming cognitive domain among older individuals. Further longitudinal studies are necessary to validate the predictive efficacy of RC.

KEYWORDS

remnant cholesterol, amnestic mild cognitive impairment, Alzheimer's disease, cross-sectional, older adults, community

1 Introduction

Mild cognitive impairment (MCI) is a transitional state between normal aging and dementia (Petersen et al., 2001; Langa and Levine, 2014). The key distinction between MCI and dementia is that the level of cognitive decline in MCI is not severe enough to significantly impact one's daily functioning (Petersen et al., 2018). Amnestic mild cognitive impairment (aMCI) is the most common subtype of MCI that carries a high risk for transitioning into Alzheimer's disease (AD), which unfortunately is irreversible and currently lacks effective treatment methods (Petersen, 2000; Van der Mussele et al., 2014). However, the aMCI stage still offers controllability and potential reversibility, which implies that the cognitive function of individuals with aMCI can be restored to a normal state or maintained relatively stable for a period of four to 5 years, or potentially even longer (US Preventive Services Task Force et al., 2020). This window of opportunity makes it the optimal period to delay or prevent the onset of AD. Our previous research discovered that aMCI often goes unnoticed in the communities; and Chinese older adults of aMCI and their families are less likely to actively seek medical attention until the condition has progressed to the dementia stage (Sun et al., 2018; Yang et al., 2021). Therefore, early identification of factors associated with aMCI becomes crucial.

Unfortunately, many studies primarily focus on exploring factors related to the progression from aMCI to AD (Van Rossum et al., 2012; Li et al., 2016; Rossini et al., 2022), rather than identifying risk factors specific to MCI itself. Some studies investigated associated factors of MCI, but solely relied on assessments such as the Mini-Mental State Examination (MMSE) or the Montreal Cognitive Assessment (MoCA), which may impact the reliability of research findings (Li et al., 2021; Huang et al., 2022; Zhong et al., 2023). Furthermore, the specific subtypes of MCI are often overlooked, leading to inconsistencies in research results.

Various factors may be associated with MCI, such as age, gender, education level, genetic factors, chronic disease factors, and lifestyle factors (Katayama et al., 2020; US Preventive Services Task Force et al., 2020; Huang et al., 2022; Zhong et al., 2023). Chronic disease factors such as hypertension, diabetes, hypercholesterolemia, heart disease, pulmonary disease (Katayama et al., 2020; US Preventive Services Task Force et al., 2020), osteoarthritis (Ribeiro et al., 2022), kidney disease (Viggiano et al., 2020) may affect cognitive function of the older individuals. Hobbies such as watching TV, reading, taking physical exercise, walking, playing cards/chess (Rundek and Bennett, 2006; Geda et al., 2011; Zhao et al., 2015), keeping pets (Friedmann et al., 2023), dancing (Zhu et al., 2020) may affect the advanced and instrumental daily living abilities of older individuals, as well as overall cognitive and executive functions. However, there is still no consensus on many of these factors. In a rigorous research design, chronic diseases and hobbies should be considered as control variables when exploring associated factors of aMCI.

Similarly, research on laboratory biological indicators of MCI has been inconclusive. Some studies have examined the relationship between individual indicators in peripheral blood and MCI, such as homocysteine (Bhargava et al., 2018), neutrophil lymphocyte ratio (An et al., 2019), standard deviation of red blood cell distribution width (Du et al., 2020), and fasting blood glucose (Li et al., 2021). Currently, there is a lack of specific biological diagnostic indicators, and thus it may be promising to further explore the predictive value of blood indicators for aMCI in older adults.

Hyperlipidemia was found to be a potential risk factor for cognitive impairment (Anstey et al., 2017). However, the association between plasma lipids and MCI among older individuals remains controversial (He et al., 2016). Cross-sectional or epidemiological studies were advocated to further investigate the role of blood lipids in MCI (McFarlane et al., 2020). This study diverted our effort to the relationship between remnant cholesterol (RC) and MCI, as it has been often overlooked or not fully explored (Sandesara et al., 2019).

RC refers to the cholesterol content present in remnants, which can be measured in a laboratory setting or calculated based on the values of LDL-C and HDL-C. These remnants are a subset of lipoproteins that are rich in triglycerides. RC particles are larger and more abundant, posing a greater risk on arterial endothelium (Packard, 2022). Evidence suggested that the relationship between RC and cognitive function can be attributed to the increased risk of cardiovascular disease secondary to higher RC levels (Xiao et al., 2023). This link is thought to be mediated by adverse effects on the arterial endothelium.

Research on the relationship between RC and cognitive function has been limited. A small sample ($n = 36$) cross-sectional study has preliminarily confirmed the correlation between RC and MCI (Zhang et al., 2023). Another study suggests that levels of RC are linked to verbal learning and memory function, suggesting that reducing RC levels could have potential benefits in preventing cognitive impairment in older individuals (Xie et al., 2022). Furthermore, accumulating evidence suggests that higher RC levels can increase the risk of residual atherosclerotic cardiovascular diseases (Wadström et al., 2022), stroke (Yang et al., 2023), hypertension (Chen et al., 2022), and diabetes mellitus (Petersen, 2004). Considering the extensive connection between these diseases and MCI, we hypothesized that plasma RC levels were associated with aMCI. Further researches are needed to validate the roles of RC in cognitive function.

To address these gaps, we conducted a community-based cross-sectional study, focusing on older individuals aged 65 and above. Through rigorous aMCI diagnosis, controlled for confounding factors, aimed to further investigate the relationship between RC levels and aMCI, and provide new data to support the exploration of the predictive value of RC in diagnosing aMCI.

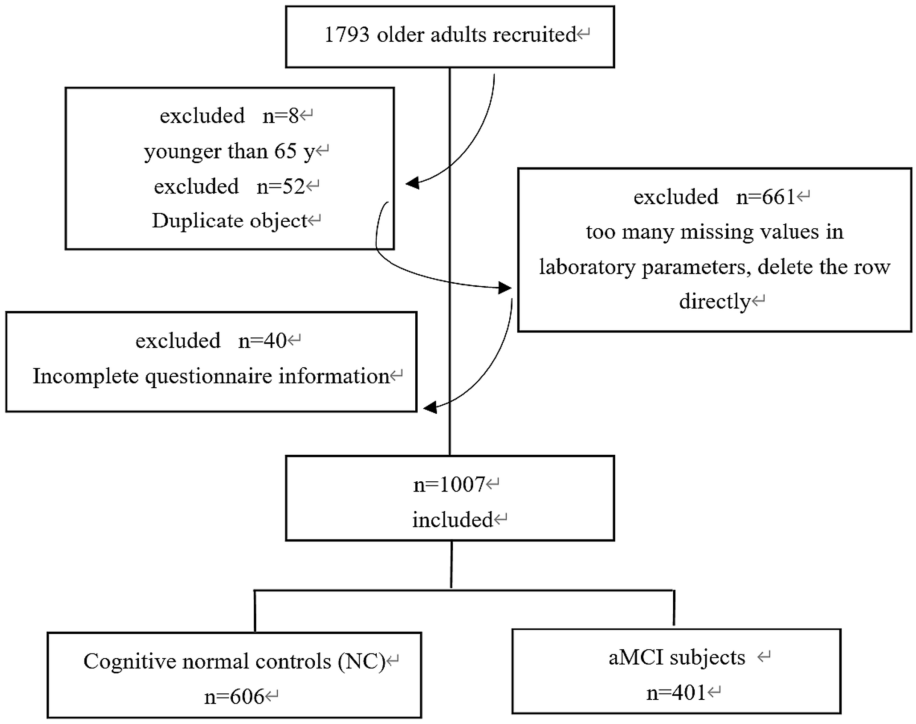

FIGURE 1
Flow chart detailing the derivation of the study sample.

2 Materials and methods

2.1 Participants

A multi-stage whole-group sampling was carried out from January 2022 to July 2022 to select older individuals from the communities under the jurisdiction of Wunancun Community Health Service Station in Wuchang District and Hongshan District Hospital of TCM, Wuhan City, Hubei Province, China. Participants were included and excluded by the criteria defined below.

2.1.1 Inclusion criteria

① age ≥ 65 years old; ② having lived in the target communities in Wuhan for more than 1 year and not planning to move out within 2 years; ③ having sufficient visual and auditory discrimination to undergo neuropsychological testing; ④ provided informed consent for voluntary participation.

2.1.2 Exclusion criteria

① those who did not meet the above criteria and had incomplete information; ② those who had cognitive impairment caused by other diseases like brain injury, drug poisoning, etc.; ③ those who had slurred conscious speech, psychiatric disorders, or severe heart, liver, or kidney diseases; ④ those who did not want to accept the study or could not cooperate for other reasons.

As shown in Figure 1, the final sample of 1,007 participants were screened out for the analysis. All these subjects were examined by experienced geriatric psychiatrists according to the diagnostic criteria of cognitive impairment. They were divided into two groups: the normal cognitive group (NC) ($n = 606$) and the aMCI group ($n = 401$).

2.2 Cognitive evaluation

A total of 1793 older people participated in the questionnaire survey through the testing port of a brain benefiting cloud platform[1] developed by the Brain Health Cognitive Management Team, Hubei University of Chinese Medicine. This cloud platform was developed based on two national projects, integrating cognitive function screening, intervention, follow-up and management of older adults in Wuhan communities. The assessment included general demographic data, cognitive screening, and some exclusion scales, taking approximately 30–50 min.

2.3 Diagnostic criteria for aMCI

According to the Petersen revised criteria (Writing Group of Dementia and Cognitive Impairment of Neurology Branch of Chinese Medical Association, 2010), the Chinese Guidelines for the Diagnosis and Treatment of Dementia and Cognitive Impairment (Chinese Society of Dementia and Cognitive Impairment, 2022), expert consensus (Shi et al., 2012), and the Chinese Guidelines for the Treatment of Dementia (Jinzhou et al., 2021; Hu et al., 2022) regarding the diagnostic criteria of aMCI include: ① complaints of memory impairment, confirmed by others; ② evidence of mild cognitive impairment or psycho-behavioral assessment confirmed by objective assessment; ③ MMSE score between 24 and 30 points,

1 https://hbtcm.66nao.com/assess/

MoCA score less than 26 points; ④ intact or very slightly impaired activities of daily living, such as activities of daily living (ADL) score less than 16; ⑤ Clinical Dementia Rating Scale (CDR) = 0.5; ⑥ Hachinski Inchemic Score (HIS) <4; ⑧ Hamilton Depression Scale (HAMD) <20.

2.4 Blood sampling and laboratory tests

After fasting overnight for 12 h, blood samples were collected from the anterior cubital vein by professionals from 7:30 am to 9:00 am, and a coded container was used to collect clean morning urine samples as required. Laboratory indicators including fasting blood glucose, Total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) were tested by the hospital laboratory center and uploaded to the hospital laboratory information system. The RC was calculated by subtracting HDL-C and LDL-C from total cholesterol (TC): RC = TC – HDL-C – LDL-C.

2.5 Ethical statement

This study followed the guidelines of the World Medical Association Declaration of Helsinki. The Medical Ethics Committee of Hubei University of Chinese Medicine reviewed and approved the study protocol (No.: 2019IEC003). All participants signed informed consent for the study. Participants' personal information was strictly confidential, and the medical examination number was used as the unique identification code instead of their names.

2.6 Statistical analysis

The data were exported to Excel format from the background management port of the brain benefiting cloud platform.[2] Statistical analysis was performed using SPSS 25.0 and Python 3.9. Differences in the demographics and laboratory tests between the two groups were first examined with statistical tests appropriate for the variable types. Specifically, continuous data were expressed as mean and standard deviation (mean ± SD), normal tests, homogeneity of variance tests and independent sample t-tests were used for continuous variables; Categorical variables were expressed as frequencies (%) and the chi-square tests were chosen when compare the two groups (NC vs. aMCI). Second, binary logistic regression analysis was run to determine the associated factors of aMCI, and the results were reported in odds ratio (OR) and 95% confidence intervals (CI). Third, partial correlation analysis was conducted to examine the correlation between RC and cognitive function in aMCI elders. A two-sided $P<0.05$ was considered statistically significant. As the last step, receiver operating characteristic (ROC) curve analysis was conducted to explore the predictive efficacy of RC in predicting aMCI, irrespective of other covariates.

2 https://hbtcm.66nao.com/admin/

3 Results

3.1 Demographic and clinical features of the NC and aMCI groups

To minimize confounding factors and ensure the comparability of the research participants, dementia family history, chronic disease history and hobbies of older individuals were controlled (Supplementary Tables S1, S2).

Table 1 shows that compared to the NC group, the aMCI group had a higher proportion of manual work and lower income levels ($p<0.05$); Besides, the aMCI group also performed worse in cognitive subtests except orientation (all $p<0.05$).

3.2 Lipid parameters of the NC and aMCI groups

Compared to the NC group, the aMCI group had lower HDL-C, HDL-C/LDL-C levels, and higher RC levels ($p<0.05$); However, there were no significant differences in TC, TG, and LDL-C levels between the two groups ($P>0.05$), more details see Table 1.

3.3 Logistic regression analysis of the possible correlates for aMCI

Table 2 shows the results of binary logistics regression with aMCI as a dependent variable (0 = No, 1 = Yes); Model 1 did not control any covariates, RC was treated as the independent variables, and the results showed that RC increased the risk of aMCI ($p=0.000$, OR = 1.890, 95%CI: 1.396–2.558). Taking into account statistically significant variables ($p<0.05$), Model 2 further controlled for occupation, income, HDL-C and HDL-C/LDL-C, the relationship between RC and aMCI has been weakened but still exists ($p=0.046$, OR = 1.453, 95%CI: 1.006–2.097), other associated factors of aMCI were occupation ($P<0.001$, OR = 0.543, 95%CI: 0.430–0.685) and income ($p=0.018$, OR = 0.715, 95%CI: 0.542–0.943). Taking into account professionally significant variables, excluding multicollinear covariates, and simplifying the model, Model 3 retained significant variables in univariate analysis, and further controlled for age, gender and education, excluded HDL and HDL-C/ LDL-C, the results did not change. Model 3 showed that occupation ($P<0.001$, OR = 0.533, 95%CI: 0.423–0.673) and RC ($p=0.014$, OR = 1.477, 95%CI: 1.081–2.018) were associated factors of aMCI. Specifically, the risk of aMCI was higher in elders engaged in manual work before retirement compared to those engaged in mental work. RC levels were positively associated with the possibility of aMCI, in that every 1-unit (mmol/L) increase in RC, the odds of aMCI increased by 1.477 times (95%CI: 1.081–2.018).

3.4 Associations between RC and cognitive performance in aMCI elders

Partial correlation analysis was conducted to control for occupation. Table 3 showed a significant negative correlation between RC levels and MoCA score ($r=0.059$, $p=0.046$), Naming score

TABLE 1 Demographic properties and laboratory parameters of the two groups ($n = 1,007$).

variables	NC(n = 606)	aMCI(n = 401)	χ^2 or t	*P*
Age, years	71.14 ± 4.944	71.25 ± 4.708	−0.342	0.733
Gender, male *n* (%)	255 (42.1)	153 (38.2)	1.542	0.214
Education, *n* (%)			6.029	0.110
Primary school and below	93 (15.3)	61 (15.2)		
Junior high school	187 (30.9)	149 (37.2)		
Technical secondary school/high school	198 (32.7)	126 (31.4)		
College degree or above	128 (21.1)	65 (16.2)		
Marriage, single[#] (%)	122 (20.1)	75 (18.7)	0.313	0.576
Living, single (%)	62 (10.2)	37 (9.2)	0.274	0.600
Occupation[^], *n* (%)			54.105	<0.001*
Manual	332 (54.8)	310 (77.3)		
Mental	221 (36.5)	68 (17.0)		
Uncertain	53 (8.7)	23 (5.7)		
Income, over ¥4,000(%)	229 (37.8)	121 (30.2)	6.170	0.013*
Family history, yes (%)	51 (8.4)	23 (5.7)	2.546	0.111
Hypertension, yes (%)	282 (46.5)	178 (44.4)	0.448	0.503
Diabetes, yes (%)	115 (19.0)	82 (20.4)	0.332	0.564
Hyperlipidemia, yes (%)	63 (10.4)	50 (12.5)	1.041	0.308
SBP (mmHg)	134.23 ± 19.921	133.34 ± 18.975	0.705	0.481
DBP (mmHg)	75.68 ± 11.638	76.82 ± 11.043	−1.541	0.124
FBGLU (mmol/L)	5.70 ± 1.485	5.63 ± 1.573	0.698	0.485
TC (mmol/L)	4.86 ± 1.030	4.92 ± 1.107	−0.830	0.407
Triglyceride (mmol/L)	1.61 ± 1.217	1.58 ± 1.069	0.416	0.677
HDL-C (mmol/L)	1.45 ± 0.435	1.38 ± 0.348	2.809	0.005*
LDL-C (mmol/L)	2.89 ± 0.822	2.89 ± 0.851	−0.101	0.919
HDL-C/ LDL-C (mmol/L)	0.55 ± 0.266	0.52 ± 0.201	2.307	0.021*
RC (mmol/L)	0.52 ± 0.447	0.64 ± 0.431	−4.293	<0.001*
MMSE	26.69 ± 3.074	27.19 ± 2.008	−3.105	0.002*
MoCA	22.18 ± 5.077	21.07 ± 3.367	4.159	<0.001*
Visuospatial and Executive	3.28 ± 1.445	3.04 ± 1.220	2.786	0.005*
Naming	2.41 ± 0.814	2.29 ± 0.794	2.455	0.014*
Attention and Calculation	5.74 ± 1.346	5.91 ± 0.998	−2.333	0.020*
Language	1.63 ± 0.840	1.45 ± 0.740	3.724	<0.001*
Abstraction	1.14 ± 0.758	0.96 ± 0.690	3.773	<0.001*
Recall	2.33 ± 1.604	1.71 ± 1.329	6.668	<0.001*
Orientation to time and place	5.66 ± 0.733	5.72 ± 0.622	−1.524	0.128

P.S.: [#]means unmarried/widowed/divorced; [^]means occupation one's engaged before retirement; *means $P < 0.05$; FBGLU, Fasting blood glucose; TC, Total cholesterol; RC, Remnant cholesterol.

($r = 0.070$, $p = 0.026$), indicating that higher RC levels were associated with worse cognitive performance in aMCI participants. No significant correlation with other subtest was found ($p > 0.05$).

3.5 The independent predictive efficacy of RC level on aMCI

ROC curve analysis indicated that RC levels had an independent predictive efficacy in predicting aMCI, with an area under the curve (AUC) of 0.580 ($p < 0.001$, 95%CI: 0.544–0.615), see Table 4. The results suggest that higher RC levels were associated with a higher likelihood of aMCI, see Figure 2.

Independent predictive value of other blood lipid parameters for aMCI were shown in Table 4.

4 Discussions

This study investigated the correlations between blood lipids and aMCI and subsequently discovered that RC levels were associated with aMCI. To our knowledge, this is the first study to establish this

TABLE 2 Results of logistic regression analysis of the possible correlates for aMCI.

Variable	*β*	SE	Wals	*P*	OR (95%CI)
Model 1					
RC	0.636	0.155	16.968	0.000	1.890(1.396 ~ 2.558)
constant	−0.780	0.111	49.520	0.000	0.458
Model 2					
occupation	−0.611	0.119	26.435	0.000	0.543(0.430 ~ 0.685)
income	−0.335	0.141	5.637	0.018	0.715(0.542 ~ 0.943)
HDL-C	−0.129	0.220	0.343	0.558	0.879(0.571 ~ 1.353)
HDL-C/ LDL-C	0.123	0.386	0.102	0.749	1.131(0.531 ~ 2.412)
RC	0.373	0.187	3.976	0.046	1.453(1.006 ~ 2.097)
constant	0.793	0.432	3.370	0.066	2.210
Model 3					
age	−0.001	0.014	0.007	0.934	0.999(0.972 ~ 1.026)
gender	−0.051	0.149	0.117	0.733	0.950(0.710 ~ 1.273)
education	−0.069	0.071	0.929	0.335	0.934(0.812 ~ 1.074)
occupation	−0.628	0.119	27.973	0.000	0.533(0.423 ~ 0.673)
income	−0.284	0.166	2.938	0.087	0.753(0.544 ~ 1.042)
RC	0.390	0.159	6.010	0.014	1.477(1.081 ~ 2.018)
constant	1.026	1.118	0.843	0.359	2.791

TABLE 3 Correlations between RC levels and cognitive performance.

		MOCA	Visuospatial and executive	Naming	Attention and calculation	Language	Abstraction	Recall	Orientation
RC	*r*	−0.063	−0.059	−0.070	−0.008	−0.022	−0.051	−0.034	−0.044
	P	0.046*	0.060	0.026*	0.793	0.491	0.107	0.287	0.165

P.S.: control variable: occupation. *$P < 0.05$, considered statistically significant.

TABLE 4 AUC of lipid parameters to predict aMCI.

variable	AUC	SE	*P*	95% CI	
				Lower	Upper
RC	0.580	0.018	0.000	0.544	0.615
TC	0.513	0.019	0.487	0.476	0.550
TG	0.493	0.019	0.689	0.456	0.529
HDL-C	0.459	0.018	0.028	0.423	0.495
LDL-C	0.503	0.019	0.890	0.466	0.539
HL	0.477	0.019	0.224	0.441	0.514

connection using data from over 1,000 community older individuals. Specifically, the key findings include: ① the aMCI group exhibited higher RC levels compared to the group with normal cognitive function; ② plasma RC levels were positively linked to the likelihood of developing aMCI; ③ RC levels were associated with impaired cognitive performance, particularly in the naming cognitive domain, among older individuals with aMCI; ④ plasma RC levels independently predicted aMCI.

These results were consistent with subgroup analysis result that the association between RC and the risk of cardiovascular events is not dependent on factors such as pre-existing diseases, diabetes, total cholesterol, triglyceride levels, ApoB (apolipoprotein B) levels, or BMI stratification (Yang et al., 2023). As the regression modeling controlled for comorbidities such as hypertension, diabetes, or stroke, chronic diseases, and occupations, no concerns seemed to be necessary regarding whether the risk of aMCI associated with RC depends on comorbidities and occupation.

Is it possible that the risk of RC was dependent on other lipid parameters? To address this question, a collinearity diagnosis was performed on blood lipid parameters, and no multicollinearity was found among the blood indicators related to cognitive function

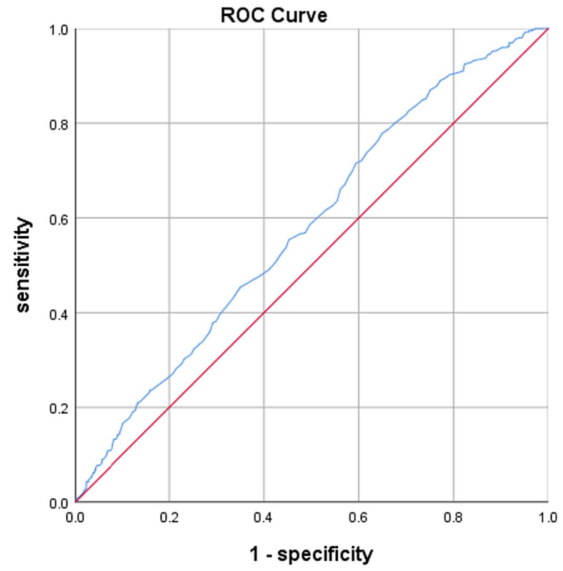

FIGURE 2
ROC curves for the predictive efficacy of RC on aMCI.

(tolerance: 0.248–0.564, VIF:1.774–4.036). No additional differences were found in TG, TC and LDL-C between aMCI elders and normal controls. However, the average HDL-C level and HDL/LDL ratio in the aMCI group were lower, compared to the normal group. A cross-sectional study reported that higher circulating TC, HDL-C and HDL/LDL ratio indicated an increased risk of MCI (Guo et al., 2020). On the other hand, another observational study including 125,727 individuals suggested that higher plasma triglycerides concentrations were associated with an increased risk of non-Alzheimer dementia and ischemic stroke but not with AD and aMCI (Nordestgaard et al., 2021). Therefore, the association between blood lipid parameters and cognitive function remains controversial.

The biological mechanisms of the association between RC and aMCI are beyond the scope of this study and still unclear. Several possibilities can be considered, with the first involving genetic factors. Using Mendelian randomization, a previous research found that APOE4 carriers had less favorable lipid profiles, which were associated with a greater risk of dementia and cognitive impairment (Dunk et al., 2023). Second, RC may interact with beta-amyloid (Aβ), which is biologically plausible (Zhang et al., 2023). Cholesterol transport may be involved in the development and progression of cognitive impairment (Zhang et al., 2023). Last, the association between high RC levels and aMCI could be explained by the pathophysiological processes of atherosclerosis (Hu et al., 2022; Nordestgaard et al., 2022). Other potential mechanisms including anti-oxidation, anti-inflammation, anti-thrombosis, and modulation of immune function (Yang et al., 2023). All these possible explanations entail further studies.

The demographic characteristics were not found statistically different in age, gender and education attainment between aMCI group and the normal controls. However, the aMCI group had a higher average age, a larger proportion of women, and a lower proportion of individuals with high school education or above, which is consistent with previous research (Garibotto et al., 2008; Overton et al., 2019; US Preventive Services Task Force et al., 2020; Huang et al., 2022). Additionally, compared to the normal group, the aMCI group had a lower average monthly income, which aligns with previous findings (Guo et al., 2023). These demographics differences did not shadow the unique association of RC with aMCI identified from the logistic regression, as they were controlled.

4.1 Limitations and strengthens

There are some limitations to this study. First, it was only a cross-sectional study, and RC levels were measured only once. Although RC may change over time, it is generally considered relatively stable, so this limitation would not significantly impact the main aim of the study. However, in order to establish a causal relationship between RC and aMCI, more longitudinal or randomized controlled trials (RCT) studies are needed. Second, the study population consisted of individuals residing in an urban area of central China, which may limit the generalizability of the findings to rural populations and other ethnic groups; Third, the intermittent outbreaks of COVID-19 in Wuhan China caused missing laboratory indicators in many participants, whom had to be excluded from the analyses. It is uncertain whether this exclusion affected the representativeness of the sample and result.

Despite these limitations, this study still has several important strengths. This study design was rigorous, with cognitive function assessments conducted by experienced geriatric psychiatrists according to strict criteria. The diagnosis of MCI did not rely solely on one scale such as MMSE or MoCA, a complete diagnostic program enhanced the validity of the findings. Additionally, the detailed questionnaire allowed for the consideration of various important confounding factors related to the associations found. The study also excluded the effects of diseases and vascular factors on MCI and included older individuals with aMCI who mainly experienced memory decline, ensuring homogeneity within the study sample. Furthermore, our research team developed a cloud platform for data collection and storage, which minimized potential errors in data entry that could arise with paper questionnaires.

5 Conclusion

The study findings indicated that higher RC levels were identified as an independent indicator for aMCI, particularly in the naming cognitive domain among older individuals. In addition to conventional lipid parameters, clinicians should pay close attention to RC for prevention of MCI. Further longitudinal studies are necessary to validate the predictive efficacy of RC.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Medical Ethics Committee of Hubei University of Chinese Medicine. The studies were conducted in accordance with the local legislation and

institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

YA: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Software, Writing – original draft, Writing – review & editing. CZ: Conceptualization, Formal analysis, Investigation, Methodology, Software, Validation, Writing – original draft, Writing – review & editing. MW: Data curation, Formal analysis, Investigation, Resources, Validation, Writing – review & editing. CY: Writing – original draft, Writing – review & editing, Methodology. SZ: Conceptualization, Data curation, Formal analysis, Investigation, Writing – review & editing. XD: Conceptualization, Data curation, Formal analysis, Investigation, Writing – review & editing. NY: Conceptualization, Data curation, Formal analysis, Investigation, Writing – review & editing. YL: Data curation, Formal analysis, Investigation, Writing – review & editing. LW: Conceptualization, Methodology, Writing – review & editing. HR: Conceptualization, Formal analysis, Writing – review & editing. XG: Methodology, Software, Writing – review & editing. MX: Formal analysis, Methodology, Writing – review & editing. HH: Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing. YW: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

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Effectiveness of a multicomponent exercise intervention in community-dwelling older Chinese people with cognitive frailty: protocol for a mixed-methods research

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Aims: To evaluate the effectiveness of a multicomponent exercise intervention and to clarify the underlying mechanisms of the program in community-dwelling older adults with cognitive frailty. Additionally, the perception of participants in the program will be explored.

Design: A mixed-methods design, including a randomized controlled trial and an exploratory qualitative study, was used.

Methods: Each group consists of 41 participants. The experimental group will undergo a 12-week multicomponent exercise intervention, including warm-up, exergaming aerobic exercise, elastic-band resistance exercise, and cool-down. This intervention was developed based on the Health Belief Model (HBM) and Self-Efficacy Model (SEM). The control group will not receive any intervention. Physical frailty and cognitive function will be considered as primary outcomes. Data will be collected both at baseline and at the end of the intervention period. Fisher's exact test, analysis of covariance, and generalized linear models will be conducted to compare mean changes between the two groups. Additionally, the mediation models will be used to examine whether any intervention effects are mediated through exercise self-efficacy.

Discussion: The findings of this study are anticipated to provide valuable insights for healthcare providers, enabling them to learn about effective strategies to enhance exercise adherence and promote improved functionality, independence, and quality of life for older adults with cognitive frailty.

Clinical trial registration: [https://clinicaltrials.gov/], identifier [ChiCTR2200058850].

KEYWORDS

exercise intervention, exergaming, resistance exercise, community-dwelling, older adults, cognitive frailty, mixed methods

1 Introduction

Physical frailty emerges as a prevalent geriatric syndrome globally, which is characterized by age-associated declines in physiologic reserve and function across multiorgan systems (Fried et al., 2001). One of the most common physical frailty models described in the literature is the Fried frailty phenotype, which defines frailty as a clinical syndrome meeting three or more of the five indicators: unintentional weight loss, physical inactivity, exhaustion, weakness, and slowness (Fried et al., 2001). One recent systematic review provides prevalence proportions for older adults in population-level studies from 62 countries/territories for using the Fried frailty phenotype approaches to define frailty, generating a pooled prevalence of 12% for physical frailty (O'Caoimh et al., 2020). Physical frailty overlaps with other geriatric syndromes, such as cognitive impairment, resulting in increased vulnerability to various adverse health outcomes (Kelaiditi et al., 2013; Chu et al., 2021).

Cognitive frailty has been defined as the presence of both physical frailty and cognitive impairment without a clinical diagnosis of Alzheimer's disease and other dementias (Kelaiditi et al., 2013). The prevalence of cognitive frailty among community-dwelling older adults is 6% (Zhang et al., 2022). Compared to either physical frailty alone or cognitive impairment alone, cognitive frailty poses a higher vulnerability to adverse outcomes, including disability, dementia, and mortality (Kelaiditi et al., 2013; Ruan et al., 2015). Cognitive frailty has been considered an intervention window because older adults with cognitive frailty are more likely to revert to a robust state through appropriate interventions compared to those with dementia and disability (Solfrizzi et al., 2017). Research has shown that exercise intervention is a highly recommended strategy for improving the health outcomes of older adults with cognitive frailty (Chen et al., 2021). Exercise, as a subset of physical activity, is characterized by planned, structured, and repetitive implementation (Caspersen et al., 1985; Thivel et al., 2018). It aims to improve or maintain one or more components of physical fitness (Dasso, 2019). Exercise can be performed in different forms and can differ in intensity, duration and type (e.g., aerobic and strength). According to the American College of Sports Medicine (ACSM) recommendations, multicomponent physical activity, including both aerobic and muscle-strengthening activities, should be adopted among older adults (Nelson et al., 2007).

2 Background

Older adults with cognitive frailty are acknowledged to be frailer compared to their healthier peers. Furthermore, they tend to have sedentary lifestyle and engage less in physical activity (Kwan et al., 2020). Research has indicated that a sedentary lifestyle and physical inactivity are associated with adverse health outcomes (Theou et al., 2017). Conversely, physical exercise may enhance physical performance, cognitive function, and mental health in individuals with cognitive frailty (Yoon et al., 2018; Chen et al., 2021; Li et al., 2022). This highlights the importance of promoting physical exercise within this group.

However, it is challenging to change people's physical exercise behaviors. Adherence to physical exercise interventions is often low among older population (Valenzuela et al., 2018; Moral-Munoz et al., 2022). Exercise adherence plays a crucial role in determining whether and how much the exercise intervention could be effective. Some exercise interventions have failed to achieve the intended effectiveness due to poor exercise adherence (Clegg et al., 2014; Gwyther et al., 2018). Previous studies have identified common reasons for this lack of adherence, such as physical limitations, environmental barriers, and time constraints (André and Agbangla, 2020; Collado-Mateo et al., 2021). Additionally, lack of motivation and enjoyment of exercise have been recognized as significant factors influencing adherence (André and Agbangla, 2020; Collado-Mateo et al., 2021).

Exergaming, a form of enjoyable aerobic exercise-based video games that combine physical activity and cognitive stimulation within a virtual environment, has emerged as an innovative way to encourage exercise among older adults (Choi et al., 2017; Karssemeijer et al., 2019). Several studies have examined the adherence and effectiveness of exergaming in older adults, revealing promising results that underscore its ability to enhance motivation for sustaining exercise programs (Lamoth et al., 2011; Altamimi and Skinner, 2012). However, while these programs target older people in general, they do not focus on older adults with cognitive frailty (Cacciata et al., 2019; Yen and Chiu, 2021). Additionally, these exergaming programs typically focus solely on aerobic activities, lacking of muscle-strengthening exercises, which may potentially limit their overall health benefits (Stojan and Voelcker-Rehage, 2019; Esmaeilzadeh et al., 2022). The ideal exercise prescription for older individuals should incorporate both aerobic and muscle-strengthening exercise (Venegas-Sanabria et al., 2022). Both forms of exercise are crucial for successful performance in activities of daily living (ADLs) and for maintaining physical and psychological wellbeing (Chodzko-Zajko et al., 2009). Relying solely on a single form of exercise may not provide comprehensive benefits (Chodzko-Zajko et al., 2009).

Furthermore, the selection of assessments is pivotal in intervention studies. Previous studies among cognitive frailty have predominantly focused on intervention effectiveness related to frailty, cognitive function, muscle-related outcomes, physical functional abilities, and quality of life. However, there's been a lack of attention to intervention effects on senior fitness, sleep quality, and mental health (Yoon et al., 2018; Kwan et al., 2020). Researchers are encouraged to explore the effectiveness of exercise interventions from a broad perspective for comprehensive effectiveness evaluation, considering exercise interventions have been proven to offer a wide range of health benefits (Qiao et al., 2022).

Moreover, most previous exercise studies lack a theoretical basis for understanding exercise behavior change (Hauer et al., 2020; Huang, 2020), thereby limiting the exploration of potential intervention mechanisms among older adults with cognitive frailty. Currently, the Health Belief Model (HBM) and the Self-Efficacy Theory (SET) are two commonly used theoretical frameworks in physical exercise research (Biddle and Nigg, 2000). Our proposed intervention program is guided by theoretical constructs drawn from the HBM and SET (Figure 1). Self-efficacy, defined as one's confidence in performing particular behaviors, significantly influences health behavior performance, subsequently impacting health outcomes (Bandura, 1994). Perceived threat, perceived benefits, perceived barriers, mastery experience, verbal persuasion, and physical and psychological states stand as key sources contributing to self-efficacy (Bandura, 1994). Studies have shown that self-efficacy predicts physical exercise behavior in older adults and plays a role in both the

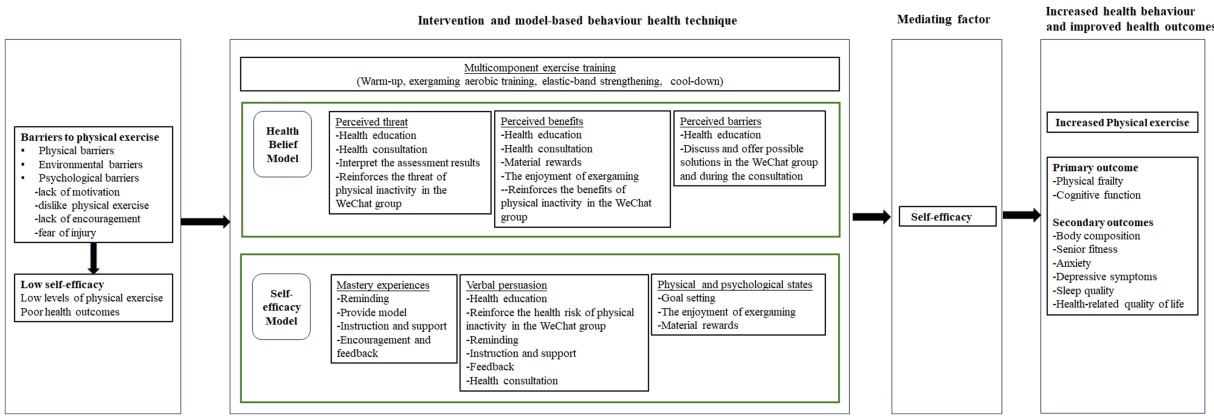

FIGURE 1
Conceptual framework for the intervention.

adoption and maintenance of physical exercise (Di Maio et al., 2021; Bateman et al., 2022). Additionally, experimental findings support the idea that changes in self-efficacy can act as a mediator in the impact of behavior interventions on objectively measured physical exercise behavior (Ratz et al., 2020).

The proposed intervention aims to enhance the participant's self-efficacy by employing a series of model-based behavior health technique. Techniques such as reminders, goal setting, encouragement, and feedback, when coupled with incentives, serve as motivators to improve self-efficacy (Ashford et al., 2010; Eather et al., 2013; Lewis et al., 2016). Consequently, the intervention program, incorporating multicomponent exercise training and model-based behavior health technique, is hypothesized to provide older adults with a stronger sense of self-efficacy, leading to increased physical exercise and improved health outcomes.

Therefore, the objectives of this study were: (1) to evaluate the effectiveness of a multicomponent exercise intervention in improving the health outcomes (physical frailty, cognitive function, body composition, senior fitness, mental health, sleep quality, and health-related quality of life) among older adults with cognitive frailty; (2) to examine whether any health-improving effects are mediated through exercise self-efficacy; and (3) to explore the participants' perception of the multicomponent exercise intervention.

3 Methods

3.1 Research hypotheses

To assess the impact of the multicomponent exercise intervention, our study hypothesizes several outcomes across physical, cognitive, mental, and quality-of-life domains. We aim to explore the potential effects of this intervention on various parameters and examine the mediating role of exercise self-efficacy.

(1) We hypothesized that participants who receive the multicomponent exercise intervention will report greater improvements in physical frailty, cognitive function, body composition, senior fitness, mental health, sleep quality, and health-related quality of life upon completion of the intervention compared to those in the control group.

(2) We hypothesized that the effects of the multicomponent exercise intervention on physical frailty, cognitive function, body composition, senior fitness, mental health, sleep quality, and health-related quality of life are mediated through an increase in exercise self-efficacy.

(3) No starting hypothesis has been established for the qualitative part of the study because it is oriented through an exploratory study.

3.2 Methodology

3.2.1 Study design, setting, and participants

This mixed methods study comprises a single-blind (outcomes assessor) randomized controlled trial (RCT) and a descriptive qualitative study. It will be conducted in community settings targeting older adults with cognitive frailty in Changsha City, Hunan Provence, China. Community settings will be chosen based on approval from local committees and the availability of eligible older adults. To engage older residents and encourage their participation, we will utilize posters, flyers, and social media platforms to disseminate information about the study. Additionally, recruitment will be conducted in collaboration with healthcare personnel who are responsible for the preventive home visits for the local residents.

Inclusion criteria:

(1) Aged ≥60 years.

(2) Fulfilling the definition of cognitive frailty, which includes:

(a) pre-physical frailty or physical frailty (Fried frailty phenotype score ≥ 1), and.

(b) Montreal Cognitive Assessment (MoCA) scored between 18 and 25, but in the absence of dementia (Kelaiditi et al., 2013).

(3) Providing informed consent and voluntary participation in the study.

Exclusion criteria:

(1) Poorly controlled or severe status of cardiovascular diseases, chronic obstructive pulmonary disease, diabetes, or hypertension.

(2) Inability to walk independently.

(3) Severe hearing or visual impairments.

(4) Other health conditions that prevent participation in sports exercise.

(5) Currently enrollment in other intervention programs.

The trial will run for a 12-week period. Participants will be enrolled based on inclusion and exclusion criteria. Measurements will be conducted at baseline and at the end of the intervention period. An overview of the study design is presented in Figure 2. Regarding the qualitative study, a subgroup of participants assigned to receive the multicomponent exercise intervention will undergo semi-structured interviews to explore their perception of the program.

3.2.2 Intervention

Based on literature review, interviews with cognitive frail older adults, and consultations with physiotherapist, a preliminary multicomponent exercise intervention has been recommended for older adults with cognitive frailty. During the 12-week multicomponent exercise intervention period, participants will engage in moderate physical exercise tailored to their individual abilities, with each session lasting 50 min, held 3 times per week in a group setting at the local community center. Trained research assistants will provide assistance during these sessions. To control for concomitant exercise and diet, all participants will be advised not to seek any other exercise and instructed to maintain their normal diets throughout their enrollment in the study.

The daily session will be divided into warm-up, exergaming aerobic exercise, elastic-band resistance exercise, and cool-down. Each session will start and end with a 5-min warm-up and cool-down routine to stretch the main muscle groups being trained. Ping-Pong exergaming on the Xbox 360 4GB Console with Kinect will be chosen as the aerobic exercise because Ping-Pong is familiar to most older adults in China and requires fewer skills compared to other types of exergaming. This type of exergaming is suitable for older adults with cognitive frailty because it is easier to learn. The progression of ping-pong exergaming will be managed by adjusting

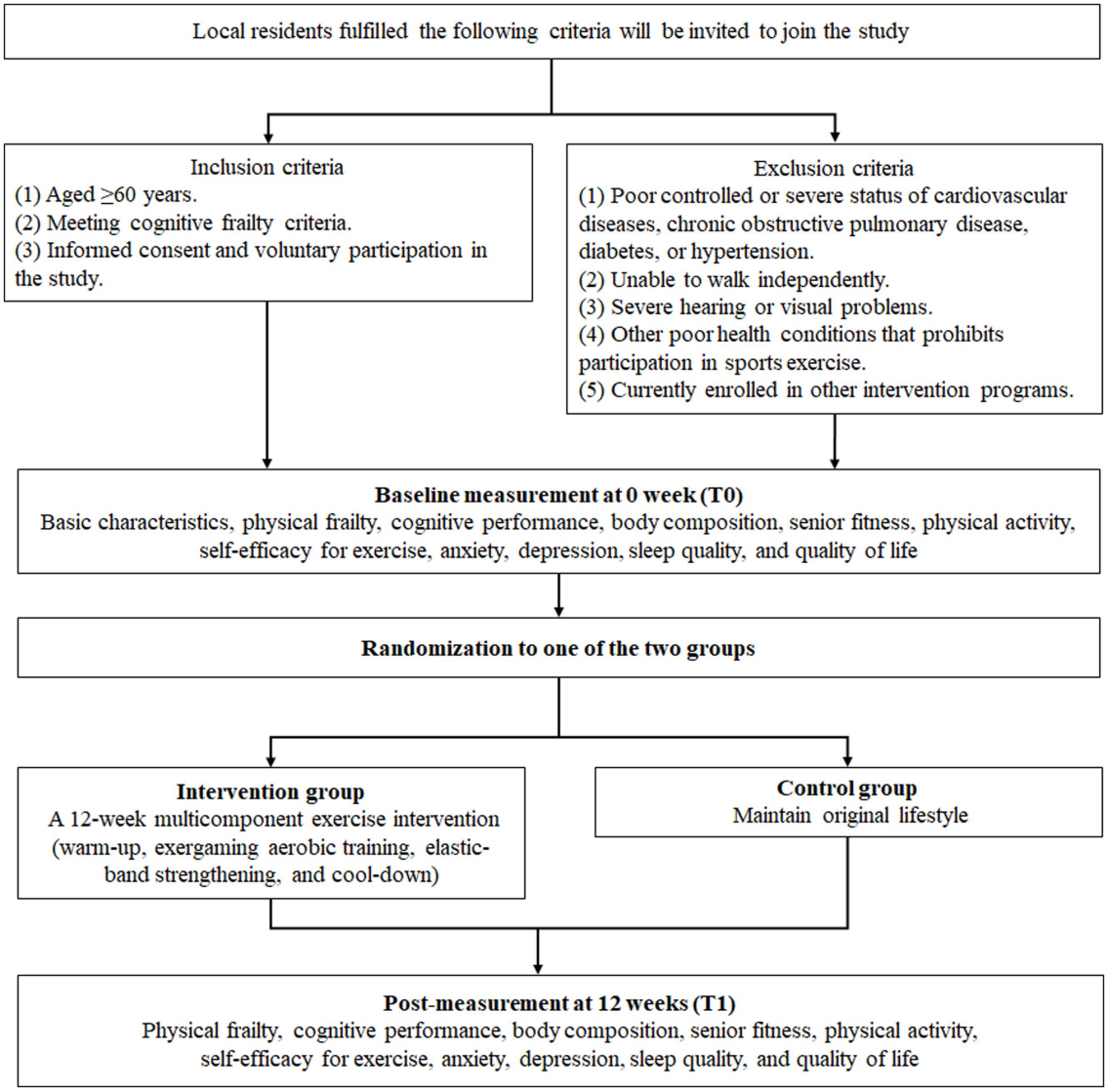

FIGURE 2
Study design.

the exercise intensity. The duration of the ping-pong exergaming would be approximately 20 min per daily session. The intensity will be gradually increased throughout the entire intervention period based on the self-reported tiredness and assessment conducted by trained exercise supervisors. Resistance exercise will utilize an elastic band (Thera-Band elastic band). The general recommendation will be an exercise intensity of 70–80% of 1 repetition maximum (1RM) allowing older adults to perform 8–10 repetitions (Liguori and American College of Sports Medicine, 2020). The duration of the resistance exercise will be about 20 min per session. The elastic-band is color-coded, with different colors representing different levels of resistance. In this study, yellow, red, green, and blue elastic-bands will be used alternately to increase resistance intensity. To ensure participants exercise at the appropriate intensity, their perceived effort levels will occasionally be assessed using the Borg Rating of Perceived Exertion scale, which ranges from 6 to 20 (Borg, 1982). Participants will be asked to report their average intensity level during the exercise sessions. Depending on the participant's fitness level, exercises should be performed with a perceived exertion range between 9 and 16 points during both aerobic and resistance training (Borg, 1982). Further details are presented in Table 1. The final exercise intervention protocol will be determined based on a pilot study involving 10 participants to assess feasibility.

In the control group, participants will maintain their normal daily activities without receiving any special intervention. Throughout the 12-week intervention period, if participants engage in additional physical activity, they will be required to document the details, including the activity time, type, and intensity. To avoid cross-contamination between the two groups, control over the exergaming power switch will remain with the intervention team, not the participants. Additionally, the elastic bands provided during sessions will be collected afterwards rather than kept by the participants.

3.2.3 Strategies to support behavior change

To enhance adherence to the multicomponent exercise intervention, strategies supporting behavior change will be implemented, integrating elements from the HBM and SET. Previous studies suggest that exercise interventions among older adults should prioritize strengthening their beliefs and self-efficacy. This involves educating them about the negative consequences of physical inactivity, highlighting the benefits of exercise, and teaching coping strategies to overcome potential barriers. It also focuses on helping participants mastery exercise experiences, maintain good physical and psychological states, and employ persuasion strategies (Biddle and Nigg, 2000; McAuley and Blissmer, 2000; Glanz et al., 2015). Details of the behavior change techniques (BCTs) (Michie et al., 2011) and how they are incorporated into this exercise intervention program are presented in Table 2.

TABLE 1 Description of the multicomponent exercise intervention.

Category	Description
Warm-up	Freehand training range of motion exercise for the wrists, hip, shoulder, knees, and ankles (about 5 min)
Aerobic exercise	Exergaming-based Ping-Pong aerobic exercise involves dynamic body movements, including swinging motions with virtual Ping-Pong paddles, upper body rotation to hit the ball accurately, and leg movements to position oneself correctly (about 20 min)
Resistance exercise	The action includes elastic-band pull-apart, front and lateral raises, elbow flexion/bicep curl, and elastic-band lateral leg abductions, etc. (about 20 min)
Cool-down	Freehand stretching and relaxing exercises involve the main muscles and joints of the whole body (about 5 min)

3.2.4 Sample size estimation

For the RCT, the sample size will be calculated using PASS software, based on improvement in the primary outcome (physical frailty) in this trial. Previous findings from a similar exercise program reported a reduction in physical frailty score of 0.22 in the control group and 1.59 in the intervention group (Sadjapong et al., 2020). Given a power of 90% and level $\alpha = 0.05$, 34 participants are needed. Considering a 20% attrition rate, with 41 participants in each group, a total of 82 participants are needed. Regarding the qualitative interviews, a purposive subsample of 20 participants who have completed the multicomponent exercise intervention will be recruited.

3.2.5 Randomization and blinding

A biostatistician, not involved in the trial, will randomize all eligible participants using a computer-generated random number list. Group assignments will be concealed in consecutively numbered sealed envelopes that will be opened sequentially upon the enrollment of each participant. Eligible subjects will be randomly allocated into two groups: the multicomponent exercise group and the control group. Participants and interveners will not be blinded to the intervention assignment due to the nature of exercise intervention. However, outcome assessors and data analysts will be blinded to group assignments.

3.2.6 Measurement

3.2.6.1 RCT

The measurements in this trial will consist of basic characteristics, physical frailty, cognitive performance, body composition, senior fitness, self-efficacy for exercise, anxiety, depressive symptoms, sleep quality, and health-related quality of life. Exercise self-efficacy will be chosen as the mediating factor. Physical frailty and cognitive function will be considered as the primary outcomes, while the rest are secondary outcomes. All these variables will be assessed at baseline and at the end of the intervention period. Additionally, we will collect data on adherence, dropout rate, satisfaction, and adverse events as complementary measures. Trained research assistants specializing in geriatrics will conduct these assessments.

3.2.6.1.1 Basic characteristics

Participants' demographic characteristics (e.g., age, sex, education, marital status, living arrangements, occupation, and income), lifestyle information (drinking and smoking), comorbidities, and medication use will be collected using a self-designed questionnaire.

3.2.6.1.2 Mediating factor

The Self-Efficacy for Exercise (SEE) Scale is a self-report of exercise self-efficacy. This scale has a range of total scores from 0–90.

TABLE 2 Behavior change techniques used in this exercise intervention program.

Beliefs and self-efficacy	Behavior change technique	How the technique is in this intervention
Perceived threat (HBM)	Provide information on consequences of behavior in general	Health education, interveners give information about correlation between insufficient physical activity and potential adverse effects in the general case. Interveners reinforce the health risk of physical inactivity through WeChat group.
	Provide information on consequences of behavior to the individual	Interveners interpret the baseline assessment results for participants, describe to the participants the underlying impairments identified at the baseline assessment. Interveners reinforce the health risk of physical inactivity during the consultation.
Perceived benefits (HBM)	Provide information on consequences of behavior in general	Health education, interveners disseminate knowledge regarding the health benefits of physical activity. Interveners reinforce the health benefits of physical activity through WeChat group.
	Provide information on consequences of behavior to the individual	Interveners interpret the baseline assessment results for participants, describe to the participants the health benefits of physical activity.
Perceived barriers (HBM)	Barrier identification /problem solving	Interveners ask the participants possible barriers and problems, discuss and offer possible solutions in the Wechat group and during the consultation. A brief medical safety check before each session to reduce injury risk.
Mastery experiences (SET)	Provide instruction on how to perform the behavior	Provide instruction and support on how to use exergaming equipment and elastic-band. Tips on wearing suitable clothing, shoes, and avoiding empty stomach, reminding when and where of each session will be sent to WeChat group.
	Model/Demonstrate the behavior	Each session will have a model showing the participants how to perform the multicomponent exercise training.
	Facilitate social comparison	Interveners will encourage participants to communicate and compare with other participants during training.
	Action planning	At week 1, interveners tell participants of detailed planning of what they will do including when, where, and how to act.
Physical and psychological states (SET)	Goal setting	At week 1, interveners and participants set individual goals concerning exercise training based on consider of participants' physical and psychological states.
	Stimulate anticipation of future rewards	Participants are informed at the beginning (week 1) that they will be rewarded based on their behavioral achievement.
Verbal persuasion (SET)	Provide information on consequences of behavior in general	Health education, interveners give information about correlation between insufficient physical activity and potential adverse effects in the general case. Interveners reinforce the health risk of physical inactivity through WeChat group.
	Provide feedback on performance	Participants will receive real-time feedback when playing exergaming. Intervener praise participants if they behave well during the training.
	Provide instruction on how to perform the behavior	Provide instruction and support on how to use exergaming equipment and elastic-band. Tips on wearing suitable clothing, shoes, and avoiding empty stomach, reminding when and where of each session will be sent to WeChat group.
	Provide normative information about others' behavior	Intervener provide information about other's good performance and encourage individuals to learn from successful experience through WeChat group.
	Prompt review of outcome goals	Intervener helps participants to review or analysis of the extent to which previously set outcome goals were achieved during the consultation.

A higher score indicates higher self-efficacy for exercise (Resnick and Jenkins, 2000).

3.2.6.1.3 Primary outcomes

Physical frailty will be measured according to the Cardiovascular Health Study criteria (Fried et al., 2001) to enable comparability. The assessment includes five components:

- Shrinking: Determined by unintentional weight loss exceeding 4.5 kg or more than 5% of body mass in the past 12 months.
- Weakness: Assessed through Body mass index (BMI) and sex-adjusted handgrip strength. Men cut-off points: 29, 30, and 32-kg handgrip strength for normal-weight, overweight and obese, respectively. Women: 17, 17.3,18, and 21 kg for underweight, normal-weight, overweight and obese, respectively.
- Exhaustion: Assessed by the frequency of fatigue in the last week using two items of the Center of Epidemiological Studies-Depression Scale (CES-D) (Orme et al., 1986).
- Slowness: Determined by height- and sex-adjusted gait speed. Cut-off points are 0.65 m/s of walking speed over a 4.57-m

distance for men and women ≤173 cm and ≤159 cm, respectively, and 0.76 m/s for height above these ranges.

- Low physical activity: Assessed using the International Physical Activity Questionnaire-Short Form (IPAQ-SF). Energy expenditure (kcal/week) will be calculated for each participant, and low physical activity will be identified by an expenditure of <383 kcal/week in men and <270 kcal/week in women (Brunner et al., 2018; Piotrowicz et al., 2023).

Individuals will be categorized into three groups based on their total score: robust (0), prefrail (1–2), and frail (3–5) groups (Fried et al., 2001). For this study, frailty status will be classified into two groups: the frail group (1–5) and the robust group (0).

The Montreal Cognitive Assessment (MoCA) is a brief screening tool for global cognition that reveals mild cognitive impairment and an early stage of Alzheimer's disease (Nasreddine et al., 2005). This tool evaluates various cognitive domains, including attention, concentration, executive function/visuospatial ability, memory, language, conceptual thinking, calculations, and orientation. MoCA scores range from 0 to 30, with scores of 26 and higher generally considered normal. Scores falling between 25 and 18 indicate mild cognitive impairment, while scores lower than 18 are indicative of Alzheimer's disease (Nasreddine et al., 2005). The Chinese version of MoCA (Beijing version) is widely utilized in China due to its established validity, reliability, and sensitivity (Yu et al., 2012).

3.2.6.1.4 Secondary outcomes

Body composition assessment will be conducted using the InBody S10. BMI will be calculated by dividing weight in kilograms by the square of height in meters. The senior fitness test battery referred to *Senior Fitness Test Manual, Second Edition* (Rikli and Jones, 2013), will be performed in the following order to minimize fatigue: (1) chair stand test (lower-body muscular strength); (2) arm curl test (upper-body muscular strength); (3) chair sit-and-reach test (flexibility); (4) back scratch test (flexibility); (5) 2.4-meter up-and-go test (dynamic balance); (6) single leg stand test (dynamic balance); and (7) 2-min step test (aerobic endurance). Anxiety will be assessed using the Generalized Anxiety Disorder Scale (GAD-7) (Dear et al., 2011), while depressive symptoms will be assessed using the Patient Health Questionnaire-9 (PHQ-9) (Löwe et al., 2004). Sleep quality will be determined by the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989), and health-related quality of life will be measured using the validated Chinese version of the Short Form Health Survey questionnaire (SF-12) (Ware et al., 1996). All these assessment tools have been demonstrated to have relatively good reliability and validity when used with the Chinese population.

3.2.6.1.5 Other collected data

Adherence to the program will be documented via an activity diary completed by the research assistants, and reasons for dropouts and poor adherence will also be documented. Reasons for dropout, including adverse events, medical problems, death, and participant decisions, will be collected. Program satisfaction will be evaluated using a self-designed questionnaire. Participants will rate their satisfaction based on perceived enjoyment of the training, the appropriateness of the content, the form of the training, the benefits obtained by the training, and the likelihood of recommending the program to others. Rating will use a 4-point Likert scale, with "1" indicating "not at all" and "4" representing "definitely." Any adverse event, such as muscular soreness, falls, or injury, will also be recorded by the research team.

TABLE 3 Interview guide.

Interviewing questions for the perception of the multicomponent exercise intervention
1. How do you feel about the multicomponent exercise intervention? [probes: content, format, arrangement]
2. How would you describe your participation in this multicomponent exercise intervention?
3. Are there any barriers or hindering factors for your participation in this intervention? What are they?
4. Can you think of any strategies which can facilitate your participation in this intervention?
5. How does your health conditions change after engaging in this intervention? [probes: physical health, cognitive function, psychological health]
6. What are the possible reason for the changes in your health condition, if any? [probes: self-efficacy]
7. Does participating in this exercise training affect your daily life? Do your relatives and friends support your participation in this program?
8. Would you be willing to continue participating in this intervention program in the future? What are the reasons behind your decision?
9. Would you recommend this exercise program to your relatives and friends?
10. Is there anything else you would like to share with me about this exercise program?

3.2.6.2 Semi-structured interviews

Semi-structured interviews will be conducted to assess participants' perspectives and opinion regarding the multicomponent exercise intervention they received. The interviews will involve some broad open-ended questions about their experience and acceptability of the intervention. See Table 3 for the interview guide.

3.2.7 Safety protocol

Several measures will be implemented to ensure participants' safety during the intervention. (1) Participants meeting exercise contraindications or assessed as high risk for exercise-related injuries will be excluded. (2) Instructions for the exercise intervention will include healthy advice to prevent injuries. (3) Prior to each exercise session, the exercise supervisor will conduct a brief medical safety check following ACSM recommendations. (4) If the participant reports concerning health changes, alterations in medications/dosage, or exhibits abnormal vital signs (e.g., blood pressure ≥ 180/100 mmHg), their participation in activities will be immediately paused, until they are seen and cleared to proceed by the study physician. (5) Participants will periodically report their perceived effort level on the Borg Rating of Perceived Exertion scale during each session to ensure proper exercise intensity. (6) There will be a warm-up routine before each session, and a cool-down routine after completion. (7) A multidisciplinary team (e.g., nurses, geriatricians, physiotherapists) has been involved in designing and implementing this trial to eliminate possible risks and prioritize participants safety.

3.2.8 Ethics and dissemination

This study was approved by the ethics committee of Central South University (reference number E202249) and will be conducted according to the ethical standards of the Helsinki Declaration. After thoroughly discussing potential risks and benefits, written informed consent will be obtained from all participants before inclusion.

The study protocol has been registered and can be obtained through the Chinese Registry website (registered on ChiCTR.org with the identifier ChiCTR2200058850). The findings of the study will be published in scientific journals to target a wide range of groups and be reported at international conferences in the field of gerontology. Additionally, the results will be disseminated among study participants, healthcare professionals, healthcare providers and the public through courses, presentations, and online platforms.

3.2.9 Data management and security

All potential participants will be assigned a unique ID number at the start of the assessment to maintain the participants' confidentiality. Any handwritten information such as written consent forms or other related research materials will be stored securely in a locked cabinet when not in use. All electronic data will be securely stored on a server within the principal investigator's institute. All data will be analyzed anonymously.

3.2.10 Data analysis

Summary statistics, including means with standard deviations, frequencies, and percentages, will be generated for baseline characteristics. To compare the baseline characteristics between the two groups, Student's *t*-test or the Wilcoxon rank-sum test will be utilized for continuous variables, while Chi-square or Fisher's exact tests will be employed for categorical variables. Analysis of covariance (ANCOVA) and generalized linear models (GLM) will be performed to compare mean changes in continuous variables between the two groups. Adherence, dropout rates, program satisfaction, and adverse events will be tabulated and summarized using descriptive statistics. Mediation models will be used to test whether exercise self-efficacy mediates the relationship between the multicomponent exercise intervention and physical frailty, cognitive function, body composition, senior fitness, mental health, sleep quality, and health-related quality of life. Any missing data on outcomes will be approximated through multiple imputation. All analyses will be performed with the intention-to treat (ITT) principle. Two-sided tests will be performed for all analyses, and *p*-value less than 0.05 will be considered to be statistical significance. Additionally, sensitivity analyses will be adopted to assess the robustness of the findings based on the per-protocol analysis set.

Regarding qualitative data, audio-recorded interview will be transcribed word-for-word. Content analysis will be adopted to code the data on their perceptions of the intervention. Two authors will independently code the data, and any discrepancies will be resolved through discussion.

3.2.11 Validity and reliability

A panel of six experts, encompassing fields such as geriatric nursing, sports medicine, exergaming, and public health, reviewed the study protocol. The protocol was finalized after making necessary modifications as suggested by the panel.

This study will adopt a stringent experimental design to enhance the internal validity of the study findings. The randomization of participants into different study groups will minimize the selection bias. Additionally, the characteristics of the study sample will be compared to determine any significant differences at baseline. The use of instruments with good validity and reliability will further enhance the credibility of the study findings.

Regarding qualitative data, interviews will be audio-taped to enhance trustworthiness. Two authors will independently code the data, comparing their coding to identify and resolve any discrepancies through discussion.

4 Discussion

As the global population ages, the number of older adults with cognitive frailty is rapidly increasing and expected to escalate in coming decades. This trend could result in an increased burden on families, caregivers, and healthcare systems (Kelaiditi et al., 2013). Consequently, the concept of healthy aging has been widely advocated (Keating, 2022). The World Health Organization (WHO) defines "healthy aging" as "the process of developing and maintaining the functional ability that enables wellbeing in older age"(Keating, 2022). Physical activity is one of the most crucial determinants identified for healthy aging (Abud et al., 2022). Substantial evidence supports the beneficial effects of exercise program in promoting health aging.

While exercise can yield numerous benefits for older population, not all forms of exercise offer equal health benefits. Exergaming, an aerobic exercise that combines cognitive stimulation and physical exercise, has shown specific potential in preventing cognitive decline (Zhao et al., 2020). Neurologic research demonstrates that older adults engaging in exergaming exhibit enhanced neuroplasticity, reducing the risk of developing dementia (Stojan and Voelcker-Rehage, 2019). Moreover, a recent systematic review indicated that exercise intervention positively impacts global cognition in individuals with mild cognitive impairment or dementia only when aerobic exercise is included in the program (Venegas-Sanabria et al., 2022). However, resistance exercise is the most effective method for enhancing muscle strength and physical functionality and should be prioritized within exercise program delivered to the older people living with physical frailty (Hurst and Sayer, 2022). Multicomponent exercise programs are highly recommended for older adults (Venegas-Sanabria et al., 2022). Considering cognitive frailty as a geriatric syndrome characterized by the simultaneous presence of cognitive impairment and physical frailty, a multicomponent exercise program that integrates exergaming and resistance exercise have the potential for simultaneously enhancing cognitive and physical functionality, maximizing overall health benefits among this vulnerable population.

To the best of our knowledge, this is the first mixed methods research to evaluate the effectiveness of a motivating multicomponent exercise, to explore the potential mechanisms of intervention effects among older adults with cognitive frailty, and to explore their perception of this program. By integrating exergaming into the program, we anticipate an increase in exercise self-efficacy and adherence to the physical exercise intervention, reinforcing the proven benefits of the exercise in this vulnerable population. The findings of this study could hold significance for public health and social policy. It is expected that the results of this research will guide clinical practice in community settings, so that clinicians and policymakers can provide more evidence-based practice for the health promotion for this vulnerable population.

5 Limitations

There are potential limitations that should be acknowledged. Firstly, although a large number of assessments give richer information about the study, the number of tests may pose the risk of missing data and dropout. Secondly, due to funding constraints, this study will only examine the effects over a 12-week period and will not include laboratory measurements (e.g., blood chemistry analysis). Future research that explores the long-term effects of the program and includes clinical measures and biomarkers testing in these samples are recommended. Thirdly, this study employs a single-blind design, with the data collector being blinded. However, blinding of the participants and interveners is not feasible. It is important to acknowledge that potential biases could arise from performance or expectation.

6 Conclusion

Due to the rapid aging of the population and the limited treatment options for disability and dementia, it is essential to promptly explore effective strategies to alleviate the considerable burden on the health and social care system. The proposed physical exercise intervention is based on a strong theoretical foundation and follows international recommendations for prescribing exercise in older adults. The findings of this study are expected to contribute meaningful knowledge about the beneficial effects of this novel exercise program, which will promote better functionality, independence, and improved quality of life for older adults with cognitive frailty.

What problem will the study address?

In the field of exercise intervention for older adults with cognitive frailty, there exist major problems such as low adherence to the proposed program, reliance on a singular form of exercise, and limited exploration of the mechanisms underlying intervention effects. This study aims to address these challenges by conducting a mixed-methods research initiative among older Chinese community-dwelling people with cognitive frailty. The study will explore a novel multicomponent exercise training program designed to enhance both adherence and experience to physical exercise in this vulnerable group. Moreover, this intervention program, founded on the integrated Health Belief Model (HBM) and Self-Efficacy Model (SEM), seeks to elucidate the underlying mechanisms of the program. This study provides an effective evaluation of the exercise program from a broad perspective, including physical frailty, cognitive function, muscle-related outcomes, physical functional abilities, quality of life, senior fitness, sleep quality, and mental health.

Data availability statement

The datasets presented in this article are not readily available because the waiver of consent and our IRB approval does not allow us to share the dataset used, without appropriate modifications. Requests to access the datasets should be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by the ethics committee of Central South University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

HN: Conceptualization, Methodology, Software, Writing – original draft, Writing – review & editing. FC: Conceptualization, Data curation, Investigation, Resources, Writing – original draft, Writing – review & editing, Supervision. JL: Conceptualization, Methodology, Supervision, Visualization, Writing – review & editing. YD: Conceptualization, Methodology, Resources, Supervision, Writing – review & editing. XC: Data curation, Investigation, Resources, Writing – review & editing. SW: Investigation, Visualization, Writing – review & editing, Methodology. AJ: Resources, Writing – review & editing. YG: Data curation, Formal analysis, Resources, Writing – review & editing. ZC: Methodology, Resources, Supervision, Writing – review & editing. HF: Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Valid olfactory impairment tests can help identify mild cognitive impairment: an updated meta-analysis

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Background: Olfactory testing is emerging as a potentially effective screening method for identifying mild cognitive impairment in the elderly population.

Objective: Olfactory impairment is comorbid with mild cognitive impairment (MCI) in older adults but is not well-documented in subdomains of either olfactory or subtypes of cognitive impairments in older adults. This meta-analysis was aimed at synthesizing the differentiated relationships with updated studies.

Methods: A systematic search was conducted in seven databases from their availability to April 2023. A total of 38 publications were included, including 3,828 MCI patients and 8,160 healthy older adults. Two investigators independently performed the literature review, quality assessment, and data extraction. The meta-analyses were conducted with Stata to estimate the average effects and causes of the heterogeneity.

Results: Compared to normal adults, MCI patients had severe impairments in olfactory function and severe deficits in specific domains of odor identification and discrimination. Olfactory impairment was more severe in patients with amnestic mild cognitive impairment than in patients with non-amnestic MCI. Diverse test instruments of olfactory function caused large heterogeneity in effect sizes.

Conclusion: Valid olfactory tests can be complementary tools for accurate screening of MCI in older adults.

KEYWORDS

mild cognitive impairment, olfactory function, cognitive function, meta-analysis, smell test

1 Introduction

Cumulative evidence showed that olfactory impairment is comorbid with mild cognitive impairment and Alzheimer's disease, with their common underlying neurodamages in the brain (Rahayel et al., 2012; Roalf et al., 2017; Dong et al., 2022; Pusswald et al., 2023). Olfactory impairment occurs earlier than visual impairment in MCI patients (Hagemeier et al., 2016) and predicts AD onset better than hearing and vision (Olofsson et al., 2020). As MCI usually

harbingers AD, screening olfactory impairment has been recommended as a supplemental tool for identifying MCI (Jak et al., 2009); however, its efficacy remained uncertain in subdomains of olfactory and cognitive impairments.

Different aspects of olfactory impairment appeared to predict cognitive functions differentially. Olfactory impairment has been measured by detecting the minimum amount of odor (detection threshold), identifying a specific odor from a given list (identification), differentiating between odors (discrimination), and memorizing an odor and then identifying it (memory; Hedner et al., 2010). Odor detection threshold relies on the peripheral structural functions of the olfactory system and basic perceptual processing (Sohrabi et al., 2012), as opposed to odor identification and discrimination that involve higher brain centers and complex olfactory information processing systems (Stevenson and Boakes, 2003). Odor identification impairment was found to coincide with tau-mediated neuronal damage and occur before memory impairment and clinical symptoms in the course of AD (Bathini et al., 2019).

Subtypes of cognitive impairment include non-amnestic mild cognitive impairment (naMCI) and amnestic MCI (aMCI), which may be associated with olfactory dysfunction differentially. naMCI is more likely to progress to AD-unrelated dementia, such as frontotemporal dementia (FTD) or dementia with Lewy bodies (DLB; Devanand et al., 2015), and some studies suggest that both may be accompanied by severe olfactory dysfunction (Vyhnalek et al., 2015). However, this conclusion is controversial, as there are opposing studies showing that olfactory dysfunction in FTD and DLB patients is minimal or even absent (Luzzi et al., 2007). Most aMCI cases progress to AD dementia, caused by the degeneration of the internal olfactory cortex and hippocampus, which affects the individual's ability to identify odors (Vyhnalek et al., 2015; Roberts et al., 2016). While aMCI patients usually exhibit more severe olfactory impairment than naMCI patients (Quarmley et al., 2017), others show similar or indistinguishable degrees of olfactory impairment between the aMCI and naMCI subtypes (Roalf et al., 2017) and odor identification deficits (Devanand et al., 2010; Vyhnalek et al., 2015). What complicates the association of olfactory impairments with MCI is that olfactory deficits in odor detection threshold, identification, discrimination, and memory can coexist in MCI patients (Yap et al., 2022). In addition, odor detection thresholds decline in the normal elderly population as well, though faster than discrimination and identification (Hummel et al., 2007). It remained uncertain how reliable it is to use olfactory impairment tests as supplemental tools for identifying MCI.

Earlier meta-analyses investigating olfactory function in MCI and AD patients have not differentiated domains of olfactory impairments and MCI subtypes. For instance, Roalf's meta-analysis found that olfactory function in MCI patients is slightly worse than that in the normal population (Roalf et al., 2017), but only a few studies included MCI subtypes. In addition, there was no statistically significant impairment of odor memory in MCI patients due to the small number of included studies. Jung's meta-analysis showed that MCI patients have significant deficits in odor identification compared to AD patients (Jung et al., 2019) but this did not extend to odor discrimination and detection thresholds. Other studies did not consider the heterogeneity of demographics, Mini-Mental State Examination (MMSE) scores, and olfactory test instruments (Wang et al., 2018; Yang et al., 2022). These different approaches to synthesizing previous findings have not rendered differentiated efficacies of olfactory impairment tests for identifying MCI.

This meta-analysis was to synthesize studies that might reveal the differentiated relationships between olfactory impairments and MCI, with a focus mainly on the following issues: (1) domains of olfactory impairment in MCI patients, (2) olfactory function in two subtypes of MCI patients, and (3) differences caused by test instruments of olfactory function, etc. This updated study differs from previous ones in that strict inclusion–exclusion criteria were applied in the literature search, only higher-quality and recent studies were included, and the whole research process adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement that can be readily retrieved online (see Supplementary material).

2 Methods

2.1 Literature search strategy

The literature about olfactory function in MCI patients was searched in PubMed, Embase, the Cochrane Library, Web of Science, China Knowledge Network, Wanfang Data, and Vipul.com, within the time frame from their availability to April 2023. Using the Boolean logic for literature retrieval, the search strategy combined subject terms and free words without language restrictions as follows: "Cognitive Dysfunction" OR "Mild Cognitive Impairment" AND ("Smell" OR "Sense of Smell" OR "Olfaction" OR "Olfaction Disorders" OR "Olfaction Dysfunction" OR" Olfaction Impairment") (see Supplementary material).

2.2 Inclusion and exclusion criteria

The inclusion and exclusion criteria for the studies complied with the requirements of the 2020 PRISMA. The inclusion criteria for this study were as follows: (a) The study subjects were MCI patients aged 50 years and older without co-morbidities or other neurodegenerative diseases. (b) There was a healthy population matched to the age of the MCI group as a control group. (c) The study subjects were MCI patients diagnosed by traditional methods. (d) The subjective olfactory function assessment was judged by the test subjects' autonomous sniffing of odors. (e) The research design was a cohort or a case–control study.

Studies with the following characteristics were excluded from the meta-analysis: (a) the research reports omitted original effect sizes and the authors could not be contacted or provide them; (b) full reports could not be downloaded and accessed; (c) reports duplicated published data as determined by identical authors, study sites, participating institutions, details of olfactory tests, sample sizes, baseline situations, or study durations; (d) low-quality reports with a score of <7 on the Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomized studies.

Abbreviations: UPSIT, University of Pennsylvania Odor Identification Test; SSIT, Sniffin' Sticks Identification Test; OSIT-J, Japanese odor stick identification test; CA-SIT, Culturally adapted version of the odor identification test; CC-SIT, Cross-cultural version of the olfactory identification test; YSK OFT, YSK Olfactory Function Test.; DESK, The DEmentia Screening Kit; CSIT, The Chinese Smell Identification Test; OE, Open Essence; SS-16, Sniffin' sticks test with 16 odors; aMCI, Amnestic mild cognitive impairment; naMCI, Non-amnestic mild cognitive impairment.

Figure 1 depicts the literature search and selection process for this study. The initial search yielded 2,628 pieces of pertinent reports in total. After meticulous screening, 30 case–control studies and 8 cohort studies were finally selected, including 12 from North America, 17 from Asia, and 9 from Europe. This meta-analysis comprised 3,828 MCI patients and 8,160 healthy controls.

2.3 Data extraction and quality evaluation

Data extraction and study quality evaluation were performed independently by two investigators of this study trained in evidence-based care according to the inclusion and exclusion criteria and cross-checked. A third investigator was requested to adjudicate any disagreement collaboratively. The extracted data included general information about the literature: title, year of publication, authors, country of study, type of study, sample size, age of participants in the control and MCI groups, olfactory function test instruments, and test scores of neuropsychological scales such as MMSE and MoCA. The quality of the included studies was evaluated using the NOS (Stang, 2010) and rated low (0–4 points), medium (5–6 points), or high (7–10 points). Only high-quality studies (scores ≥ 7) were included in this study. The literature was summarized and organized using Endnote X9 software, and data were extracted using Excel 2019. The fundamental characteristics and quality assessment of these studies are displayed in Table 1.

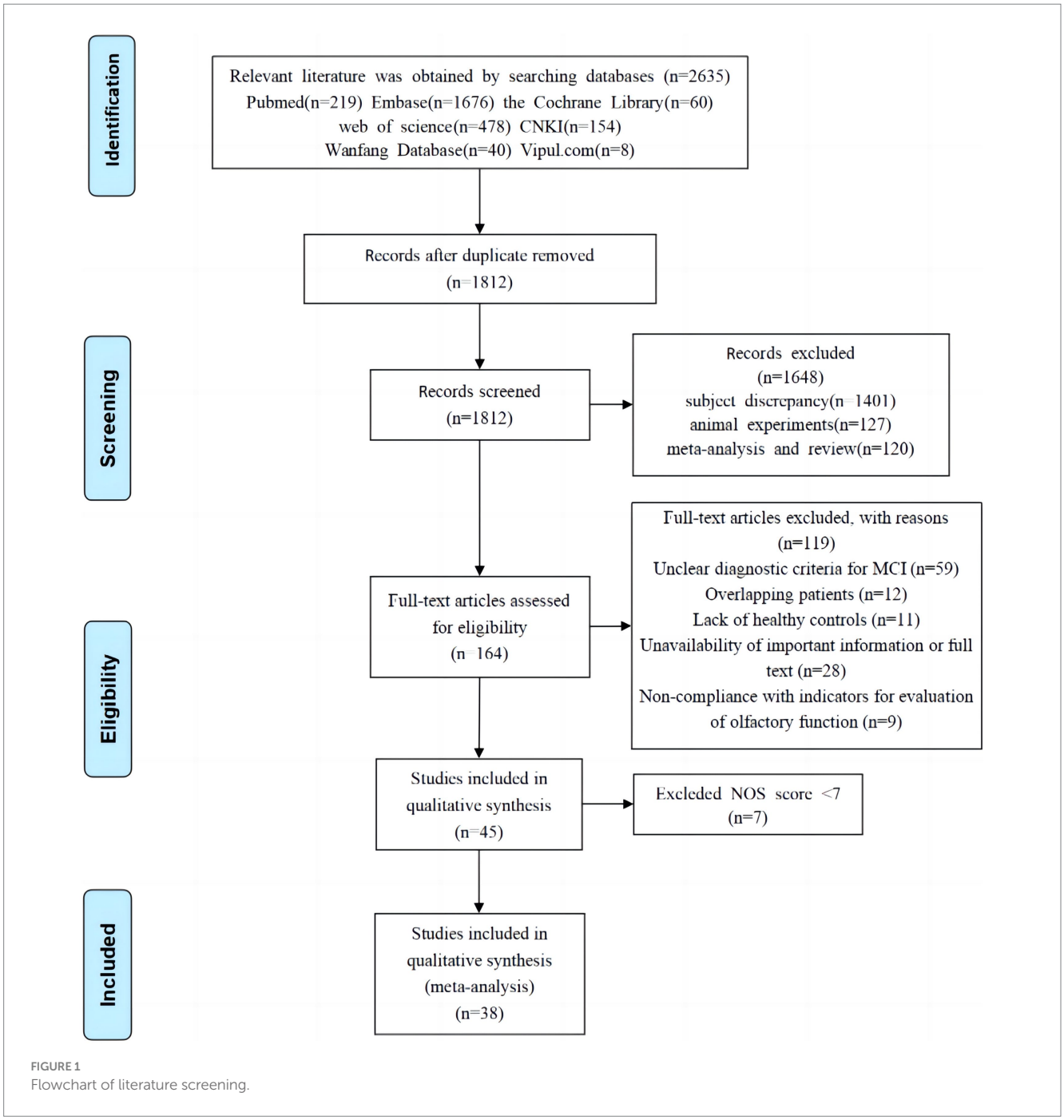

FIGURE 1
Flowchart of literature screening.

TABLE 1 Characteristics of the included studies.

Study	Country	Study type	Measures	MCI			HC			Neuropsychological scales	NOS score
				Sample size	Age	Olfactory function score	Sample size	Age	Olfactory function score		
Devanand et al. (2000)	USA	Case–control	UPSIT	90	66.70 ± 10.70	31.00 ± 7.40	45	64.00 ± 10.00	35.20 ± 3.90	MMSE	8
Wang et al. (2002)	China	Case–control	CC-SIT	28	71.90 ± 7.78	7.25 ± 1.41	30	73.84 ± 5.90	9.27 ± 1.26	MMSE	7
Peters et al. (2003)	Germany	Case–control	SSIT	8	72.50 ± 5.00	8.98 ± 2.83	8	73.90 ± 9.40	11.34 ± 2.48	MMSE	8
Tabert et al. (2005)	USA	Cohort	UPSIT	147	67.43 ± 9.85	31.22 ± 6.45	63	65.71 ± 9.38	34.86 ± 4.18	MMSE	7
Laakso et al. (2009)	Finland	Case–control	Homemade	72	73.00 ± 4.00	4.40 ± 2.48	486	71.00 ± 4.00	4.95 ± 2.42	MMSE	7
Yin et al. (2010)	China	Case–control	UPSIT	8	70.30 ± 11.00	25.40 ± 9.90	20	71.00 ± 10.00	30.80 ± 5.70	MMSE	7
Conti et al. (2013)	Italy	Cohort	CA-SIT	88	73.50 ± 6.78	11.68 ± 7.12	46	73.70 ± 7.30	14.25 ± 7.30	MMSE	8
Seligman et al. (2013)	USA	Case–control	SSIT	112	72.63 ± 8.19	10.10 ± 3.39	132	72.57 ± 9.52	12.55 ± 2.52	NA	7
Woodward et al. (2017)	USA	Cohort	UPSIT	110	74.05 ± 9.03	28.01 ± 7.97	194	72.29 ± 8.41	32.32 ± 5.47	MMSE	7
Huart et al. (2015)	Belgium	Case–control	Homemade	13	70.46 ± 5.97	23.90 ± 7.70	13	69.69 ± 8.35	27.00 ± 3.70	NA	8
Servello et al. (2015)	Italy	Case–control	SSIT	25	NA	9.15 ± 3.76	28	NA	10.35 ± 2.97	MMSE	8
Vasavada et al. (2015)	USA	Case–control	UPSIT	21	73.20 ± 9.00	24.20 ± 8.60	27	69.50 ± 10.40	34.00 ± 4.20	MMSE	7
Hagemeier et al. (2016)	USA	Case–control	UPSIT	19	NA	22.90 ± 8.60	19	NA	30.00 ± 6.70	MMSE	7
Liang et al. (2016)	China	Case–control	SSIT	345	73.00 ± 7.80	7.10 ± 2.30	1,437	69.40 ± 6.80	8.20 ± 2.00	MMSE	7
Kreisl et al. (2018)	USA	Cohort	UPSIT	46	68.80 ± 7.40	29.00 ± 6.40	25	67.90 ± 7.70	31.90 ± 5.80	MMSE	7
Quarmley et al. (2017)	USA	Case–control	SSIT	174	72.46 ± 8.57	9.94 ± 3.28	292	70.96 ± 8.74	12.43 ± 2.53	MoCA	8
Risacher et al. (2017)	USA	Case–control	UPSIT	5	75.70 ± 10.60	28.70 ± 7.00	19	68.50 ± 6.90	34.50 ± 2.30	MoCA	7
Tonacci et al. (2017)	Italy	Case–control	SSIT	85	74.60 ± 4.90	7.51 ± 3.72	41	73.50 ± 4.30	9.49 ± 3.87	MMSE	7
Umeda-Kameyama et al. (2017)	Japan	Case–control	OSIT-J	28	81.00 ± 6.00	5.00 ± 3.10	12	77.10 ± 6.40	7.30 ± 2.40	MMSE	7
Ward et al. (2017)	USA	Case–control	UPSIT	8	76.13 ± 6.29	21.63 ± 10.17	20	76.65 ± 6.48	33.60 ± 3.39	MOCA	7
Chen (2017)	China	Case–control	SSIT	63	67.80 ± 9.20	8.55 ± 3.02	57	65.20 ± 7.20	9.90 ± 3.00	MMSE	7
Woodward et al. (2018)	USA	Case–control	UPSIT	192	73.18 ± 9.05	26.98 ± 8.00	234	71.26 ± 8.05	32.19 ± 5.36	MMSE	8
Lu et al. (2019)	USA	Case–control	UPSIT	19	72.80 ± 9.40	25.58 ± 7.69	31	70.40 ± 10.00	33.42 ± 4.19	MMSE	7
Jiang (2019)	China	Case–control	UPSIT	24	65.00 ± 5.27	20.83 ± 5.56	30	62.13 ± 7.25	26.20 ± 3.75	MMSE, MoCA	7
Doorduijn et al. (2020)	Netherlands	Cohort	SSIT	22	69.80 ± 7.20	25.50 ± 1.40	40	62.50 ± 6.80	30.20 ± 1.10	MMSE	7
Kim et al. (2020)	Korea	Case–control	YSK OFT	26	74.96 ± 9.58	15.58 ± 6.36	104	69.30 ± 6.16	18.93 ± 5.07	MMSE	8
Iritani et al. (2021)	Japan	Case–control	OE	23	81.30 ± 8.10	3.55 ± 2.24	64	77.20 ± 5.90	6.14 ± 2.50	MMSE	7
Kjelvik et al. (2020)	Norway	Cohort	SSIT	17	74.40 ± 6.50	8.45 ± 3.10	28	67.40 ± 7.60	11.25 ± 3.02	MMSE	9

(Continued)

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TABLE 1 (Continued)

Study	Country	Study type	Measures	MCI			HC			Neuropsychological scales	NOS score
				Sample size	Age	Olfactory function score	Sample size	Age	Olfactory function score		
Chen et al. (2022)	China	Case–control	SSIT	118	67.90 ± 7.70	10.60 ± 2.30	50	64.50 ± 4.40	12.80 ± 2.00	MMSE	8
Suzuki et al. (2022)	Japan	Case–control	OE	26	77.40 ± 5.00	7.50 ± 2.20	12	73.10 ± 6.70	4.90 ± 2.00	MMSE	7
Yap et al. (2022)	Singapore	Cohort	Homemade	143	67.70 ± 5.90	5.30 ± 2.00	527	67.90 ± 5.20	5.70 ± 2.00	MMSE	7
Yi et al. (2022)	China	Case–control	SSIT	1,102	71.65 ± 5.04	7.80 ± 3.20	3,112	70.64 ± 4.46	9.25 ± 3.10	NA	8
Fukumoto et al. (2022)	Japan	Case–control	DESK	61	72.8 ± 10.6	14.7 ± 4.5	100	57.4 ± 11.7	18.4 ± 1.6	MMSE, MoCA	7
Tan et al. (2022)	China	Cohort	SSIT	157	68.8 ± 7.4	5.65 ± 2.44	447	67.9 ± 7.7	6.35 ± 2.23	MMSE, MoCA	8
Delgado-Lima et al. (2023)	Spain	Case–control	SSIT	55	77.5 ± 6.47	9.67 ± 2.44	46	72.6 ± 5.56	12.7 ± 2.05	MoCA	9
Liang et al. (2023)	China	Case–control	CSIT	85	76.0 ± 7.8	12 ± 3.02	135	71.7 ± 8.1	14.67 ± 0.75	MMSE, MoCA	8
Guo et al. (2023)	China	Case–control	SS-16	75	70.5 ± 5.2	10.7 ± 2.1	50	70.5 ± 5.0	11.7 ± 1.8	MMSE, MoCA	7
Mi et al. (2023)	China	Case–control	CSIT	188	62.45 ± 7.15	13.06 ± 2.05	136	60.43 ± 7.61	14.6 ± 1.57	MMSE, MoCA	8

2.4 Olfactory function test instruments used in the included studies

The *University of Pennsylvania Odor Identification Test (UPSIT)* is a forced-choice odor identification assessment in which each subject is sequentially exposed to 40 odors and scores 1 point for each correctly identified odor (Doty et al., 1984).

The *Sniffin' Sticks Identification Test (SSIT)* was developed in Germany to measure detection threshold, discrimination, and identification function (Hummel et al., 1997). Subjects were presented with 16 felt-tipped pens containing common household odors, requested to freely identify each with a verbal description, and scored one point for each correct identification.

The *Japanese odor stick identification test (OSIT-J)* is an identification tool to identify odors familiar to Japanese patients (Shino et al., 2006). Subjects were required to sniff out a target odor from four samples and choose "detectable but unrecognizable" or "no odor detected" (no score). A correct identification was scored 1 point.

The *Open-Essence (OE) test* is a similar card-based odor identification tool with 12 odors, designed to overcome the inconvenience of odor sample storage (Okutani et al., 2013).

The *culturally adapted version of the odor identification test (CA-SIT)* is an Italian culture-adapted version of the UPSIT, with six odors removed from the original, which can be easily misidentified by Italians (Doty et al., 1996) and scoring similar to the UPSIT.

The *cross-cultural version of the olfactory identification test (CC-SIT)* is a cross-cultural version of the UPSIT (Doty et al., 1996) that consists of 12 odors familiar to US, Chinese, French, and Japanese patients. One point was scored for each correct identification, up to a total of 12.

The *YSK Olfactory Function Test* is a Korean olfactory threshold test used for early screening for dementia in older adults (Kim et al., 2021). The tool consists of a series of kits, such as odorless distilled water as a blank stimulus and 10-step concentrations (0%–16%) of rose-scented 2-phenylethanol. Scores range from 1 to 7, with lower scores indicating higher olfactory thresholds.

The *DEmentia Screening Kit (DESK)* is an odor identification test tool developed for Japanese patients with dementia or AD (Fukumoto et al., 2022). The kit includes 10 odorants in 2 concentrations (weak/strong), for a total of 20 combinations. Two different concentrations of odors were tested separately with a paper cup each time and a 5-min interval between. Patients were requested to choose an answer from six alternatives to indicate whether they could identify an odor, and they scored 1 point for each correct odor identification.

The *Chinese Smell Identification Test (CSIT)* is an odor identification test developed by the Institute of Psychology of the Chinese Academy of Sciences in 2019 which contains 40 or 16 odors familiar to Chinese patients (Feng et al., 2019).

In addition, researchers of the three studies created "homemade tests" for participants to identify, discriminate, or detect odors. These could be as simple as small containers (e.g., jars or vials) filled with different scents (e.g., essential oils or spices) for the participants to smell and identify.

2.5 Data analysis

Data from the included studies were meta-analyzed using the statistical software Stata (v14). The group mean differences in olfactory

function scores were converted to standardized mean differences (*SMDs*), which are also referred to as Cohen's *d* to render differences commensurate across the studies (small ≤ 0.2, medium = 0.05, and large ≥ 0.8; Cohen, 1977). Medians and quartiles were converted to means and standard deviations using the methods of Luo et al. (2018) and Wan et al. (2014). Random effect models (REMs) were employed to estimate the average effect sizes and heterogeneity (I^2) between studies (unavailable *for a* single study), whose sources were further explored through subgroup analyses and meta-regressions. $I^2 \geq 50\%$ and $p \leq 0.05$ indicate high heterogeneity between studies and the necessity of REM. Sensitivity analysis was also conducted to detect the influence of individual studies on the average effect size. Egger's test was used to examine the presence of publication bias, with a *p*-value of ≤0.05 indicating the presence.

3 Results

3.1 Literature screening process and overall effect size

The initial research yielded 2,635 pieces of pertinent literature in total. After meticulous screening, 30 case–control studies and 8 cohort studies, including 12 from North America, 17 from Asia, and 9 from Europe, were finally included. The final meta-analysis comprised 3,828 MCI patients and 8,160 healthy controls. Table 2 displays the fundamental characteristics as well as the quality assessment of the selected studies. The overall effect size obtained from a random effect model was *SMD* = −0.78, 95% CI: −0.89~−0.66, I^2 = 81.3%.

3.2 SMD by regions, participants' age, and education

Figure 2 presents the basic characteristics of the 38 included studies and SMD by certain potential moderators. First, *SMD* was −0.80 (95% CI: −0.92~−0.67, I^2 = 30.1%) for 12 studies in North America, −0.76 (95% CI: −0.92~−0.60, I^2 = 84.6%) for 17 studies in Asia, and −0.93 (95% CI, −1.44~−0.43, I2 = 89.8%) for 9 studies in Europe.

Second, 3 age groups had *SMD* = −0.74 (95% CI: −0.93~−0.55, I^2 = 89.4%) in 15 studies with participants' mean age ≤ 71 years, *SMD* = −0.78 (95% CI: −0.98~−0.58, I^2 = 75.4%) in 11 studies with participants' mean age between 71 and 75 years, and *SMD* = −0.96 (95% CI: −1.29~−0.64, I^2 = 0%) in 4 studies with participants' mean age greater than 75 years.

Third, 3 education groups showed *SMD* = −0.82 (95% CI: −1.33~−0.31; I^2 = 80.0%) in 4 studies whose participants had less than 9 years of education; *SMD* = −0.57 (95% CI: −1.46~−0.57; I^2 = 83.9%) in 3 studies whose participants had between 9 and 12 years of education; and *SMD* = −0.72 (95% CI: −0.87~−0.57; I^2 = 71.3%) in 15 studies whose participants had more than 12 years of education.

3.3 SMD by test instruments

The effect sizes also varied by test instruments used in the included studies, with *SMD* = −0.80 (95% CI: −0.96~−0.64, I^2 = 32.2%) by UPSIT; *SMD* = −0.79 (95% CI: −0.99~−0.59, I^2 = 88.7%) by SSIT; *SMD* = −1.13 (95% CI: −0.96~−0.64, I2 = 32.2%) by OE; *SMD* = −0.22 (95% CI: −0.37~−0.07) by homemade instruments; *SMD* = −0.84 (95% CI: −1.01~−0.66) by CSIT; *SMD* = −0.36 (95% CI: −0.72~−0.00) by CA-SIT, *SMD* = −1.51 (95% CI: −2.10~−0.93) by CC-SIT, *SMD* = −0.79 (95% CI: −1.49~−0.09) by OSIT-J, *SMD* = −0.63 (95% CI: −1.06~−0.19) by YSK OFT, *SMD* = −1.22 (95%CI: −1.56~−0.87) by DESK, and *SMD* = −0.50 (95% CI: −0.87~−0.14) by SS-16.

3.4 SMD by studies designs

Two types of research design had *SMD* = −0.80 (95% CI: −0.92~−0.68; I^2 = 74.2%) in the 30 case–control studies and *SMD* = −0.76 (95% CI: −1.12~−0.40; I^2 = 90.8%) in the 8 cohort studies.

3.5 SMD by olfactory function domains in 38 studies

As shown in Figure 3, MCI patients were lower than the healthy controls in odor detection thresholds (*SMD* = −0.33, *95% CI:* −0.57~0.08, $p < 0.001$), memory (*SMD* = −0.48. *95% CI:* −0.69~−0.27, $p < 0.001$), discrimination (*SMD* = −0.70, *95% CI:* −0.59~−0.46, $p < 0.001$), and identification (*SMD* = −0.89, *95% CI:* −1.05~−0.73, $p < 0.001$) in ascending order of the effect size.

3.6 SMD by subtypes of MCI in six studies

The degrees of olfactory impairment were more severe in the aMCI group (*SMD* = −0.65, 95% CI: −0.91~−0.38, $p = 0.001$) than in the naMCI group (*SMD* = −0.50, 95% CI: −0.19~0.19, $p = 0.155$), where the difference in the naMCI group was not statistically significant from zero, as shown in Figure 3. Six studies reported patients with aMCI, with a total sample size of 524 cases (I^2 = 76.6%, $p = 0.001$). Two studies

TABLE 2 Meta-regression results.

Results	Region	Age	Education	Design	MMSE	MoCA
Regression coefficient	−0.03	−0.06	−0.02	−0.09	−0.03	−0.08
95%CI	−0.29~0.24	−0.35~0.24	−0.24~0.27	−0.52~0.33	−0.18~0.13	−0.14~−0.02
P	0.846	0.702	0.880	0.662	0.727	0.017

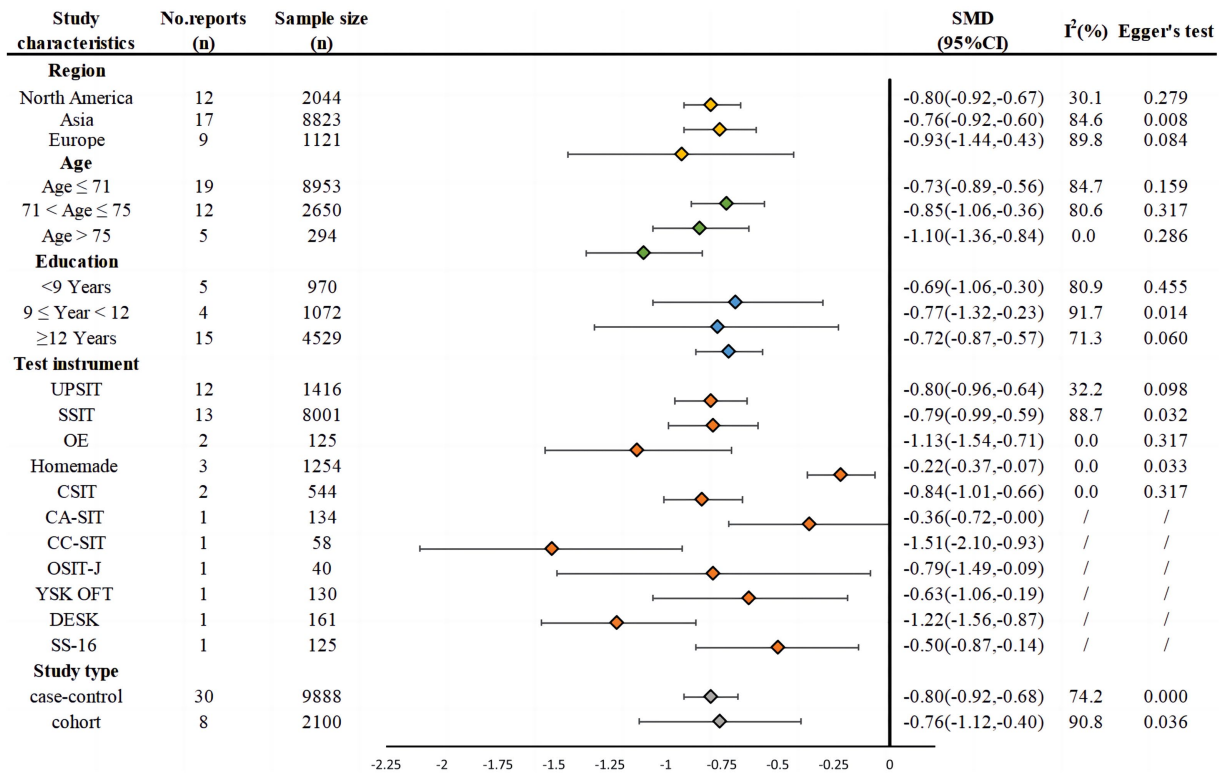

FIGURE 2
Basic characteristics of the studies and SMD by different moderating variables.

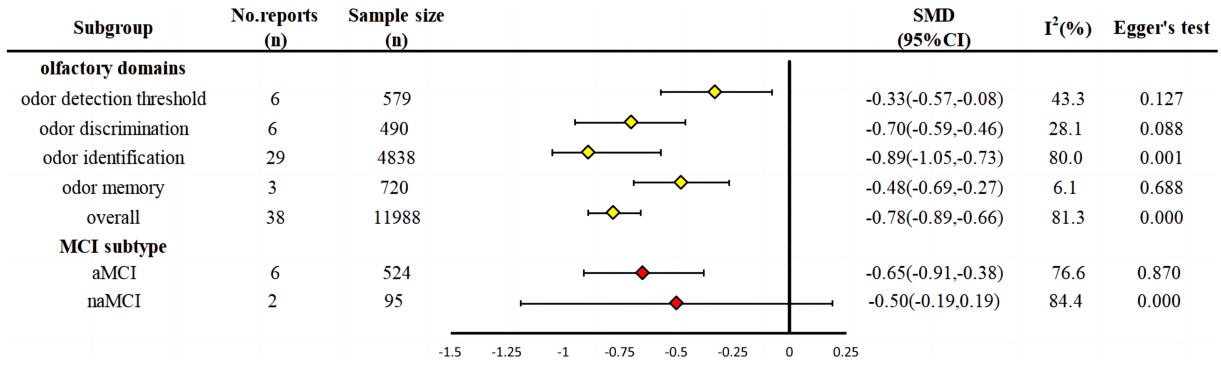

FIGURE 3
Subgroup analysis.

reported patients with naMCI with a total sample size of 95 cases ($I^2 = 84.4\%$, $p = 0.005$). The heterogeneity between the two groups was $I^2 > 50\%$, as indicated by a random effect model.

3.7 Heterogeneity by demographics and MCI tests

As shown in Table 2, meta-regression was performed on the effect-coded region (Daly et al., 2016), age, education levels, study design, and cognitive test scores (MMSE and MoCA). The results showed that olfactory impairment varied only with MoCA scores when pitted against one another in the model.

3.8 Sensitivity analysis and publication bias

Publication bias was evaluated by Egger's test ($p = 0.372$), which suggested that there was no significant evidence of publication bias. After excluding studies one by one, the effect size and the 95% CIs showed robustness in all results (see Supplementary material).

4 Discussion

The current meta-analysis of 38 high-quality studies revealed that MCI patients had much lower overall olfactory function than the healthy participants in terms of the large effect size. The overall difference also varied across domains of olfactory function, test instruments of olfactory function, subtypes of MCI (naMCI and aMCI), and cognitive tests of MCI.

The effect size in the overall olfactory function was close to the large effect found in the early meta-analysis that compared MCI patients with normal adults (Roalf et al., 2017), but much less than those in studies that compared AD patients (Rahayel et al., 2012; Vyhnalek et al., 2015; Roberts et al., 2016; Kotecha et al., 2018; Jung et al., 2019). This was expected, as the included studies also compared MCI patients with normal adults.

Specific domains of olfactory function in this meta-analysis showed that MCI patients had the most drastic lower function in odor identification and discrimination than normal adults, in terms of the effect size (Cohen, 1977). These large effects imply that these tests may be used exclusively or conjointly with other MoCA to identify MCI in clinical settings. In contrast, the smaller effects in odor detection thresholds and odor memory imply that these tests cannot differentiate MCI patients from normal aging adults (Hummel et al., 2007), and thus may be recommended to the general public to guard against any further deterioration and symptoms of MCI due to neurobiological changes.

Test instruments of olfactory function appeared to contribute largely to the overall olfactory function differences between the MCI and normal individuals, with the effects ranging from the smallest by homemade instruments ($SMD = -0.22$) to the largest by CC-SIT ($SMD = 1.51$). Homemade odor samples could have been familiarized and sensitized to the participants in the three studies, so that the odors in these studies could also be detected, identified, or discriminated against easily by MCI patients, resulting in small effect sizes. Small effect sizes suggest that the odor test instruments were not as sensitive and efficacious as those that yielded larger effects. Therefore, certain odor test instruments may be improved for better validity/efficacy.

The aMCI subtype patients exhibited more pronounced deficits in odor identification and discrimination than those with naMCI ($SMD = -0.65 > 0.50$), which suggests that olfactory impairment is associated with aMCI (Vyhnalek et al., 2015; Roberts et al., 2016). However, as the effect size of the two studies that involved naMCI patients was non-significant due to small samples and few studies, the differential predictive powers of the two subtypes of MCI need to be ascertained with further studies, especially prospective longitudinal ones.

The meta-regression suggested that the effect sizes were similar across regions and age and education groups when controlled for MCI measures and study designs. This suggests that olfactory function between MCI and normal adults was similar across regions, age groups, and education groups. This might also suggest that the underlying mechanism for the association of olfactory dysfunction with MCI can be universally bio-neurological and that olfactory impairment could be a reliable biomarker and predictor for cognitive decline (Deary et al., 2009; Windon et al., 2020).

MoCA outweighed MMSE in moderating the overall effect size. This may be because the MoCA scale assesses a broader range of cognitive domains, including executive function, visuospatial ability, and language, and is more sensitive in detecting mild cognitive impairment (MCI) and early dementia than the MMSE. MoCA also has fewer ceiling effects than the MMSE by including tasks that are challenging even for high-functioning individuals (Jia et al., 2021). Thus, the MoCA scale appeared to be more sensitive for screening early cognitive decline (Shao et al., 2021).

Despite the rigorous selection of high-quality studies and stringent inclusion criteria applied in this research, it is unfortunate that a considerable degree of heterogeneity persists. This may be due to the inclusion of a wide array of olfactory tests, each assessing different domains of olfactory function. Variability may also arise from the application of identical olfactory tests across diverse populations and countries, leading to potential discrepancies in outcomes. The Sniffin' Sticks Identification Test (SSIT) in particular demonstrated the greatest heterogeneity, which can be attributed to the multiplicity of testing methodologies employed in various countries, each with its unique approach. Moreover, within the subgroup analysis of olfactory domains, olfactory identification tests revealed the most pronounced heterogeneity. This is likely a consequence of the global emphasis on olfactory identification abilities in the majority of olfactory assessment tools, contributing to a broad spectrum of tools and types and, thus, heightened heterogeneity.

5 Limitations and future directions

Although this study provides valuable insights into the relationship between olfactory impairment and MCI, several limitations must be considered. First, the high heterogeneity in this study may have been influenced by clinical factors, such as smoking, alcohol consumption, genetic factors, and COVID-19 infection status, which were not controlled for in the included studies. Second, the limited number of original studies on olfactory impairment in different subtypes of MCI patients means that they did not permit explorations of more complicated interactions between olfactory subdomains, subtypes of MCI, and other factors. Future studies may adopt prospective longitudinal designs, improve olfactory function tests, and probe into the neurological causes of the association between olfactory and MCI.

6 Conclusion

Olfactory impairment accompanies MCI, but the magnitude of the association depends on the measured domains of olfactory function, test instruments to measure both olfactory function and MCI, and subtypes of MCI. Severe deficits in odor identification and discrimination are more associated with MCI in aMCI patients. Valid odor identification and discrimination tests are recommended to complement MoCA and improve screening accuracy.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

CZ: Data curation, Writing – original draft. CY: Formal analysis, Methodology, Writing – review & editing. YA: Data curation, Writing

– review & editing. XF: Data curation, Formal analysis, Writing – review & editing. AZ: Investigation, Visualization, Writing – review & editing. YW: Funding acquisition, Methodology, Supervision, Writing – review & editing. HH: Funding acquisition, Resources, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2024.1349196/full#supplementary-material

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Dual-task turn velocity – a novel digital biomarker for mild cognitive impairment and dementia

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Background: Disorders associated with cognitive impairment impose a significant burden on both families and society. Previous studies have indicated that gait characteristics under dual-task as reliable markers of early cognitive impairment. Therefore, digital gait detection has great potential for future cognitive screening. However, research on digital biomarkers based on smart devices to identify cognitive impairment remains limited. The aim of this study is to explore digital gait biomarkers by utilizing intelligent wearable devices for discriminating mild cognitive impairment and dementia.

Methods: This study included 122 subjects (age: 74.7 ± 7.7 years) diagnosed with normal cognition (NC, $n = 38$), mild cognitive impairment (MCI, $n = 42$), or dementia ($n = 42$). All subjects underwent comprehensive neuropsychological assessments and cranial Magnetic Resonance Imaging (MRI). Gait parameters were collected using validated wearable devices in both single-task and dual-task (DT). We analyzed the ability of gait variables to predict MCI and dementia, and examined the correlations between specific DT-gait parameters and sub-cognitive functions as well as hippocampal atrophy.

Results: Our results demonstrated that dual-task could significantly improve the ability to predict cognitive impairment based on gait parameters such as gait speed (GS) and stride length (SL). Additionally, we discovered that turn velocity (TV and DT-TV) can be a valuable novel digital marker for predicting MCI and dementia, for identifying MCI (DT-TV: AUC=0.801, sensitivity 0.738, specificity 0.842), and dementia (DT-TV: AUC=0.923, sensitivity 0.857, specificity 0.842). The correlation analysis and linear regression analysis revealed a robust association between DT-TV and memory function, as well as the hippocampus atrophy.

Conclusion: This study presents a novel finding that DT-TV could accurately identify varying degrees of cognitive impairment. DT-TV is strongly correlated with memory function and hippocampus shrinkage, suggests that it can accurately reflect changes in cognitive function. Therefore, DT-TV could serve as a novel and effective digital biomarker for discriminating cognitive impairment.

KEYWORDS

cognitive impairment, turn velocity, dual-task gait, digital biomarker, wearable device

1 Introduction

With the coming acceleration of global population aging, it is expected that the number of dementia patients worldwide will triple by 2050 [American Psychiatric Association (APA), 2013; Organization, W.H, 2021], which will place a heavy burden on families and nations. Mild cognitive impairment (MCI) serves as an intermediary state between healthy aging and the initial phases of dementia (Petersen, 2004). Consequently, timely identification and intervention to impede the progression of MCI towards dementia assume paramount importance. Currently, the assessment and detection of dementia are time-consuming and laborious, highlighting the urgent need for convenient screening methods. Previous studies have pointed out that gait disturbances are highly probable to function as an initial screening indicator for MCI (Waite et al., 2005; Garcia-Pinillos et al., 2016; Ramirez and Gutierrez, 2021). Therefore, the search for digital gait markers holds significant importance for future cognitive impairment screening.

Early gait studies on MCI or AD (Alzheimer's disease) have primarily utilized a single-task paradigm, recent researchers have proposed a dual-task paradigm that closely resembles daily life. This paradigm involves combining motor tasks (such as walking) with cognitive tasks (particularly those related to executive function, such as naming animals or counting backward). Substantial evidence indicates that individuals with MCI or AD exhibit poorer gait performance under dual-task conditions, including slower gait, increased gait instability and variability (Oh, 2021; Ramirez and Gutierrez, 2021). Systematic reviews and meta-analyses conducted by Bahureksa et al. (2017) and Fuentes-Abolafio et al. (2021) have demonstrated that gait speed, stride length, and stride time can accurately differentiate MCI patients from healthy controls, particularly in dual-task conditions. Furthermore, Toulotte et al. (2006) found that dual tasks negatively impacted walking ability in older individuals who had experienced falls, leading to compromised static balance. Shumway-Cook et al. also discovered that balance training under dual-task condition was more effective than single-task training in improving balance and cognitive performance in older adults with balance impairments (Silsupadol et al., 2009). Current neural theories suggest that there may be shared neural networks between motor and cognitive functions, and performing dual tasks may overload these networks (Tombu and Jolicoeur, 2003). AD patients, in particular, have impaired ability to share cognitive resources (Perry and Hodges, 1999; Sheridan et al., 2003). As a result, dual-task gait assessment based on smart and wearable digital technologies holds significant potential for detecting MCI and dementia.

However, the majority of current gait studies on cognitive impairment primarily rely on non-portable gait analysis techniques, which is inconvenient and fails to accurately capture the patient's gait changes during daily activities, making it unsuitable for home settings. In recent years, portable sensor devices have emerged as a new type of equipment and have been extensively used in studying neurological disorders of gait abnormalities, such as multiple sclerosis, hydrocephalus, as well as Parkinson's disease. Nevertheless, it is rarely used to analyze gait in individuals with cognitive impairment diseases, such as AD. In limited studies, most have solely focused on fall prognosis (Mancioppi et al., 2021; Weizman et al., 2021).

In studies involving portable devices, these equipment are predominantly designed to detect gait in straight-line walking mode and are limited to tracking the motor performance of the lower limbs (Auvinet et al., 2017), resulting in the gait parameters available are finite. In this study, we are the first to apply the intelligent and portable APDM's Mobility Lab system for gait detection in patients with cognitive impairment. The device is equipped with 6 sensors that can be utilized in open flat areas. It is capable of collecting data on gait and balance function in both straight and turn modes, which includes complex spatiotemporal gait and kinematic parameters. It automatically analyzes and calculates the collected data, providing gait information upon completion of the detection. In comparison, other portable devices in cognitive study often have only one sensor and can collect limited gait data. Some even require fixed laboratory monitoring, and very few devices are capable of detecting turning data (Fuentes-Abolafio et al., 2020, 2021).

Our primary objective is to utilize intelligent wearables to analyze the changes in gait parameters among patients with MCI and dementia under single-task and dual-task conditions and explore new gait indicators that can distinguish patients with cognitive impairment (MCI and dementia) from normal older adults. Additionally, we will investigate the correlations between these gait prediction indicators and various cognitive domains as well as hippocampal atrophy. We anticipate that the findings from this study will serve as a theoretical foundation for the future application of digital gait parameters detected by smart wearable devices in the screening of MCI and dementia patients.

2 Methods

2.1 Study design and participants

The old adults with or without cognitive impairment were invited into this study. Old patients with cognitive decline were recruited from the Memory Disorders Clinic of the Department of Geriatrics in the First Affiliated Hospital of Soochow University, and the individuals who were cognitively intact and healthy were invited as control group. All participants had to meet the following criteria: age 60 years and older, able to walk independently for 10 min without gait assistance, and without severe physical disease or contraindications for MRI. The study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Soochow University. Prior to participating in this study, all participants and their caregivers signed informed consent forms.

Exclusion criteria included:(1) having neurological and skeletal muscle diseases that may cause gait abnormalities (such as stroke, Parkinson's disease, severe arthritis, severe trauma, or surgery to the lower limbs); (2) having severe mental disease (such as people with severe depression, schizophrenia, alcohol use disorder, bipolar disorder, and anxiety disorder, etc., who are unable to cooperate and complete gait and cognitive assessments); (3) severe visual impairment and hearing impairment; (4) subjects with obvious white matter lesions (Fazekas score of 3 or higher).

Then, all participants underwent comprehensive neuropsychological testing and assessment of daily living abilities and were diagnosed with normal cognitive (NC), MCI or dementia by expert neurologists. According to Petersen et al. (2001), if a participant: (a) complaint for cognitive decline; (b) smaller than −1.5 standard deviation from mean of local population in at least one cognitive domain with the standard

neuropsychological assessments; (c) preserved basic activities of daily living (ADL) with slightly impaired instrumental activities of daily living (IADL) (Lawton and Brody, 1969); (d) failure to meet the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV); (e) 18 ≤ the Montreal Cognitive Assessment (MoCA) < 26 adjusted and education (Nasreddine et al., 2005), will be diagnosed with MCI. According to the DSM-IV [American Psychiatric Association (APA), 1994], participants who meet the following conditions are diagnosed with dementia. They have previously had normal intelligence and then have acquired cognitive decline (impairment of memory, execution, language, or visuospatial ability) or abnormal mental behavior that interferes with work or daily living and cannot be explained by delirium or other psychiatric disorders, assessed in combination with an objective scale, and has at least 2 of the following 5 items: (a) impaired memory and learning ability; (2) impaired executive functions such as reasoning, judgment and handling of complex tasks; (3) impaired visuospatial ability; (4) impaired language function (listening, speaking, reading, writing); (5) Changes in personality, behavior, or demeanor. The NC group consisted of individuals with normal cognitive performance, independent daily living (MoCA score ≥ 26 adjusted education, and normal ADL and IADL). Subsequently, all subjects underwent gait assessment and cerebral Magnetic Resonance Imaging (MRI) tests.

2.2 Sociodemographic characteristics and cognitive assessment

Sociodemographic information including age, gender, height, weight, years of education, and medical history (Hypertension, Diabetes mellitus, Coronary heart disease) was collected through face-to-face interviews. Global cognition was assessed by the Mini-Mental State Examination (MMSE) (Folstein et al., 1975) and the Montreal Cognitive Assessment of Beijing version (MoCA-BJ) (Yu et al., 2012) (1 point is added for participants with less than 12 years of education). The Clock Drawing Test (CDT) and the Stroop Color-Word Test-Victoria version (SCWT-VST) (Spreen and Strauss, 1998) were employed to evaluate spatial–temporal and executive function. Attention function was estimated by the Digit Span Test (DST) (Wechsler, 1955). Memory function was measured using the Auditory Verbal Learning Test-HuaShan version (AVLT-H) (Guo et al., 2007). Animal naming trials were conducted to assess participants' semantic fluency. To assess the participants' activities of daily living and independent living skills, we used the Instrumental Activities of Daily Living Scale (Shouxi Tao, 1992). Additionally, Hamilton Anxiety and Depression Rating Scales were used to measure the participants' mental state (Hamilton, 1959; Hamilton, 1960).

2.3 Magnetic resonance imaging data acquisition

MRI scanning of the cerebrum was performed on a GE Signa Hdxt 3.0 T scanner (Signa HDxt, GE Healthcare, Milwaukee, WI, United States) by one experienced physician. 3D-T1WI were as follows: TR = 6.52 ms, TE = 2.80 ms, flip angle = 12°, thickness/gap = 1.0/0 mm, field of view (FOV) = 260 × 260 mm, voxel = 1 × 1 × 1 mm3, and acquisition time = 4.25 min. The scan parameters of the T2-FLAIR-weighted imaging were as follows: TR = 8,000 ms, TE = 147 ms, TI = 1,500 ms, thickness/gap = 5.0/1.5 mm, FOV = 240 × 240 mm, and matrix = 256 × 192. Two experienced radiologists used two visual rating scales to identify White matter hyperintensity (WMH) and hippocampal atrophy on baseline images in each subject without knowing the clinical information of the subjects (In the event of disagreement, take the mean of the results of the two assessments). Fazekas scale was used for quantification of WMH, the medial temporal lobe atrophy rating scale (MTA) score was used to judge the degree of bilateral hippocampal atrophy (Fazekas et al., 1987; Scheltens et al., 1995). Finally, patients with severe cerebral small vessel disease (based on the detailed rules of the CSVD Global Burden Rating Scale proposed by Klarenbeek et al. (2013) and Staals et al. (2014), a score of 3 or more was considered), severe cerebral infarction (large-scale cerebral infarction, acute cerebral infarction, and old infarction malacing foci, and the infarction range is more than 1.5 cm), subdural effusion, and hydrocephalus were excluded.

2.4 Gait assessment

The gait parameters under single- and dual-task conditions were collected by the wireless APDM Movement Monitoring inertial sensor system (APDM Inc., Portland, OR, United States) which assesses spatial and temporal gait characteristics. APDM's Mobility Lab™ (APDM, Inc) (Mancini et al., 2011) automatically analyzed gait feature. Six Opals were worn on the body of subjects (one on the low back, two on the shanks, one on the sternum, and two on the wrists, see Supplementary material S1). Subjects were instructed to walk at their usual velocity with comfortable shoes on a 7-meter-long straight sidewalk (marked with colored tape at the start and end points), turn 180°, and return to the starting point. This entire process lasted for 2 min. Before conducting the trials, the subjects were given standard guidance and demonstrations. In the single-task test, subjects were asked to walk at their usual pace. In the dual-task condition, they were instructed to name as many different animals as possible while walking at their usual speed (All participants were not informed in advance of the need to name the animal). An experienced geriatrician walked behind the subjects to prevent falls. We selected 9 gait parameters of interest for further analysis in each condition. Supplementary material S2 provides an explanation of all gait parameters. In the end, a total of 122 subjects successfully completed all the evaluations.

2.5 Statistical analysis

All data and analyses were performed using SPSS for Windows Version 23.0 (IBM Corp., NY, United States). Shapiro–Wilk test assessed the normality of distributions. The data obtained from our study met the assumption of normal distribution for tests. Mean ± standard deviation was used to present continuous data, while percentages were used for categorical data. Differences in sociodemographic features, clinical features, and gait characteristics among dementia, MCI, and NC subjects were examined using one-way ANOVA with the Bonferroni test as a post-hoc analysis (for parametric variables) or the Kruskal–Wallis test (for non-parametric variables). Categorical variables were analyzed using the $\chi 2$ test. To

examine the relationship between specific gait parameters and different cognitive functions, we standardized the comprehensive scores of neuropsychological tests for each cognitive domain (The test results of each cognitive domain were summed separately and converted into Z-scores). We then conducted multiple linear regression and partial Spearman rank order correlation analysis, while adjusting for classical confounders such as age and educational level. Additionally, the Person product–moment correlation was used to analyze the associations between specific DT gait indicators with the MTA score of the hippocampus. Univariate logistic regression analysis was performed for all gait parameters. To determine the accuracy of gait parameters in distinguishing between dementia, MCI, and NC groups, we analyzed the area under the curve (AUC) of the Receiver Operating Characteristics (ROC).

3 Results

3.1 Participant characteristics

In this study, a total of 122 older adults (mean age 74.7 ± 7.7 years) were included. The participants were diagnosed with dementia ($n = 42$), MCI ($n = 42$), or normal cognitive function (NC) ($n = 38$) respectively. The sociodemographic and medical characteristics of participants are presented in Table 1. Age, years of education showed significant differences between the three groups ($p < 0.05$). No significant differences were found in the proportion of sex, height, BMI, hypertension, diabetes, coronary heart disease, anxiety, and depression scores between the three groups. Compared to the NC individuals, the dementia participants exhibited greater difficulty with instrumental ADL. The differences of global cognitive function and sub-cognitive functions (AVLT-H, DT span, CDT, SCWT, and the average number of Animal Naming) across the three groups were statistically significant.

3.2 Gait characteristics between the groups under the single- and dual-task walking

According to Table 2, in both single- and dual-task conditions, individuals with cognitive impairment performed worse in overall gait compared to NC participants. In single-task test, subjects with dementia and MCI presented with slower gait speed (GS: 63.5 ± 18.9 cm/s vs. 71.8 ± 16.6 cm/s vs. 83.2 ± 13.3 cm/s), slower turn velocity (TV: 123.9 ± 29.9 degree/s vs. 138.0 ± 31.4 degree/s vs. 165.3 ± 30.0 degree/s), shorter stride length (SL: 75.7 ± 19.3 cm vs. 83.3 ± 17.3 cm vs. 97.8 ± 13.5 cm) than NC group, and the differences were found to be statistically significant among the three groups. Furthermore, as the degree of cognitive impairment increased, individuals tended to have longer double support and standing phases,

TABLE 1 Demographics and clinical characteristics ($N = 122$).

Variable	NC ($n = 38$)	MCI ($n = 42$)	Dementia ($n = 42$)
Demographics and clinical characteristics			
Age, years	70.6 (7.0)	75.7 (7.2)*	76.9 (7.7)*
Male, *n* (%)	24 (63.2%)	23 (54.8%)	17 (40.5%)
Female (%)	14 (36.8%)	19 (45.2%)	25 (59.5%)
Education, years	10.9 (3.5)	8.8 (4.1)*	5.1 (5.0)*†
BMI (kg/m^2)	23.1 (3.3)	22.9 (4.4)	23.1 (7.2)
Height (m)	1.64 (0.08)	1.61 (0.08)	1.60 (0.08)
Hypertension, *n* (%)	13 (34.2%)	19 (45.2%)	13 (28.6%)
Diabetes mellitus, (*n*%)	7 (18.4%)	6 (14.3%)	10 (23.8%)
Coronary heart disease, (*n*%)	1 (2.6%)	2 (4.8%)	3 (7.1%)
MMSE score	27.6 (1.6)	23.1 (3.2)*	12.1 (4.2)*†
MoCA score	26.2 (2.6)	19.7 (2.9)*	9.9 (3.2)*†
Hamilton anxiety scale	3.9 (3.8)	2.5 (2.3) *	2.9 (3.1)
Hamilton depression scale	3.5 (4.3)	2.8 (2.9)	2.9 (3.9)
ADL	8.0 (0.0)	9.1 (2.8)	10.0 (4.5)*
IADL	12.2 (0.6)	15.7 (7.2)*	17.7 (8.5)*
AVLT-H (Immediate recall)[#]	16.2 (4.1)	11.3 (4.4)*	4.9 (4.5)*†
DST (Forward) [#]	7.9 (0.8)	7.1 (1.0)*	5.8 (1.2)*†
Animal Naming	14.7 (2.8)	12 (3.6)*	6.9 (3.6)*†
CDT	3.9 (0.2)	2.7 (1.1)*	1.2 (0.8)*†
SCWT (Color (s)) [#]	39.7 (1.9)	56.2 (30.8)*	62.9 (24.7)*

NC: normal cognitive; MCI: mild cognitive impairment; BMI: body mass index; MMSE: mini-mental state examination; MoCA: montreal cognitive assessment; ADL/IADL: instrumental/activity of daily living; AVLT-H: auditory verbal learning test-HuaShan version; DST: digital span test; CDT: clock drawing test; SCWT: stroop color word test;*$p<0.05$, versus NC; †$p<0.05$, versus MCI; [#] See Supplementary material S7 for more details.

TABLE 2 Gait parameters in single- and dual-task ($N = 122$).

Variable	NC ($n = 38$)	MCI ($n = 42$)	Dementia ($n = 42$)
Single-task [#]			
Gait speed (cm/s)	83.2 (13.3)	71.8 (16.6)*	63.5 (18.9)*†
Stride length (cm)	97.8 (13.5)	83.3 (17.3)*	75.7 (19.3)*†
Turn velocity (degrees/s)	165.3 (30.0)	138.0 (31.4)*	123.9 (29.9)*†
Dual-task			
Gait speed (cm/s)	65.2 (11.3)	48.8 (14.3)*	42.6 (14.4)*†
Cadence (steps/min)	90.3 (12.8)	88.8 (16.5)	89.1 (15.7)
Stride length (cm)	86.9 (11.8)	66.4 (15.9)*	58.5 (16.7)*†
Double support L (%GCT)	26.7 (3.4)	30.7 (6.0)*	32.2 (6.8)*
Double support R (%GCT)	26.6 (3.3)	31.0 (5.8)*	33.1 (8.1)*
Lateral step variability (cm)	7.7 (2.7)	5.6 (2.7)*	5.1 (2.4)*
Stance (%GCT)	63.3 (1.7)	65.8 (2.9)*	66.5 (4.2)*
Swing (%GCT)	36.7 (1.7)	34.5 (2.9)*	33.7 (3.5)*
Turn velocity (degrees/s)	151.0 (38.5)	117.9 (29.1)*	101.3 (23.0)*†

NC: normal cognitive; MCI: mild cognitive impairment;*$p<0.05$, versus NC; †$p<0.05$, versus MCI; [#] See Supplementary material S7 for more details.

shorter swing phases, and smaller lateral step variability. However, significant differences were only observed between the NC group and the dementia group ($p < 0.05$). Under dual-task gait assessment, the dementia and MCI patients exhibited significantly slower GS and TV, as well as significantly shorter SL than NC group (DT-GS: 42.6 ± 14.4 cm/s vs. 48.8 ± 14.3 cm/s vs. 65.2 ± 11.3 cm/s; DT-TV: 101.3 ± 23.0 degree/s vs. 117.9 ± 29.1 degree/s vs. 151.0 ± 38.5 degree/s; DT-SL: 58.5 ± 16.7 cm vs. 66.4 ± 15.9 cm vs. 86.9 ± 11.8 cm, see Supplementary material S3), the post-hoc test also revealed significant differences between the three groups. Additionally, there were significant differences observed in double support, standing phases, swing phases, and lateral step variability not only between the dementia and NC groups, but also between the MCI and NC groups ($p<0.05$). Either in single or dual-task, there was no significant difference in cadence between the three groups. Whatever the condition, the GS, SL, and TV always presented significant differences among the three groups.

3.3 Univariate logistic regression

As shown in Table 3, univariate logistic regression analysis was used for data processing, after adjusting for confounders (age, years of education). The results showed that, compared to single-task, almost all DT parameters were associated with an increased risk of cognitive impairment, reaching statistical significance (such as the longer double support times, shorter swing phases, and smaller lateral step variability). The gait features that were more significantly different between the three groups under two different task conditions were GS, TV, and SL, these three parameters were found to increase the risk of MCI and dementia, with statistical significance, each 1 cm/s increase in DT-GS decreased the risk of MCI by 18.3% and the risk of dementia by 26.2%, each 1 degree/s increase in DT-TV decreased the risk of MCI by 4.5%and the risk of dementia by 9.3%, each 1 cm increase in DT-SL decreased the risk of MCI by 14.9% and the risk of dementia by 24.8%.

3.4 Receiver operating characteristics curves

As shown in Table 4, we examined the predictive power of different gait parameters for varying degrees of cognitive impairment during different tasks (in previous univariate logistic analyses, they were found to independently affect MCI or dementia). For single-task walking, three characteristics including GS (AUC = 0.689, sensitivity = 59.5%, specificity = 81.5%), SL (AUC = 0.726, sensitivity = 54.8%, specificity = 86.8%), and TV (AUC = 0.761, sensitivity = 81.0%, specificity = 63.1%) were able to discriminate reasonably well between the NC and MCI groups. However, under dual-task conditions, the discrimination ability of all gait characteristics significantly improved, such as DT-GS (AUC = 0.788, sensitivity = 59.5%, specificity = 86.8%), DT-SL (AUC = 0.844, sensitivity = 59.5%, specificity = 94.7%), DT-TV (AUC = 0.801, sensitivity = 73.8%, specificity = 84.2%), DT-lateral step variability (AUC = 0.721, sensitivity = 81.0%, specificity = 65.8%). Moreover, when differentiating between the NC and dementia groups, no matter in the case of single- or dual-task, the discrimination ability of GS, SL and TV are excellent, especially DT-GS (AUC = 0.897, sensitivity = 78.6%, and specificity = 81.5%), DT-SL (AUC = 0.926, sensitivity = 71.4%, and specificity = 97.4%), DT-TV (AUC = 0.923, sensitivity = 85.7%, and specificity = 84.2%). Our findings consistently demonstrate that DT-GS, DT-SL, and DT-TV outperformed other gait indexes in terms of prediction ability. Additionally, the predictive model for TV exhibited high sensitivity and specificity in both single- and dual-task conditions (see Figure 1).

3.5 Correlations of different cognitive functions with dual-task gait characteristics

We examined correlations of DT-GS, DT-SL, and DT-TV with global cognitive function and sub-cognitive functions separately. Age,

TABLE 3 Logistics regression analysis of gait characteristics (NC-MCI & NC-Dementia).

Variable	NC-MCI			NC-Dementia		
	OR	*P*	95%CI	OR	*P*	95%CI
Single task						
Gait speed	0.943	0.006	0.904–0.983	0.934	0.008	0.888–0.982
Stride length	0.938	0.003	0.898–0.979	0.925	0.006	0.875–0.978
Double support L	1.193	0.024	1.023–1.390	1.149	0.077	0.985–1.340
Double support R	1.187	0.032	1.015–1.390	1.152	0.072	0.988–1.343
Lateral step variability	0.853	0.073	0.717–1.015	0.808	0.058	0.646–1.001
Stance	1.390	0.036	1.022–1.890	1.350	0.055	0.994–1.832
Swing	0.720	0.036	0.529–0.978	0.741	0.055	0.546–1.006
Turn velocity	0.975	0.007	0.958–0.993	0.967	0.005	0.945–0.990
Dual-task						
Gait speed	0.817	0.000	0.734–0.910	0.738	0.001	0.615–0.885
Stride length	0.851	0.000	0.782–0.926	0.752	0.001	0.632–0.894
Double support L	1.359	0.001	1.130–1.634	1.305	0.004	1.088–1.565
Double support R	1.431	0.000	1.171–1.749	1.368	0.002	1.123–1.666
Lateral step variability	0.762	0.008	0.624–0.931	0.692	0.006	0.534–0.898
Stance	1.945	0.001	1.328–2.8647	1.741	0.003	1.211–2.504
Swing	0.515	0.001	0.352–0.753	0.574	0.003	0.400–0.825
Turn velocity	0.955	0.000	0.932–0.979	0.907	0.000	0.866–0.950

Adjusted for age, sex, years of education.

TABLE 4 Area under the curve (AUC) and 95% confidence interval (CI) of gait variables between the groups during single- and dual-task walking (NC vs. MCI & NC vs. Dementia).

Variable	AUC	95%CI	Sensitivity	Specificity	AUC	95%CI	Sensitivity	Specificity
	NC vs. MCI				NC vs. Dementia			
Single task								
Gait speed	0.689	0.572–0.806	0.595	0.815	0.796	0.698–0.894	0.714	0.815
Stride length	0.726	0.615–0.836	0.548	0.868	0.829	0.740–0.918	0.643	0.921
Turn velocity	0.761	0.657–0.866	0.810	0.631	0.829	0.742–0.916	0.690	0.815
Dual task								
Gait speed	0.788	0.690–0.886	0.595	0.868	0.897	0.832–0.962	0.786	0.815
Stride length	0.844	0.761–0.926	0.595	0.947	0.926	0.873–0.979	0.714	0.974
Double support L	0.704	0.588–0.820	0.548	0.868	0.747	0.640–0.854	0.571	0.895
Double support R	0.735	0.625–0.845	0.571	0.868	0.770	0.667–0.874	0.524	0.947
Lateral step variability	0.721	0.608–0.835	0.810	0.658	0.755	0.649–0.861	0.786	0.657
Stance	0.723	0.611–0.835	0.476	0.947	0.759	0.654–0.864	0.571	0.947
Swing	0.727	0.615–0.838	0.476	0.947	0.763	0.659–0.868	0.571	0.947
Turn velocity	0.801	0.703–0.900	0.738	0.842	0.923	0.868–0.977	0.857	0.842

sex, and years of education were corrected during examination. Then, strong correlations were observed between the three indicators and MoCA (see Supplementary material S4), DT-TV exhibited the strongest correlation with memory, executive function, and language function (memory: $r_s = 0.428$, $p < 0.01$; executive: $r_s = -0.278$, $p < 0.01$; language: $r_s = 0.392$, $p < 0.01$; see Figure 2) compared to the other two indicators, DT-SL showed the strongest correlation with attention function (attention: $r_s = 0.347$, $p < 0.01$). However, the correlation between DT-GS and each cognitive domain was not prominent.

As we observed significant correlations between sub-cognitive function with DT-gait parameters. To assess the potential impact of sub-cognitive function on DT gait performance, we conducted a linear regression analysis (refer to Supplementary material S5). Our findings indicate that only memory function had a significant effect on DT-GS

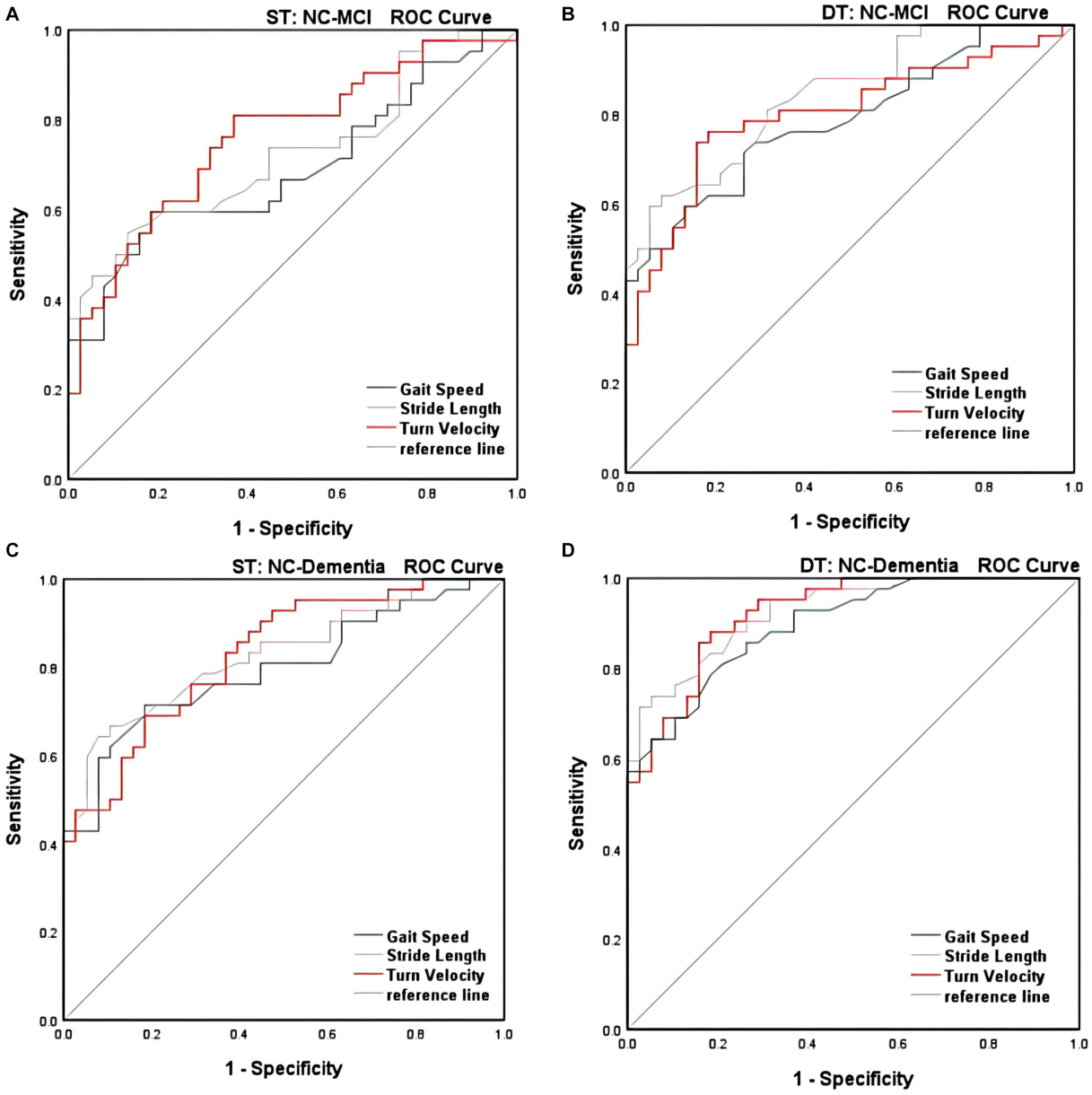

FIGURE 1
(A) Global performance of gait parameters under single-task walking for identification of NC with MCI. **(B)** Global performance of gait parameters under dual-task walking for identification of NC with MCI. **(C)** Global perfonnance of gait parameters under single-task walking for identification of NC with dementia. **(D)** Global perfonnance of gait parameters under dual-task walking for identification of NC with dementia.

($\beta = 0.322$, $p = 0.003$), DT-SL ($\beta = 0.274$, $p = 0.007$) and DT-TV ($\beta = 0.285$, $p = 0.006$) individually.

3.6 Correlations of MTA grade of the hippocampus with dual-task gait characteristics

Subsequently, we conducted an analysis on the correlations between DT-gait characteristics and the MTA grade of the hippocampus (see Supplementary material S6). The findings revealed a negative correlation between the DT-gait parameters and hippocampus atrophy. Notably, the correlation was more pronounced on the right side compared to the left. Moreover, we observed that the correlations between hippocampus atrophy and stride length, as well as turn velocity, was stronger than that with gait speed (DT-GS $r_s = -0.264$, $p < 0.01$; DT-SL $r_s = -0.406$, $p < 0.01$; DT-TV $r_s = -0.381$, $p < 0.01$).

4 Discussion

Nowadays, the development of convenient and efficient digital wearable device technology is continuously progressing, playing an increasingly important role in the early screening of neurodegenerative diseases (Kourtis et al., 2019). In this study,

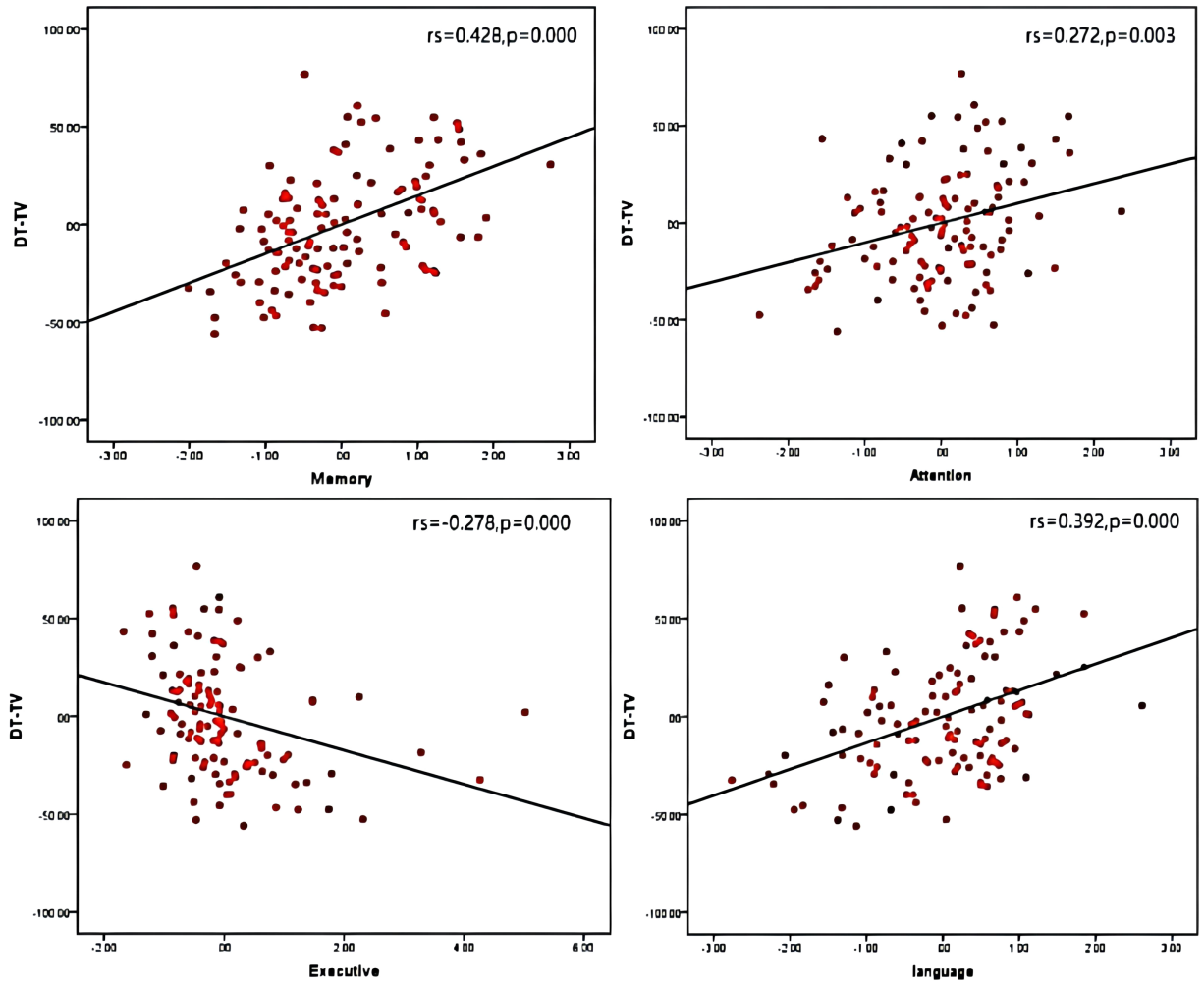

FIGURE 2
Correlations between the turn velocity under dual-task walking (DT-TV) with different cognitive function.

we have applied intelligent devices (APDM Movement Monitoring inertial sensor system) for the first time to gait detection in patients with MCI and dementia. Our results suggested that gait parameters obtained through the intelligent sensor device can more accurately differentiate patients with MCI and dementia from cognitively healthy individuals. Furthermore, we confirmed that indicators during dual-task walking were preferable, aligning with previous research (MacAulay et al., 2017; Oh, 2021). Among these gait parameters, gait speed and stride length have consistently emerged as prominent indicators, which is in line with numerous previous studies (Montero-Odasso et al., 2014; Beauchet et al., 2018). However, our study has made a novel discovery—turn velocity (TV)—which has shown remarkable ability in accurately distinguishing between normal and cognitive decline groups, and balanced both higher sensitivity and specificity, compared to gait speed and stride length. In addition, we further confirmed that DT-TV was strongly correlated with memory and the degree of hippocampal atrophy. These significant findings highlight the potential for intelligent wearable devices to be utilized in the future for screening individuals with MCI and dementia.

In previous studies, wearable devices are rarely used to assess the gait changes of patients with cognitive impairment, and as a result of technical limitations, these studies were unable to collect indicators related to turning function. The APDM gait analysis system overcomes these limitations by comprehensively acquiring data in both straight walking and turning modes. While it has been widely used in neurological disorders with gait abnormalities such as Parkinson's and multiple sclerosis, there is limited literature available on its application in gait analysis for diseases related to cognitive impairment. In our study, we leveraged the APDM gait analysis system and found that DT-TV exhibited a particularly excellent performance, which had a high predictive value for MCI and dementia (DT-TV for MCI, AUC 0.801, sensitivity 0.738, specificity 0.842; DT-TV for dementia, AUC 0.923, sensitivity 0.857, specificity 0.842).

Turning is a complex motor pattern which involves more coordination between limbs, coupling between posture and gait, and modifications of movement patterns (Patla et al., 1999), as well as requires higher cognitive demands than straight-walking (Mancini et al., 2016). Previous studies have reported that higher prefrontal cortex activity is strongly linked to poorer turning performance in

patients with neurological disorders (Belluscio et al., 2019; Stuart et al., 2019). However, only a few studies that have indirectly analyzed the association between turning function and cognitive impairment. A recent study found that turning function in patients with chronic stroke was associated with cognitive impairment (Kuan et al., 2022). Mirelman et al. (2014) also discovered that individuals with MCI had lower trunk angular velocity during turning. Although no studies have directly investigated turn velocity in patients with MCI and dementia, our results firstly suggest that turn velocity could potentially serve as a novel predictor of MCI and dementia.

Specifically, our study found that DT-GS, DT-SL, and DT-TV parameters showed approximately a 10% improvement in predicting MCI and dementia compared to single-task (in terms of AUC). This improvement is higher than what has been reported in other studies, where typically only about a 6% improvement is observed (Wang X. et al., 2023; Wang Y. et al., 2023). Moreover, our study demonstrated that dual-task gait parameters collected using smart gait devices achieved a dementia prediction rate of up to 90%, highlighting the potential of wearable devices in screening for dementia.

Previous longitudinal studies have demonstrated that executive function and episodic memory have a significant impact on gait speed (Holtzer et al., 2012a; Taylor et al., 2017), and it has been observed that better executive attention is associated with longer stride length (MacAulay et al., 2015). Recent evidence suggests that, in addition to GS and SL, gait parameters related to turning are highly correlated with executive and attention function (Morris et al., 2019; Sunderaraman et al., 2019). In our study, we observed that GS, SL, and TV were all associated with multiple cognitive functions (memory, executive, attention, and language). However, when conducting linear regression analysis, we observed significant correlations only between these three gait measures and memory function. This finding may be attributed to the more detailed assessment of memory function employed in our study. Similar regression analyses conducted in other studies have also reported a strong association between DT-GS and memory function (Holtzer et al., 2012b; Doi et al., 2014). Consequently, individuals with memory impairment may exhibit specific changes in dual-task gait performance.

The association between hippocampal atrophy and decline in gait speed in patients with cognitive impairment has been confirmed by several studies (Callisaya et al., 2013; Rosso et al., 2017; Pieruccini-Faria et al., 2023). Our study further confirmed that strong associations between hippocampal atrophy and decline in DT-GS, DT-SL and DT-TV. The strong correlations between DT-TV and memory function, along with hippocampal atrophy, which are consistent with GS and SL, suggest that DT-TV could serve as a significant indicator of cognitive impairment, and highlight its potential as a more effective digital marker.

In this study, for the first time, we found that TV can serve as a unique and novel digital marker for predicting MCI and dementia. Furthermore, gait parameters (GS, SL, TV) collected through intelligent wearable devices demonstrate exceptional predictive value for MCI and dementia. The significant correlation between TV and hippocampal atrophy as well as memory function confirms its potential as a novel gait marker for cognitive impairment. These findings lay the groundwork for future research on the early screening of MCI and dementia using smart wearable devices.

This study has several limitations. Firstly, it is a cross-sectional design, which means that we cannot establish the chronological order and determine causal inference. To confirm the observed results, follow-up visits with repeated measures are necessary. A longitudinal prospective design could be employed in future studies to investigate whether the decline in cognitive function precedes impaired turning function. Secondly, the measurement of the MTA level of the hippocampus should be improved in the future using automated analysis software to improve the accuracy of the experimental results. At last, the sample size in this study is relatively small, which may limit the generalizability of the findings. Insufficient power due to the small sample size can result in reduced reproducibility and potentially yield erratic or invalid results. Therefore, future studies should aim to include a larger study population to obtain more robust and reliable conclusions.

5 Conclusion

In our study, we have found that TV can be used as a distinctive and innovative digital indicator for predicting MCI and dementia. The strong correlation observed between TV and hippocampal atrophy as well as memory function, validates its potential as a novel gait marker for cognitive impairment. We are confident that our findings can contribute fresh insights for the development of future technology designs that aim to screen cognitive impairment in older adults.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary materials, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by the Ethics Committee of the First Affiliated Hospital of Soochow University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

JW: Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – original draft. ZZ: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Visualization, Writing – original draft. SC: Formal analysis, Investigation, Methodology, Project administration, Writing – review & editing. LZ: Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Writing – review & editing. XS: Conceptualization, Project administration, Resources, Supervision, Writing – review & editing. ZS: Data curation, Investigation, Methodology, Project administration, Writing – review & editing. ZW: Data curation, Investigation, Methodology, Project administration, Writing – review & editing. JL: Conceptualization, Project administration, Resources, Supervision, Writing – review &

editing. YQ: Conceptualization, Data curation, Methodology, Project administration, Resources, Supervision, Writing – review & editing. YW: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2024.1304265/full#supplementary-material

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Association of multiple metabolic and cardiovascular markers with the risk of cognitive decline and mortality in adults with Alzheimer's disease and AD-related dementia or cognitive decline: a prospective cohort study

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Background and objectives: There is a scarcity of data stemming from large-scale epidemiological longitudinal studies focusing on potentially preventable and controllable risk factors for Alzheimer's disease (AD) and AD-related dementia (ADRD). This study aimed to examine the effect of multiple metabolic factors and cardiovascular disorders on the risk of cognitive decline and AD/ADRD.

Methods: We analyzed a cohort of 6,440 participants aged 45–84 years at baseline. Multiple metabolic and cardiovascular disorder factors included the five components of the metabolic syndrome [waist circumference, high blood pressure (HBP), elevated glucose and triglyceride (TG) concentrations, and reduced high-density lipoprotein cholesterol (HDL-C) concentrations], C-reactive protein (CRP), fibrinogen, interleukin-6 (IL-6), factor VIII, D-dimer, and homocysteine concentrations, carotid intimal-medial thickness (CIMT), and urine albumin-to-creatinine ratio (ACR). Cognitive decline was defined using the Cognitive Abilities Screening Instrument (CASI) score, and AD/ADRD cases were classified using clinical diagnoses.

Results: Over an average follow-up period of 13 years, HBP and elevated glucose, CRP, homocysteine, IL-6, and ACR concentrations were significantly associated with the risk of mortality in the individuals with incident AD/ADRD or cognitive decline. Elevated D-dimer and homocysteine concentrations, as well

as elevated ACR were significantly associated with incident AD/ADRD. Elevated homocysteine and ACR were significantly associated with cognitive decline. A dose–response association was observed, indicating that an increased number of exposures to multiple risk factors corresponded to a higher risk of mortality in individuals with cognitive decline or with AD/ADRD.

Conclusion: Findings from our study reaffirm the significance of preventable and controllable factors, including HBP, hyperglycemia, elevated CRP, D-dimer, and homocysteine concentrations, as well as, ACR, as potential risk factors for cognitive decline and AD/ADRD.

KEYWORDS

Multiple biomarkers, metabolic and vascular disorders, association analysis, risk of cognitive decline, Alzheimer's disease

Introduction

Alzheimer's disease (AD) and AD-related dementias (AD/ADRD) are intricate neurological disorders that have a profound impact on millions of Americans, presenting some of the most significant healthcare challenges of the twenty-first century. In the United States (US), it was estimated that approximately 6.2 million adults aged 65 years and above were living with AD/ADRD in 2021, with projections indicating a staggering increase to approximately 14 million by the year 2060 (Tahami Monfared et al., 2022). The pathogenesis of AD/ADRD involves a complex interplay of various factors. Individuals experiencing cognitive decline (a precursor to dementia) and AD/ADRD exhibit a range of physiological alterations, including dysglycemia, dyslipidemia, endothelial dysfunction, vascular disorders, and chronic inflammation (Tahami Monfared et al., 2022). Despite these physiological alterations, the majority of researchers have primarily concentrated on genetics and protein concentrations, with limited attention given to applied epidemiological studies that target preventable risk factors. For example, a significant number of studies have examined possible dementia risk factors using magnetic resonance imaging (MRI) to detect focal signal abnormalities. However, this method has been mostly applied for diagnosing AD at the dementia stage and it is less effective in detecting the early stages of cognitive impairment and dementia (Hojjati et al., 2018). Several other potential predictors have been utilized to examine the risk of cognitive impairment and dementia. These predictors include the presence of apolipoprotein E (APOE ε4), the Mini-Mental State Examination score, the AD assessment scale-cognitive subscale (ADAS-cog), and the functional assessment questionnaire (FAQ) score (Weiner et al., 2010; Landau et al., 2011; Lee et al., 2014; Woolf et al., 2016; Kueper et al., 2018; Fayosse et al., 2020; Arevalo-Rodriguez et al., 2021; Chen et al., 2022). Unfortunately, while various studies were conducted on independent cohorts, the generalizability of their findings has been limited by small sample sizes (Woolf et al., 2016; Kueper et al., 2018; Arevalo-Rodriguez et al., 2021; Chen et al., 2022). Several studies have found a positive relationship between midlife vascular risk factors (i.e., high blood pressure (HBP), dyslipidemia, and hyperglycemia) and the risk of cognitive impairment and AD/ADRD (Zlokovic et al., 2020; Adkins-Jackson and Belsky, 2022). The potential pathophysiology of this association is supported by findings, suggesting that increased blood pressure, blood dyslipidemia, and hyperglycemia in midlife may trigger and perpetuate chronic brain inflammation. This aspect, in turn, could heighten the risk of brain amyloid β and tau pathology, ultimately leading to an elevated risk of AD and dementia (Pietrzik and Jaeger, 2008; Taguchi, 2009; Waldstein and Wendell, 2010; Correia et al., 2012; Nägga et al., 2018; Fayosse et al., 2020). A few studies examined the associations between cognitive function and AD/ADRD with inflammatory markers (assessed using serum CRP, fibrinogen, interleukin-6 (IL-6), and homocysteine), D-dimer (a marker of fibrinolysis), factor VIII (related to arterial thrombosis) (Carcaillon et al., 2009; Yan et al., 2010; Rubio-Perez and Morillas-Ruiz, 2012; Simon et al., 2018; Lauriola et al., 2021), and the albumin-to- creatinine ratio (a marker of kidney function) (Bikbov et al., 2022). Nevertheless, several research gaps persist: (1) Inconsistent findings have been observed from previous studies, potentially due to the heterogeneous nature of study samples across different studies (Brainerd et al., 2013; Gupta et al., 2019; Liu et al., 2021b). (2) Limited biomarkers were included in previous studies, leading to biases stemming from missed opportunities to assess important biomarkers. (3) There is a scarcity of data from large-scale epidemiological longitudinal studies involving diverse ethnic populations. Our research aims to address this gap by analyzing data from the Multiethnic Study of Atherosclerosis (MESA). Our central research question is whether metabolic disorders, as assessed by the five components of metabolic syndrome (MetSyn) (waist circumference (WC), HBP, elevated glucose and triglyceride (TG) concentrations, and decreased HDL-C concentrations) and eight other biomarkers measured from blood and urine samples, are significantly associated with the risk of cognitive decline, incident AD/ADRD, and AD/ADRD-related mortality. We focused on the most measurable factors typically encountered in primary healthcare settings to examine their association between cognitive decline and the risk of AD/ADRD. The findings from our research are expected not only to underscore the importance of addressing multiple preventable and treatable risk factors in controlling cognitive decline and AD/ADRD at the population level but also to pave the way for further etiological studies. These insights will contribute to the development of more robust risk prediction models and further our understanding of the risk of AD/ADRD.

Methods

Study design and study population

MESA is an ongoing cohort study that begun in 2000, investigating the characteristics of subclinical atherosclerosis and the determinants of cardiovascular diseases (CVDs). Its design has been described

previously (Center MC, 2001; Bild et al., 2002; Liu et al., 2009). In brief, the MESA cohort comprises a population-based sample of 6,814 men and women aged 45–84 years at baseline. All participants were free of clinical CVD at baseline and were recruited from six US communities (Forsyth County, NC; Northern Manhattan and the Bronx, NY; Baltimore City and Baltimore County, MD; St. Paul, MN; Chicago, IL; and Los Angeles, CA) (Bild et al., 2002; NHLBI BioLINCC, 2022). The MESA cohort participants were 38% white, 28% African American, 22% Hispanic, and 12% Chinese. People with a history of physician-diagnosed myocardial infarction, angina, heart failure, stroke, or transient ischemic attack, or who had undergone an invasive procedure for CVD (coronary artery bypass graft surgery, angioplasty, valve replacement, pacemaker placement, or other vascular surgeries), were excluded from this study (Bild et al., 2002; Yeboah et al., 2011). This study was approved by the institutional review boards of all collaborating institutions and the National Heart, Lung, and Blood Institute (NHLBI), and all participants provided signed informed consent (Yoneyama et al., 2012). Since MESA started in 2000, six repeated examinations (exams 1–6) have been conducted from 2000 to 2018. In our study, we analyzed MESA exams 1–5 because exam 6 was not ready and was not released by the NHLBI for analysis when we developed our study. We obtained the de-identified MESA data from the NHLBI Biologic Specimen and Data Repository Information Coordinating Center (NHLBI-BioLINCC, RMDA V02 1d20120806). We obtained approval from Drexel University Institutional Review Board (#2208009381 and #2308010042). MESA exams 1–5 were conducted from July 2000 to August 2002 (baseline, exam 1), September 2002 to February 2004 (exam 2), March 2004 to September 2005 (exam 3), September 2005 to Mach 2007 (exam 4), and April 2010 to December 2012 (exam 5), respectively. Combining exams 1–5 provides follow-up data through 31 December 2012 for cardiovascular and non-cardiovascular events and through 31 December 2015 for cause-specific mortality. Out of the 6,814 participants included at baseline, we excluded 346 who had missing values for the measures of the five components of MetSyn (WC, HBP, elevated serum glucose, TG concentrations, and decreased HDL-C concentrations) and eight biomarkers [serum C-reactive protein (CRP), fibrinogen, IL-6, D-dimer, homocysteine concentrations, carotid intimal-medial thickness (CIMT), and urine albumin-to-creatinine ratio (ACR)]. We also excluded eight participants who had a clinical diagnosis of AD (assessed by taking medication for AD) and also 20 participants who had not participated in the follow-up or had missed follow-up days. Our final analyses included 6,440 participants (3,040 men and 3,400 women, representing 95% of the original cohort participants).

Assessment of exposures: Body mass index (BMI, kg/m^2) is calculated as weight (kg) divided by height squared (meters). WC was measured using a standard flexible, tension-regulated tape measure. Systolic/diastolic blood pressure (SBP/DBP) was measured using an automated monitor following a 5-min rest period, with the last two out of three readings averaged and recorded. At each clinic setting, fasting (8–12 h) blood samples were collected from participants and shipped to the MESA central laboratory to measure all the blood factors using standardized protocols (Center MC, 2001; Bild et al., 2002). Total cholesterol and HDL-C were measured from blood samples obtained following a 12-h fast. Low-density lipoprotein cholesterol levels were estimated using the Friedewald equation (Friedewald et al., 1972). Fasting blood glucose (serum) levels were measured using the glucose oxidase method on the Vitros analyzer (Johnson & Johnson Clinical Diagnostics, Rochester, New York) (Yeboah et al., 2011). To define MetSyn, the five MetSyn component cutoff values utilize the modified criteria developed by the American Heart Association, the American Diabetes Association, and the Adults Treatment Panel (ATP) III (Grundy, 2005; Aronow, 2006; Liu et al., 2009, 2014; Inzucchi et al., 2015; American Diabetes Association, 2016). Individuals with MetSyn were classified based on the presence of three or more of the five components: (1) large WC: WC >102 cm in male participants and > 88 cm in female participants, or BMI ≥ 30 kg/m^2; (2) elevated BP: SBP ≥130 or DBP ≥85 mmHg or anti-hypertensive medication use; (3) elevated TG ≥150 mg/dL; (4) elevated glucose: fasting glucose ≥100 mg/dL or use of glucose-lowering medications; and (5) low level of HDL <40 mg/dL in male participants and HDL <50 mg/dL in female participants.

We further examined the associations by including a group of biomarkers in our analysis. These biomarkers were selected because they have been considered emerging or potential risk factors for AD/ADRD. In the study, we included following eight biomarkers: (1) CRP (a marker of inflammation) measured by a high-sensitivity assay (N-high-sensitivity CRP), (2) fibrinogen (a marker of inflammation, which also plays a critical role in the hemostatic process) measured using immunoprecipitation of fibrinogen antigen using the BNII nephelometer (Dade Behring Inc., Deerfield, Illinois) (Yan et al., 2010), (3) interleukin-6 (an inflammatory interleukin and a marker of immune system activation) measured using ultra-sensitive ELISA (Quantikine HS Human IL-6 Immunoassay; R&D Systems, Minneapolis MN) (Simon et al., 2018), (4) Factor VIII (high factor VIII concentrations are associated with arterial thrombosis) measured utilizing the Sta-R analyzer (STA-Deficient VIII; Diagnostica Stago, Parsippany, NJ), (5) D-dimer (a marker of fibrinolysis and fibrin turnover) measured using an immunoturbidimetric method on the Sta-R analyzer (Liatest D-DI; Diagnostica Stago) (Folsom et al., 2009), (6) homocysteine (a marker of inflammation and vitamin B12 and folate status) measured using high-performance liquid chromatography (Karger et al., 2020), (7) common CIMT (a marker of structural and functional vessel wall properties) measured using B-model ultrasonography (O'Leary et al., 1991), and (8) urine ACR measured using the Vitros 950IRC instrument (Johnson & Johnson Clinical Diagnostics Inc.) (Yu et al., 2011). To have a consistent analysis approach with the five dichotomized MetSyn components, we categorized the other eight markers as binary variables. Elevated CRP was defined as those with CRP ≥3 mg/L and elevated homocysteine ≥12 μmol/L on the basis of previous studies (Oda et al., 2006; Castañon et al., 2007). The remaining six biomarkers were classified according to their 75th or higher than 75th percentile cutoffs (specifically, quartile 4): fibrinogen ≥384 (mg/mL), IL-6 ≥ 1.76 (pg/mL), factor VIII ≥ 199 (%), D-dimer ≥0.34 (μg/mL), CIMT score ≥ 0.95 (mm), and urinary albumin-to-creatinine ratio ≥ 10.0 (mg/g).

Outcomes: Three groups of outcomes were included in the study: (1) Cognitive decline: Cognitive function was evaluated during the fifth MESA follow-up (2010–2012), using the Cognitive Abilities Screening Instrument (CASI, version 2). It should be noted that to assess cognitive impairment and dementia, various instruments have been utilized. The CASI is one of the most commonly used tools to assess overall cognitive function in people at the risk of dementia. The CASI was designed based on symptoms diagnosed as dementia and three cognitive screening tools, such as the Mini-Mental State

Examination, the Modified Mini-Mental State Test, and the Hasegawa Dementia Screening Scale. The CASI offers two significant advantages: first, it evaluates overall cognitive function with nine dimensions, providing comprehensive cognitive portraits and second, it demonstrates cross-cultural application in measuring global cognitive function and the risk of dementia (Teng et al., 1994; Fitzpatrick et al., 2015; Chiu et al., 2021). In brief, the CASI includes 25 items representing 9 cognitive domains: attention, concentration, orientation, language, verbal fluency, visual construction, abstraction/judgment, and short- and long-term memory. The CASI score ranges from 0 to 100, with a lower score indicating worse performance (Teng et al., 1994). In the study, we classified cognitive decline as individuals with a CASI score in the lowest 25th percentile of the score distribution. In MESA exam 5, participants with a history of AD/ADRD were excluded while measuring cognitive function. It should be noted that there was no cognitive function evaluation prior to MESA exam 5. Therefore, incident cognitive decline cannot be determined in the study. Out of 4,493 participants who returned for exam 5 in the study sample (i.e., participants without missing values of the study exposures), 4,379 participants completed the CASI test (97% of those returning participants). (2) AD/ADRD: In the MESA study, all cognitive and clinical data were assessed by a convened consensus conference of clinicians (e.g., neurologists, neuropsychologists, and geriatric psychiatrists, geriatricians) experienced in the adjudication of AD/ADRD. The National Institute on Aging (NIA)—Alzheimer's Association criteria were used to identify AD/ADRD (Albert et al., 2011; McKhann et al., 2011; Hirsch et al., 2022). Hospitalized patients with AD/ADRD were classified using International Classification of Diseases (ICD) codes (ICD-9: 290, 290.1, 290.10-13, 290.2, 290.20-21, 2,903, 2,904, 290.40-43, 290.8-9, 293, 294.1, 331.0, and 331.1). We further classified incident AD for patients who reported taking acetylcholine esterase inhibitors for AD treatment (with the exclusion of baseline AD). (3) Mortality: AD/ADRD-associated death was classified in individuals with a history of incident AD/ADRD or cognitive decline.

Covariates: Several demographic, socioeconomic, and lifestyle factors that were measured in MESA exam 1 (baseline survey) were included in the analysis: age, sex, race/ethnicity, education (an indicator of socioeconomic status), smoking, physical activity, and alcohol consumption status. Race/ethnicity was categorized as white, black, or African American, Hispanic/Latino, and Chinese-American. Education was grouped as ≤ high school, some college or associate degree, and completed college or higher. Smoking was categorized as never, former, and current smokers (Bild et al., 2002). Physical activity was categorized into two groups (regular and non-regular activity). Alcohol consumption was categorized into three groups: (1) never: for those who answered "No" to the question "have you ever consumed alcoholic beverage?"; (2) former: for those who answered "Yes" to the question, "have you ever consumed alcoholic beverage?" and who does not presently drink alcoholic beverages; and (3) current drinkers: for those who reported "they presently drink alcoholic beverages."

Statistical analysis

A series of analyses were conducted. First, we described the baseline characteristics of participants based on their incident AD/ADRD status. We used Student's *t*-tests to examine differences in continuous variables and chi-squared tests in categorical variables. Second, we tested the cross-association of MetSyn and its components, and other elevated biomarkers associated with cognitive decline (defined as low cognitive function, not a change—specifically, those with a CASI score in the lowest 25th percentile at the measures of MESA exam 5) using the logistic regression analysis. Third, we estimated the hazard ratios (HRs) of MetSyn, its components, and other eight markers for the risk of incident AD/ADRD and mortality in individuals with incident AD/ADRD or cognitive decline using Cox proportional hazard (PH) regression models. We examined the Cox PH assumption using a transformation of the Schoenfeld residuals known as the empirical score process, performed via the SAS Proc PHREG/assess PH/resample approach.

All data analyses were conducted using SAS 9.4/STAT 14.2 (SAS Institute Inc., Cary, NC, United States) (SAS Institute Inc., 2014). The reported *p*-values are two-sided, and the significance level was set at 0.05.

Results

Baseline characteristics of the study participants by incident AD/ADRD status

Table 1 shows that subjects with incident AD/ADRD had a significantly higher mean age than those without AD/ADRD (73.8 vs. 61.8 years older, $p < 0.001$). Subjects with incident AD/ADRD had significantly lower mean CASI scores, lower mean BMI, higher systolic blood pressure (SBP), and higher glucose concentrations than those without incident AD/ADRD. Among the categorical factors, subjects with incident AD/ADRD had a higher proportion of those with lower education attainment (less than high school), a higher proportion of those with never drinking, and a higher proportion of elevated fibrinogen, factor VIII, D-dimer, homocysteine concentrations, CIMT score, and ACR than those without AD/ADRD.

Cross-sectional association between risk factors and cognitive decline

Table 2 shows that after adjustment for age and sex (Model 1), MetSyn was significantly associated with the odds of cognitive decline (OR = 1.32, 95%CI: 1.14–1.53). Among the individual factors, HBP, elevated TG, low high-density lipoprotein (HDL), elevated glucose, fibrinogen, factor VIII, D-dimer, and homocysteine concentrations, as well as ACR were significantly associated with cognitive decline (Model 1). However, after further adjustment by including race/ethnicity, education, and lifestyle factors (Model 2, the full-adjusted model), this MetSyn–cognitive decline association became non-significant (OR = 1.00, 95% CI: 0.85–1.18). Similar to this observation, Model 2 indicated that only elevated homocysteine concentrations and ACR remained significantly associated with increased odds of cognitive decline (OR = 1.19, 95%CI: 1.06–1.69 for homocysteine, and OR = 1.24, 95% CI: 1.03–1.48 for ACR). Given this significant change in the ORs of MetSyn associated with cognitive decline from Model 1 to Model 2, we further investigated the main factors contributing to this change by conducting two subset

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TABLE 1 Baseline characteristics of the participants by incident Alzheimer's disease (AD) and AD-related dementia (ADRD).

	Non-AD/ADRD (n = 6,298)		AD/ADRD (n = 142)		
	Mean or no.	SD or %	No, mean	%, SD	p-value
Continuous variables, mean, SD					
Age, years	61.8	10.1	73.8	6.4	**<0.001**
CASI, cognitive score*	87.1	11.2	70.4	22.3	**<0.001**
Body mass index, kg/m^2	28.3	5.4	27.0	5.0	**0.004**
Waist circumference, cm	98.0	14.3	97.3	13.3	0.59
Systolic BP, mm Hg	126.2	21.3	136.5	25.1	**<0.001**
Diastolic BP mm Hg	71.9	10.3	72.2	10.6	0.70
Triglyceride, mg/dL	50.9	14.7	52.5	15.5	0.20
HDL-C, mg/dL	131.6	87.0	130.2	94.7	0.85
Glucose, mg/dL	97.2	30.2	103.4	35.3	**0.016**
Categorical var., no, %					
MetSyn, yes	2259	35.9	52	36.6	0.85
Sex, males	2964	47.1	76	53.5	0.12
Race/ethnicity					0.87
White	2449	38.9	58	40.8	
Chinese	769	12.2	15	10.6	
African American	1699	27.0	37	26.1	
Hispanics	1381	21.9	32	22.5	
Education					**0.002**
<High school	1116	17.8	42	29.6	
High school	1140	18.2	25	17.6	
Some college	1781	28.4	32	22.5	
College and higher	2242	35.7	43	30.3	
Smoking					0.15
Never smoked	4781	75.9	114	80.3	
Ex-smokers	561	8.9	13	9.2	
Current smokers	956	15.2	15	10.6	
Physical activity					
Regular	1582	25.2	27	19.0	0.09
Alcohol consumption					**0.005**
Never use	1277	20.3	41	28.9	
Former use	1505	24.0	37	26.1	
Current use	3498	55.7	64	45.1	
Elevated biomarkers					
CRP, mg/L	2240	35.6	42	29.6	0.14
Fibrinogen, mg/dL	1568	24.9	46	32.4	**0.042**
Interleukin-6, pg/mL	1572	25.0	36	25.4	0.92
Factor VIII, %	1590	25.2	49	34.5	**0.01**
D-dimer (μg/mL)	1567	24.9	69	48.6	**<0.001**
Homocysteine, μmol/L	838	13.3	45	31.7	**<0.001**
CIMT, mm	1604	25.5	69	48.6	**<0.001**
Album/Cre ratio, mg/g	1559	24.8	58	40.8	**<0.001**

AD/ADRD, Alzheimer's disease/AD-related dementia; CASI, Cognitive Abilities Screening Instrument, measured in MESA exam 5 (n = 4,379); HDL-C, High-density lipoprotein cholesterol; CRP, C-reactive protein; CIMT, Carotid intimal-medial thickness; Album/Cre ratio, urinary albumin-to-creatinine ratio. See text for details of biomarkers cutoff values. Significant difference: $p < 0.05$ in bold.

TABLE 2 Adjusted odds ratios [ORs, 95% confidence intervals (CIs)] for cognitive decline associated with metabolic syndrome, its components, and multiple biomarkers.

	Model 1			Model 2		
	OR	(95% CI)	*p*-value	OR	(95% CI)	*p*-value
MetSyn (yes vs. no)	1.32	(1.14–1.53)	**<0.001**	1.00	(0.85–1.18)	0.99
MetSyn components						
Large WC	1.07	(0.93–1.24)	0.34	0.87	(0.74–1.03)	0.11
HBP	1.35	(1.17–1.56)	**<0.001**	1.14	(0.97–1.34)	0.12
Elevated TG	1.19	(1.02–1.38)	**0.026**	0.99	(0.83–1.17)	0.86
Low HDL-C	1.24	(1.07–1.44)	**0.004**	0.97	(0.83–1.15)	0.75
Elevated Glucose	1.58	(1.35–1.86)	**<0.001**	1.13	(0.95–1.35)	0.18
Elevated biomarkers						
C-reactive protein	0.98	(0.83–1.16)	0.81	0.84	(0.75–1.05)	0.16
Fibrinogen	1.19	(1.01–1.40)	**0.043**	0.94	(0.79–1.13)	0.51
Interleukin-6	1.08	(0.91–1.28)	0.36	0.92	(0.77–1.11)	0.39
Factor VIII	1.20	(1.02–1.41)	**0.028**	1.16	(0.97–1.39)	0.11
D-dimer	1.25	(1.06–1.47)	**0.009**	1.13	(0.94–1.35)	0.20
Homocysteine	1.22	(1.03–1.44)	**0.019**	1.19	(1.06–1.69)	**0.019**
CIMT	1.11	(0.93–1.31)	0.25	1.08	(0.89–1.30)	0.45
Album/Cre ratio	1.47	(1.24–1.73)	**<0.001**	1.24	(1.03–1.48)	**0.021**

MetSyn, Cardiometabolic syndrome; WC, Waist circumference; HBP, High blood pressure; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; CIMT, carotid intimal-medial thickness; Album/Cre, urine albumin-to-creatinine ratio; Model 1, Adjusted age and sex; Model 2, Adjusted for age, sex, race, education, smoking, physical activity, and alcohol consumption. Significant difference: $p < 0.05$ in bold.

analyses with adjusting for race/ethnicity and education in a step-by-step entry approach in Model 1b and Model 1c. The results demonstrated that after adjusting for age, sex, and race/ethnicity (Model 1b of Figure 1 and Supplementary Table S1), the OR (95% CI) of MetSyn-associated cognitive decline attenuated to 1.11 (0.95–1.30, $p = 0.18$), indicating a 64.9% of the OR reduction from Model 1 to Model 1b [estimated by (OR1-OR2)/(OR1-1)*100]. After further adjustment for education, the ORs attenuated to 1.02 (95% CI: 0.86–1.19, $p = 0.86$, Model 1c of Figure 1 and Supplementary Table S1). Among these adjusted covariates, the results show that age, race/ethnicity, education, and alcohol consumption status are significantly associated with cognitive decline (Supplementary Table S1).

Longitudinal association of MetSyn and biomarkers with risk of incident ADRD

Among 6,440 participants at baseline, followed-up by the end of 2015 (a total of 45,608 person-years follow-up), 142 participants were classified as incident AD/ADRD. Table 3 shows that, after adjustment for age and sex (Model 1) and a full adjustment for multiple covariates (Model 2), baseline MetSyn and its components were not independently associated with the risk of incident AD/ADRD. Elevated blood D-dimer concentrations had a borderline significance for the risk of incent AD/ADRD ($p = 0.048$). Elevated homocysteine concentrations and urine ACR were significantly associated with the risk of incident AD/ADRD ($p = 0.005$ in elevated homocysteine concentrations and $p = 0.038$ in elevated ACR).

Longitudinal association of MetSyn and biomarkers with all-cause mortality in those with incident AD/ADRD or cognitive decline

Among 6,440 participants in MESA exam 1, 5448 were followed-up by the end of 2015 (a total of 83,942 person-years follow-up), with valid follow-up information. 210 all-cause deaths were observed. Within this group, 83 of the deaths were among the 142 individuals who had incident AD/ADRD (a death rate of 58.5%). The remaining 127 deaths were among the 1,066 individuals who had cognitive decline but had not yet developed AD/ADRD (a death rate of 11.9%). Table 4 shows that after adjustment for multiple covariates (Model 2), HBP, elevated glucose, CRP, IL-6, D-dimer, and homocysteine concentrations, as well as urine ACR were significantly associated with all-cause mortality in those with AD/ADRD or cognitive decline ($p < 0.05$ or $p < 0.001$). Figure 2A shows that among the 210 all-cause deaths who had a history of AD/ADRD or cognitive decline, 31% of them died from CVD (15.7% from coronary heart disease, 5.7% from stroke, and 9.5% from other forms of heart disease), and 64.3% from non- CVD. Figure 2B depicts the risk trend of exposures to an increased number of the study risk factors associated with all-cause mortality in those with AD/ADRD or cognitive decline compared to their corresponding counterparts.

Discussion

AD and ADRD have emerged as significant public health concerns in the USA and globally. Historically, AD/ADRD was predominantly

approached and studied within the realm of genetics. However, recent research, including our earlier reports, has revealed several potential factors that are both preventable and treatable, such as HBP (Liu et al., 2022), dyslipidemia, dysglycemia (Liu et al., 2021a,c), elevated fibrinogen (Lauriola et al., 2021), and elevated homocysteine (Kim et al., 2019), that contribute to the development of AD/ADRD. In the present study, we explored the association between various risk factors and the risk of AD/ADRD mortality over an average follow-up period of 13 years. Among 13 factors included in this study, HBP, elevated glucose, CRP, homocysteine, IL-6, and elevated urine ACR were significantly associated with the risk of all-cause mortality in those with incident AD/ADRD or cognitive decline. Meanwhile, our results indicate that elevated D-dimer and homocysteine concentrations and ACR were significantly associated with incident AD/ADRD. Elevated homocysteine concentrations and ACR were also significantly associated with cognitive decline. Additionally, our research unveiled a dose–response association, demonstrating that an increased number of exposures to these risk factors corresponded to a higher risk of all-cause mortality in those with AD/ADRD or cognitive decline. Our comprehensive analyses shed light on the intricate web of factors influencing AD/ADRD and underscore the importance of addressing preventable and modifiable elements in the prevention and treatment of these conditions.

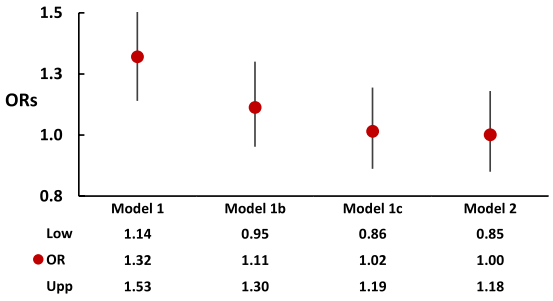

FIGURE 1
Changes in ORs of MetSyn associated with cognitive decline, when adjusting for age–sex (Model 1), plus race (Model 1b), plus education (Model 1c), and full-adjusted (Model 2).

In our study, we conducted a cross-sectional analysis to examine the association between MetSyn and biomarkers with the risk of cognitive decline. This approach was necessitated by the absence of a baseline measure of cognitive function prior to MESA exam 5. Our findings, as shown in the age–sex-adjusted model (Model 1 of Table 2), demonstrated a significant association between MetSyn, several MetSyn components, and biomarkers with the risk of cognitive decline. However, many of these associations lost significance after further adjustment for race/ethnicity, education, and lifestyle factors (smoking, physical activity, and alcohol consumption). These results indicate that multiple variables, particularly those related to demographics (age, sex, and race/ethnicity), education, and lifestyle factors, play a strong role in influencing the association between MetSyn and cognitive decline. In our previous studies, we have demonstrated that race/ethnicity, education, and lifestyle-related factors (i.e., obesity and smoking) are significantly associated with the risk of MetSyn (Liu et al., 2012, 2014, 2020). Given that our current study focuses on investigating the

TABLE 3 Adjusted hazard ratios (HRs, 95%CI) of MetSyn, its components, and biomarkers associated with incident AD/ADRD.

	Model 1			Model 2		
Case/person-yrs.	142/45,608 person-yrs.			142/45,608 person-yrs.		
HRs of risk factors	HR	(95%CI)	*p*-value	HR	(95%CI)	*p*-value
MetSyn (yes vs. no)	0.99	(0.70–1.41)	0.96	0.94	(0.66–1.33)	0.72
MetSyn components						
Large WC	0.85	(0.60–1.21)	0.37	0.82	(0.57–1.16)	0.25
HBP	1.13	(0.77–1.66)	0.52	1.10	(0.75–1.61)	0.63
Elevated TG	0.97	(0.67–1.40)	0.87	0.95	(0.65–1.38)	0.77
Low HDL-C	0.95	(0.66–1.36)	0.78	0.89	(0.61–1.29)	0.53
Elevated glucose	1.27	(0.90–1.81)	0.17	1.21	(0.85–1.73)	0.30
Elevated biomarkers						
C-reactive protein	0.85	(0.59–1.23)	0.39	0.83	(0.57–1.22)	0.34
Fibrinogen	1.20	(0.84–1.73)	0.31	1.16	(0.81–1.67)	0.41
Interleukin-6	0.86	(0.59–1.26)	0.45	0.84	(0.58–1.22)	0.36
Factor VIII	1.23	(0.86–1.75)	0.26	1.23	(0.85–1.76)	0.27
D-dimer	1.42	(1.01–1.98)	**0.043**	1.41	(1.00–1.99)	**0.048**
Homocysteine	1.79	(1.21–2.65)	**0.004**	1.76	(1.18–2.60)	**0.005**
CIMT	1.18	(0.84–1.67)	0.34	1.19	(0.84–1.68)	0.32
Album/Cre ratio	1.48	(1.05–2.08)	**0.025**	1.44	(1.02–2.03)	**0.038**

HR, Hazard ratios are estimated using Cox's models to test time-to-event risk; WC, Waist circumference; HBP, High blood pressure; TG, Triglyceride; HDL-C, High-density lipoprotein cholesterol; CIMT, Carotid intimal-medial thickness; Album/Cre ratio, Urine albumin-to-creatinine ratio; Model 1, Adjusted age and sex; Model 2, Adjusted for age, sex, race, education, smoking, physical activity, and alcohol consumption. Significant difference: $p < 0.05$ in bold.

TABLE 4 Adjusted hazard ratios (HRs, 95% confidence interval) of metabolic syndrome, its components, and biomarkers associated with all-cause mortality in those with AD/ADRD or cognitive decline.

	Model 1			Model 2		
Case/person-yrs.	210/83,942 person-years			210/83,942 person-years		
Risk factors for ADRD death	HR	(95% CI)	*p*-value	HR	(95% CI)	*p*-value
MetSyn (yes vs. no)	1.27	(0.96–1.68)	0.10	1.13	(0.85–1.50)	0.40
MetSyn components						
Large WC	1.17	(0.88–1.54)	0.28	1.07	(0.81–1.42)	0.64
High blood pressure	1.78	(1.26–2.52)	**0.001**	1.70	(1.20–2.40)	**0.003**
Elevated TG	0.96	(0.71–1.31)	0.82	0.92	(0.67–1.24)	0.57
Low HDL-C	1.15	(0.86–1.54)	0.34	1.06	(0.79–1.41)	0.72
Elevated glucose	1.58	(1.19–2.10)	**0.002**	1.41	(1.06–1.89)	**0.02**
Elevated biomarkers						
C-reactive protein	1.54	(1.16–2.05)	**0.003**	1.42	(1.06–1.88)	**0.017**
Fibrinogen	1.31	(0.97–1.77)	0.08	1.26	(0.93–1.71)	0.14
Interleukin-6	1.78	(1.34–2.36)	**<0.001**	1.66	(1.25–2.20)	**0.001**
Factor VIII	1.06	(0.78–1.43)	0.72	1.05	(0.77–1.43)	0.77
D-dimer	1.59	(1.20–2.11)	**0.001**	1.54	(1.16–2.05)	**0.003**
homocysteine	2.00	(1.46–2.72)	**<0.001**	1.89	(1.38–2.58)	**<0.001**
CIMT	1.14	(0.85–1.52)	0.38	1.11	(0.83–1.48)	0.47
Album/Cre ratio	2.21	(1.67–2.93)	**<0.001**	2.08	(1.57–2.76)	**<0.001**

HR, Hazard ratios are estimated using Cox's models to test time-to-event risk; WC, Waist circumference; HBP, High blood pressure; TG, Triglyceride; HDL-C, High-density lipoprotein cholesterol; CIMT, Carotid intimal-medial thickness; Album/Cre ratio, Urine albumin-to-creatinine ratio; Model 1, Adjusted age and sex; Model 2, Adjusted for age, sex, race, education, smoking, physical activity, and alcohol consumption. Significant difference: $p < 0.05$ in bold.

associations of metabolic disorders and biomarkers with the risk of cognitive decline and AD/ADRD, we incorporated these covariates (demographic, education, and lifestyle factors) as confounders instead of predictors in the analyses. It is essential to note that, even after adjusting for demographics, socioeconomic status (assessed by educational level), and lifestyle factors, elevated homocysteine concentrations and ACR remained independently and significantly associated with the risk of cognitive impairment.

Several studies have examined the relationship between elevated blood homocysteine concentrations and the risk of cognitive decline, with varying results. While some researchers have reported a significant association (Smith and Refsum, 2016; Kim et al., 2019; Lauriola et al., 2021), not all have yielded the same conclusions (Reitz et al., 2009). For example, Lauriola et al. conducted a study involving 929 participants aged 60–93 years, including individuals with mild cognitive impairment (MCI, $n = 126$) and those without MCI ($n = 803$). Their findings revealed a significant association between elevated homocysteine concentrations and increased odds of MCI, possible AD, and vascular AD ($p < 0.01$) (Lauriola et al., 2021). In contrast, Reitz et al. analyzed a cohort sample of 516 participants, with a mean age of 77 years, who did not have MCI or dementia at baseline. Over a 5.2-year follow-up period, the researchers found no significant association between blood homocysteine concentrations and the risk of MCI (Reitz et al., 2009). These discrepancies in findings may be attributed to differences in study populations or the relatively small sample size in the study conducted by Reitz et al. Nevertheless, the inconsistent results emphasize the need for further in-depth investigations into these associations.

The association between an elevated ACR and the risk of cognitive decline and AD/ADRD has also been observed by others (Bikbov et al., 2022). Although the precise mechanisms by which elevated homocysteine concentrations and ACR may contribute to the development of cognitive decline and AD/ADRD remain incompletely understood, there are several potential risk pathways to consider. These may include HBP, inflammation, and kidney dysfunction (assessed by ACR), all of which could lead to brain hypoxia, endothelial damage, and injuries (Rubio-Perez and Morillas-Ruiz, 2012; Smith and Refsum, 2016; Kim et al., 2019; Lauriola et al., 2021; Bikbov et al., 2022). Additionally, increased homocysteine concentrations serve as markers of impairment in vitamin B_{12} and folate metabolism, which may result in neuronal injury and an increased risk of cognitive decline and AD/ADRD (Moretti et al., 2017; Loures et al., 2019).

In the context of AD/ADRD research, substantial evidence underscores the role of amyloid-β (Aβ) deposition in the brain as the initiating factor in the pathogenesis of AD/ADRD. However, it is becoming increasingly clear that, alongside abnormal amyloid metabolism, other pathophysiological mechanisms are likely at play. Notably, hemostatic abnormalities and oxidative stress are emerging as potential contributors to the pathophysiological process associated with AD/ADRD (Rubio-Perez and Morillas-Ruiz, 2012; Loures et al., 2019). In our retrospective cohort analyses, we observed that elevated D-dimer concentrations, which are markers of hemostatic abnormalities, were significantly associated with AD/ADRD. While hypercoagulability promotes fibrin formation, it also heightens

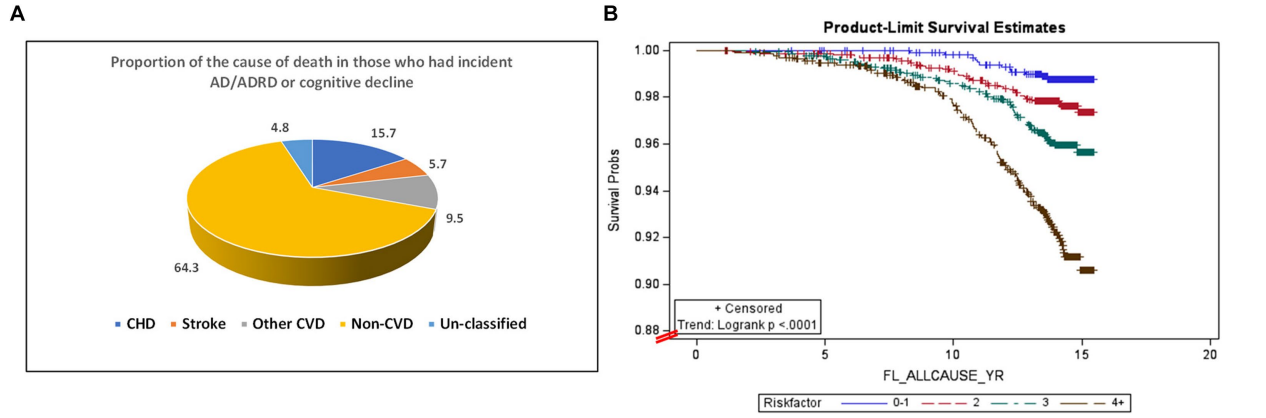

FIGURE 2
Percent of all-cause mortality from cardiovascular disease (total CVD: 30.9%, of them, CHD: 15.7%, stroke: 5.7%, and other CVD: 9.5%), and non-CVD (64.3%) in those with AD/ADRD or cognitive decline **(A)**, and the association between an increased number of exposures to the risk factors and all-cause mortality in those with AD/ADRD or cognitive decline **(B)**.

the risk of thrombosis. It is speculated that hemostatic abnormalities may predispose individuals to the development of microthrombi, which, in turn, can lead to compromised perfusion within the cerebral microcirculation. This aspect, in all likelihood, contributes to the impairment of cognitive function and other neurological processes (Carcaillon et al., 2009; Loures et al., 2019). It is important to note that, due to the nature of a large population-based MESA study, other directly AD/ADRD-related measurements obtained from samples of cerebrospinal fluid (surrounding the brain) were not available, such as tau and Aβ concentrations, nor tau neurofibrillary tangles and Aβ plaques (using positron emission tomography scans). Therefore, we are unable to test the associations of the study markers with tau and Aβ concentrations. Nevertheless, our findings emphasize the significance of further etiological investigations that consider potential pathways involving hemostatic abnormalities in the context of AD/ADRD risk.

Our current study offers several advantages. First, the MESA dataset stands out as one of the few studies that includes diverse study populations, including white, black, Hispanic, and Chinese participants. Second, the meticulous measurements of multiple factors in the study were conducted using standardized approaches, and biomarkers were centrally measured in one coordinating laboratory center within the MESA framework. This approach ensured consistency and accuracy in the study. Third, with a sample size of 6,440 participants, our study ranks among the largest in the existing literature on population-based cohort studies with the inclusion of both genders and diverse populations. Fourth, we employed a rigorous and robust analysis design to investigate both cross-sectional associations (risk factors for the odds of cognitive decline) and longitudinal associations (risk factors for the incidence of AD/ADRD and all-cause mortality in those with AD/ADRD or cognitive decline), while carefully adjusting for multiple covariates.

Nonetheless, it is important to acknowledge several limitations inherent in our analyses. First, association analyses were conducted between risk factors measured at baseline and the study outcomes at exam 5 for cognitive decline, and follow-up for measures of AD/ADRD and mortality through 31 December 2015. Our analyses do not take into account any changes in the baseline risk factors; their values may vary during the follow-up, which may potentially lead to either an over- or underestimation of the study associations. Second, the incident AD/ADRD cases may have been underestimated because of a competing cause of death that may have occurred before an individual had a chance to develop AD/ADRD. Third, given that the MESA study is ongoing, it is possible that some participants may develop AD/ADRD later in life. Therefore, findings from the current analysis may underestimate the association because some outcomes (AD/ADRD) may occur after the conclusion of the current analysis period. Fourth, because cognitive function assessments were lacking at baseline, we analyzed the cross-sectional association of baseline MetSyn and the study biomarkers with the odds of cognitive decline (measured at the MESA exam 5). Consequently, these cross-sectional analyses do not allow for an interpretation of causal associations between the study risk factors and cognitive decline.

Conclusion

Despite these limitations, the results of this study provide new evidence and highlight the significance of preventable and treatable factors, including HBP, hyperglycemia, elevated CRP, factor VII, D-dimer, homocysteine, and kidney dysfunction, as potential factors for reducing the risk of cognitive decline and AD/ADRD. This research contributes to a growing body of evidence emphasizing the interconnectedness of multiple factors with the risk of cognitive decline and AD/ADRD, which adds further suggestions to healthcare practice in controlling the risk of these conditions. However, further research is essential to explore the mechanistic pathways linking various disorders with cognitive decline and dementia risk, which includes investigating variations in the risk of AD/ADRD by race/ethnicity, sex, and the interrelations of these study factors. Additionally, there is a need to develop prediction models for the early detection of cognitive impairment

and dementia risk and to develop targeted strategies for prevention and treatment.

Data availability statement

The data, analyzed in this study, is subject to the following licenses/restrictions: The data analyzed in this study was from the National Heart, Lung, and Blood Institute (NHLBI) Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC). Investigators who are interested in the data may contact the NHLBI – BioLINCC. Requests to access these datasets should be directed to https://biolincc.nhlbi.nih.gov/home/.

Ethics statement

The present data analysis project, used unidentifiable / de-identified MESA dataset from the National Heart, Lung, and Blood Institute (NHLBI-BioLINCC). The data analysis project did not use human subject research as defined by DHHS or FDA regulations. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin for this analysis project in accordance with the national legislation and institutional requirements.

Author contributions

LL: Conceptualization, Data curation, Formal analysis, Funding acquisition, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. EG: Writing – review & editing. XZ: Writing – review & editing. GG: Writing – review & editing. NM: Writing – review & editing. SV: Writing – review & editing. JS: Writing – review & editing. RD-G: Writing – review & editing. HE: Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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A 3D pseudo-continuous arterial spin labeling study of altered cerebral blood flow correlation networks in mild cognitive impairment and Alzheimer's disease

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Objective: To investigate the abnormalities of the three-dimensional pseudo-continuous arterial spin labeling (3D PCASL) based cerebral blood flow (CBF) correlation networks in mild cognitive impairment (MCI) and Alzheimer's disease (AD).

Methods: 3D PCASL images of 53 cognitive normal (CN) subjects, 43 subjects with MCI, and 30 subjects with AD were acquired from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. Whole-brain CBF maps were calculated using PCASL and proton density-weighted images (PDWI). The 246 regional CBF values, including the cortex and subcortex, were obtained after registering the Brainnetome Atlas to the individual CBF maps. The Pearson correlation coefficient between every two regions across subjects was calculated to construct the CBF correlation network. Then the topologies of CBF networks with regard to global properties (global network efficiency, clustering coefficient, characteristic path length, and small-world properties), hub regions, nodal properties (betweenness centrality, BC), and connections were compared among CN, MCI, and AD. Significant changes in the global and nodal properties were observed in the permutation tests, and connections with significant differences survived after the z-statistic and false discovery rate (FDR) correction.

Results: The CBF correlation networks of CN, MCI, and AD all showed small-world properties. Compared with CN, global efficiency decreased significantly in AD. Significant differences in nodal properties and a loss of hub regions are noted in the middle temporal lobe in both MCI and AD. In the frontal lobe, BC is reduced in MCI while it is increased in the occipital lobe in AD. The identified altered hub regions with significant differences in MCI and AD were mainly distributed in the hippocampus and entorhinal cortex. In addition, disrupted hub regions in AD with significantly decreased connections were mainly found in the precuneus/posterior cingulate cortex (PCC) and hippocampus-cortical cortex.

Conclusions: Noninvasive 3D PCASL-based CBF correlation networks are capable of showing changes in topological organization in subjects with MCI and AD, and the observed disruption in the topological organization may underlie cognitive decline in MCI and AD.

KEYWORDS

arterial spin labeling, cerebral blood flow, brain connectivity, mild cognitive impairment, Alzheimer's disease

1 Introduction

Alzheimer's disease (AD), mainly accompanied by progressive, irreversible cognitive decline, is considered the main cause of dementia (Scheltens et al., 2021). Mild cognitive impairment (MCI) is the intermediate state between normal aging and AD, mainly accompanied by memory impairment (Anderson, 2019). It is reported that AD is a disconnection syndrome (Delbeuck et al., 2003), and abnormal brain networks in MCI and AD have been proven to be associated with cognitive decline (Celone et al., 2006; Yao et al., 2010), indicating that the application of network-based methods is of significance for understanding the mechanisms of MCI and AD.

The perfusion-based functional network plays an important role in characterizing the synchronous changes of perfusion in different regions and promotes signal transmission between regions (Melie-Garcia et al., 2013; Zhu et al., 2013). The cerebral blood flow (CBF) based network is commonly constructed for functional connectivity by providing associations between non-independent regions and their properties of interregional covariation, which can be obtained by calculating the Pearson correlation coefficient (Melie-Garcia et al., 2013). It has been proven that CBF correlation networks are related to metabolic and vascular information (Luciw et al., 2021). Importantly, group-level correlation analysis is necessary for CBF networks and the stable relationship of inter-regional CBF across subjects can be captured (Melie-Garcia et al., 2013; Zhu et al., 2015). A previous study demonstrated that the episodic memory decline in MCI is associated with the alteration of the global modularity in CBF-based networks constructed with single-photon emission computed tomography (SPECT) data (Sanchez-Catasus et al., 2018). However, there are some limitations in SPECT, such as the non-repeatable examinations caused by invasive radioactive tracers, low spatial resolution, and high time consumption.

To avoid that, arterial spin-labeling (ASL) magnetic resonance imaging (MRI), with the advantages of rapid imaging and lower costs, could be applied as a strategy for measuring arterial blood flow as an endogenous tracer to assess tissue perfusion and vitality (Detre et al., 1994). Much evidence has proved that ASL MRI has a strong correlation with the functional changes related to AD and some neurodegenerative diseases (Alsop et al., 2010; Wolk and Detre, 2012). Several studies have shown that the progression of MCI and AD can be estimated by the regional CBF values with a three-dimensional pseudo-continuous ASL (3D PCASL) (Binnewijzend et al., 2013, 2016; Suzuki et al., 2023), a widely recognized technique with high labeling efficiency, repeatability, and temporal and spatial signal-to-noise ratio (Alsop et al., 2015; Dolui et al., 2017), whereas the topological properties of CBF-based networks among CN, MCI, and AD have not been estimated in earlier studies. To follow the progression of MCI and AD, we applied the 3D PCASL to detect the disrupted CBF correlation networks in MCI and AD. Graph theory was used to characterize the topologies by exploring the regional and global properties, and significant differences ($p<0.05$) were obtained by comparing the results between each two groups. Finally, a z-statistic was calculated to obtain the significantly altered connections with the false discovery rate (FDR) correction.

2 Materials and methods

2.1 3D PCASL data from ADNI

The 3D PCASL data for this study were acquired from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). ADNI was launched in 2003 as a public–private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessments can be combined to measure the progression of MCI and early AD. For up-to-date information (see www.adni-info.org).

Each subject is assigned a unique identification number. CN subjects have a Memory Box score of 0, a Clinical Dementia Rating (CDR) of 0, and a Mini-Mental Status Exam (MMSE) score between 24 and 30. Participants with memory loss and who have a Memory Box score of at least 0.5, a CDR score of 0.5, and an MMSE score between 24 and 30 are diagnosed as having MCI. Subjects diagnosed with AD have a CDR of 0.5 or 1.0 and a MMSE score between 20 and 24 following the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA). Detailed inclusion and exclusion criteria can be found at https://adni.loni.usc.edu/wp-content/themes/freshnews-dev-v2/documents/clinical/.

2.2 Clinical assessment

All subjects from ADNI completed a comprehensive neuropsychological assessment based on standardized tests. Measures associated with cognitive domains include MMSE,

Montreal Cognitive Assessment (MoCA), and Alzheimer's Disease Assessment Scale-Cognitive (ADAS13). The demographic and clinical information was statistically analyzed by using MATLAB, one-way analysis of variance (ANOVA), and *post hoc* tests were applied to compare variables (age, education level, MMSE, MoCA, and ADAS13) among three groups. Chi-squared test was used to determine if there is any significant relationship between sex (male/female) and subjects with CN, MCI, and AD.

2.3 Image acquisition

Both high-resolution structural MRI data and resting PCASL data were downloaded for 53 CN subjects, 43 MCI subjects, and 30 AD subjects. The structural images were acquired using an accelerated sagittal inversion recovery fast spoiled gradient recall (IR-FSPGR) T1-weighted sequence with the following parameters: repetition time (TR)/echo time (TE)/inversion time (TI) = 7.39/3.06/400 ms, 196 sagittal slices, slice thickness = 1.0 mm, within the plane field of view (FOV) =256 ×256×196 mm^3, voxel size = 1× 1 × 1 mm^3.

3D PCASL data (label/control images) were acquired by a 3.0 T MRI scanner (Discovery MR 750, GE Medical Systems) with background suppression and no vascular suppression. The acquisition parameters were as follows: TR/TE = 4,888/10.5 ms, TI = 2,025 ms, post labeling delay (PLD) = 2,000 ms, slice thickness = 4.0 mm, FOV = 24 × 24 cm^2, weighting = proton density (PD).

2.4 Overview of CBF correlation network analysis

The processing steps of CBF correlation network analysis by using the 3D PCASL MRI are shown in Figure 1. First, the 3D PCASL MRI and PDWI were applied to calculate the CBF map (see "2.5 CBF maps Calculation"). Second, the Brainnetome Atlas (Fan et al., 2016) was registered from MNI space to individual space with T1 and proton density-weighted images (PDWI). Thus the CBF map was divided into 246 regions in gray matter. Third, the Pearson coefficient between regional CBF values at the group level was calculated for the construction of the correlation networks (see "2.6 Network Construction"). Finally, the changes in global properties (see "2.7 Global Properties Analysis"), hub regions (see "2.8 Hub regions in CBF correlation networks"), and nodal property (see "2.9 Nodal Property Analysis"), as well as altered connections were analyzed (see "2.10 Connection Analysis").

2.5 Calculation of CBF maps

The data of 3D PCASL (label/control images) and PDWI were converted into the 4D.nii.gz in NIFTI from DICOM format by using the tools of dcm2nii (https://www.nitrc.org/projects/dcm2nii). Then they were processed by FSL (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) with motion correction and brain tissue extraction to benefit the following processing and analysis.

$$CBF = \frac{6000 \cdot \lambda \cdot (SI_{control} - SI_{label}) \cdot e^{\frac{PLD}{T1,blood}}}{2 \cdot \alpha \cdot T_{1,blood} \cdot SI_{PD} \cdot \left(1 - e^{-\frac{\tau}{T1,blood}}\right)}$$

The above formula was applied to calculate CBF in the whole brain. The scan parameters are as follows: $T1$ of blood is assumed to be 1.4 s, the factor τ represents the label duration which is 1.5 s, λ is the brain/blood partition coefficient whose value is 0.9 (ml/g), PLD is the time of post-labeling delay and is set to 2.025 s, α is the labeling efficiency factor with a value of 0.8.

2.6 Network construction

Gray matter brain regions were obtained from CBF maps by using the FSL tools. Each subject's PDWI image was first registered to T1 data linearly, and a matrix with mutual information was obtained, with linear and non-linear methods. We normalized T1 data to MNI space. Next, the co-registered PDWI image in structure space was warped by the transform field normalized from T1 to MNI. Then, the Brainnetome Atlas in MNI space was registered to individual PCASL and PDWI space through the results we obtained in the last step (Yuan et al., 2017). Thus 246 regions in each subject were obtained with the individual atlas and whole brain CBF maps.

To construct the CBF connectivity network, three CBF data matrices for CN (53×246), MCI (43×246), and AD (30 × 246) were prepared, in which rows represent the number of subjects and columns represent the number of brain regions, and Pearson's correlation index between each two brain regions across subjects was calculated and three CBF connectivity networks were constructed. Then the CBF connectivity networks after normalization were calculated at different sparsity from 0.65 to 0.83 with the step size 0.02.

2.7 Analysis of global properties

To analyze the global properties of the CBF connectivity network, we calculated the global network efficiency, clustering coefficient, characteristic path length, and small-world properties. The global efficiency is the average inverse shortest path length in the network and is inversely related to the characteristic path length. The clustering coefficient is the fraction of triangles around a node and is equivalent to the fraction of the node's neighbors that are neighbors of each other. The small-world properties are related to the normalized average clustering coefficient and the average shortest path length. When the small-world coefficient value is >1, we consider it to have the small-world property.

We applied the non-parametric permutation approach (1,000 permutations) to compare the global network properties between every two groups. In each permutation, regional CBF values

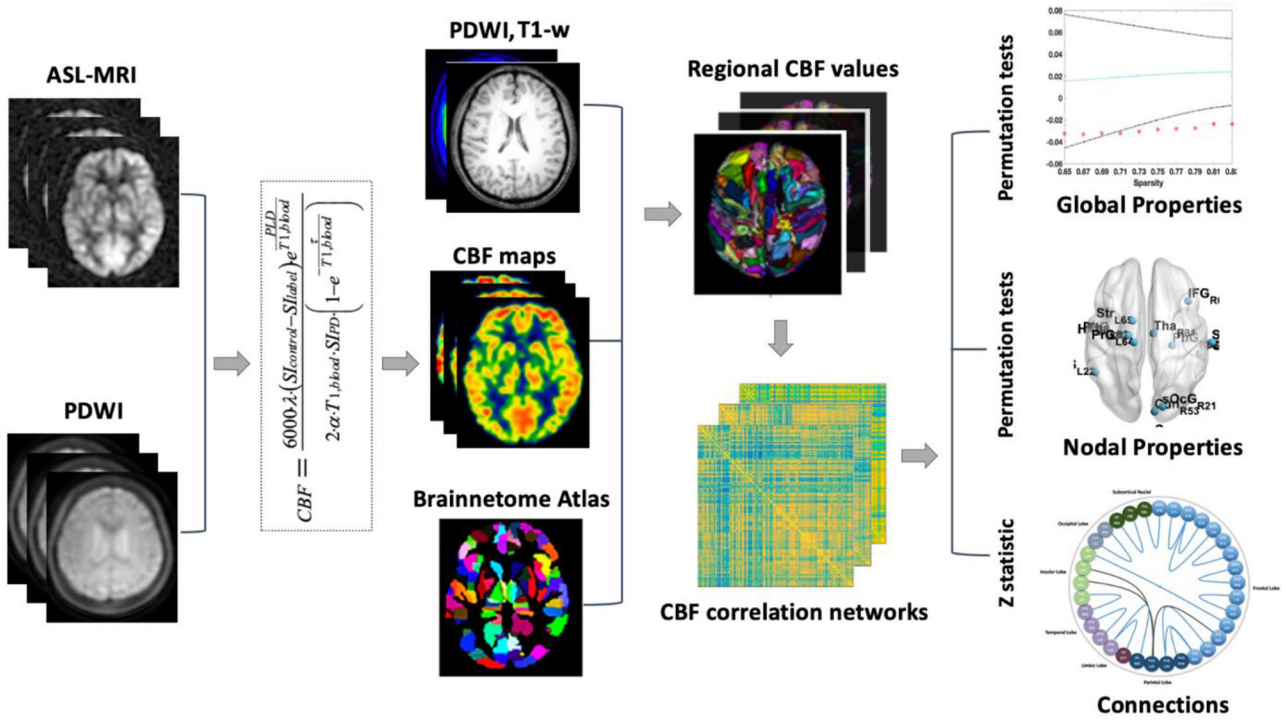

FIGURE 1
Study procedure of CBF correlation network analysis.

were randomly reassigned and the number of subjects in each randomized group was the same as that in the original group with CN (53 × 246), MCI (43 × 246), and AD (30 × 246), and the correlation connectivity network was constructed for each randomized group. We obtained the global parameters of randomized matrices at a range of sparsity 0.65–0.83 with step size 0.02 in each group with correlation connectivity networks constructed by each randomized group. Finally, the difference in the global network parameters of original networks was compared to that of randomized networks (null distributions) and the relative positions of difference as nonparametric *p*-values were obtained, in which parameters with *p*-values under 0.05 were considered to be significant.

2.8 Hub regions in CBF correlation networks

The MATLAB-based Brain Connectivity Toolbox (BCT) for complex brain network analysis (Rubinov and Sporns, 2010) was applied to analyze the properties of the CBF connectivity network in CN, MCI, and AD groups.

We identified the hub regions with node measure betweenness centrality (BC) and the fraction of all shortest network paths containing a given node, which is applied most widely in characterizing the importance of nodes in a network (Freeman, 1977). In the current study, nodes with BC two times higher than the mean value of all the nodes were defined as hub regions. Hub regions in the CN group were first detected, and then the corresponding BC values of regions in MCI and AD groups were calculated.

2.9 Nodal property analysis

To detect the changes in nodal properties of the CBF connectivity network among CN, MCI, and AD groups, the non-parametric permutation approach (1,000 permutations) was applied. With the same method described in the global properties analysis, we constructed the original and randomized correlation networks, and then BC values of nodes in original and randomized matrices at a sparsity of 0.83 in each group were obtained. Finally, the difference of BC values of nodes in the original networks was compared to that of randomized networks (null distributions), and the relative positions of difference as non-parametric *p*-values were obtained, nodes with significant differences were identified with *p*-values below 0.05.

2.10 Analysis of connections

Significant differences in the connections of CBF connectivity networks with a sparsity of 0.83 between every two groups (CN vs. MCI, CN vs. AD, and MCI vs. AD) were tested. z-values were obtained from the correlation coefficients with Fisher's *z*-transformation. Then a *z*-statistic was obtained, and connections with significantly different values survived with false discovery rate (FDR) correction ($p < 0.001$).

TABLE 1 Demographic and clinical characteristics of ADNI subjects.

Parameter	CN	MCI	AD	*P* value
	(*n* = 53)	(*n* = 43)	(*n* = 30)	
Age, years	74.1 ± 3.2	76.2 ± 3.6	75.1 ± 5.3	0.243[a]
Education, years	16.3 ± 2.1	16.4 ± 2.3	16.6 ± 2.2	0.537[a]
Sex, menwomen/men	26/27	22/21	16/14	0.931[b]
MMSE	28.9 ± 2.4	26.8 ± 3.4	21.5 ± 2.7	<0.001[a]*
MoCA	25.7 ± 2.6	23.1 ± 3.9	17.6 ± 3.9	<0.001[a]*
ADAS13	7.9 ± 4.5	16.9 ± 4.1	27.8 ± 2.9	<0.001[a]*

Data are shown as the mean ± standard deviation. *P<0.05; [a]one-way analysis of variance; [b]chi-squared test; ADNI, Alzheimer's Disease Neuroimaging Initiative; CN, cognitive normal; MCI, Mild cognitive impairment; AD, Alzheimer's disease; MMSE, Mini-Mental Status Exam; MoCA, Montreal Cognitive Assessment; ADAS13, Alzheimer's Disease Assessment Scale-Cognitive13.

3 Results

3.1 Demographic and clinical characteristics of ADNI subjects

The demographic and clinical characteristics of subjects from ADNI are shown in Table 1. Significant differences (p<0.001) were found among CN, MCI, and AD in MMSE, MoCA, and ADAS13. No significant difference was found among the three groups in terms of age, sex, and education level.

3.2 Calculated CBF maps and regional CBF values

The calculated whole brain CBF maps of CN, MCI, and AD are shown in Figure 2. After the registration of the Brainnetome Atlas to CBF maps in individual space, 246 regional CBF values in gray matter were obtained. Regional CBF with significant differences among CN, MCI, and AD were statistically analyzed with double t-tests and FDR correction ($p < 0.05$). Compared with CN, nine regions decreased significantly in MCI, mainly distributed in the frontal gyrus, middle temporal gyrus, parahippocampal gyrus, parietal lobe, and occipital lobe. Compared with CN and MCI, nine regions with significant differences were found in AD, they are mainly in the frontal gyrus, temporal gyrus, parahippocampal gyrus (e.g., entorhinal cortex), and hippocampus. Figure 3 shows the spatial location of the regions mentioned above, and the regional values with significant differences are listed in Supplementary Table 1.

3.3 Global properties of CBF correlation networks

From Figure 4, global efficiency shows a significant decrease in the AD group compared with the CN group under the sparsity of 0.71 ($p = 0.031$), 0.73 ($p = 0.016$), 0.75 ($p = 0.009$), 0.77 ($p = 0.002$), 0.79 ($p = 0.002$), 0.81 ($p < 0.001$), and 0.83 ($p < 0.001$). A significant decrease was also found from a comparison between MCI and AD at the sparsity of 0.77 ($p = 0.027$), 0.79 ($p = 0.018$), 0.81 ($p = 0.003$). No significant changes were found among the CN, MCI, and AD for clustering coefficient and characteristic path length. Figure 5 shows that all three groups exhibit small-world topologies across the sparsity from 0.65 to 0.83, and the intermediate state of MCI is shown between CN and AD in the small-world properties across all the sparsity values. From the bar plot in Figure 5, we found that, compared with CN, the mean small-world value of all sparsity in MCI decreased by 0.1 (6.85%), and that in AD decreased by 0.23 (15.75%). Meanwhile, the mean small-world value in AD decreased by 0.13 (9.56%) compared with MCI.

3.4 Hub regions in CBF correlation networks

Hub regions in the CN, MCI, and AD are shown in Figure 6. Twenty-five hub regions were identified in CN, while the number of hub regions is 25 in MCI and 24 in AD. Hub regions were identified in three groups distributed in the inferior and middle frontal gyrus, orbital gyrus, inferior and superior temporal gyrus, precuneus, and occipital gyrus. The identified hub regions are listed in Supplementary Table 2.

In addition, the middle temporal gyrus, inferior parietal lobule, and cingulate gyrus including cingulate gyrus (CG)_R_7_1 (i.e., posterior cingulate cortex, PCC) were found as hub regions in CN and MCI but disappeared in AD. Identical hub regions such as parahippocampal gyrus (PhG)_L_6_4 (i.e., entorhinal cortex), and hippocampus (Hipp)_L_2_1 were also found only in CN. For both MCI and AD groups, hub regions were found in the insular gyrus and cuneus. Additionally, hub regions in the striatum and posterior superior temporal sulcus were also observed.

3.5 Altered nodal property in CBF correlation networks

From Figure 7, we found that 18 regions with significantly different BC values in the CBF correlation networks between CN and MCI groups, including the inferior frontal gyrus, middle frontal gyrus, dorsal anterior insula, inferior temporal gyrus, orbital gyrus, cuneus, parahippocampal gyrus, superior temporal gyrus, and thalamus. Between CN and AD groups, 20 regions were detected with significant differences. They were distributed in the parahippocampal gyrus, cuneus, caudoventral anterior insula, inferior temporal gyrus, superior temporal gyrus, striatum, thalamus, fusiform gyrus, hippocampus, posterior superior temporal sulcus, and superior occipital gyrus. Compared with the MCI group, 13 regions were found to be decreased in the AD group, which include the cuneus, hippocampus, inferior frontal gyrus, inferior temporal gyrus, parahippocampal gyrus, posterior superior temporal sulcus, superior occipital gyrus,

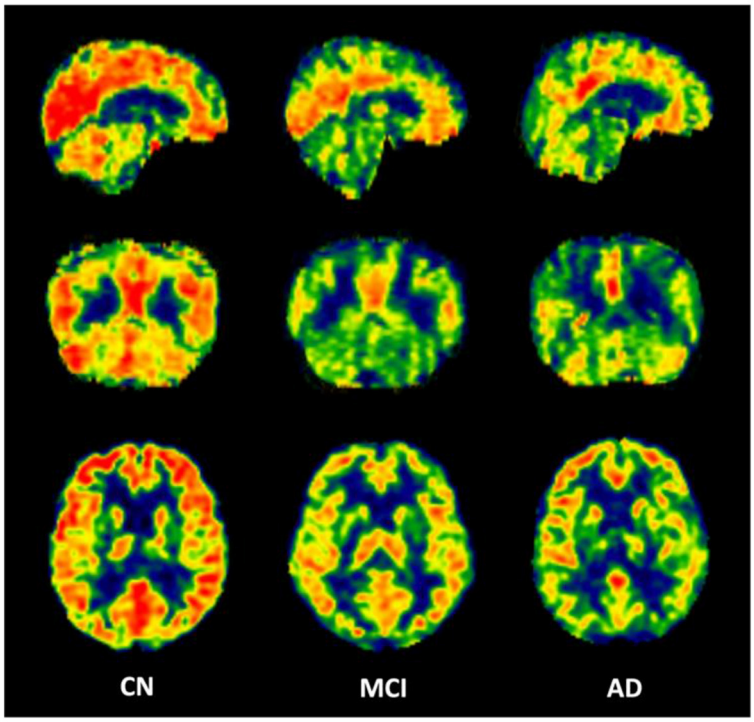

FIGURE 2
Representative CBF maps from CN, MCI, and AD groups.

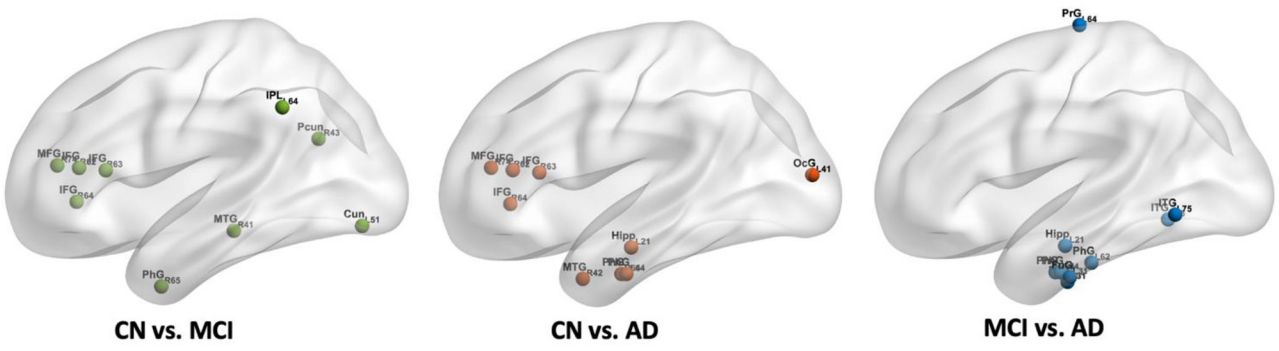

FIGURE 3
The spatial locations of regions with significant differences in CBF values among CN, MCI, and AD groups.

superior temporal gyrus, striatum, thalamus, and precentral gyrus. In addition, we found cuneus, inferior temporal gyrus, parahippocampal gyrus, superior temporal gyrus, and thalamus changed significantly between every two groups. Importantly, the significantly changed BC value of PhG_L_6_4 (i.e., entorhinal cortex) was found in MCI and AD. We found that there is no region with significant differences between CN and MCI in the hippocampus, and with progression and the BC value of Hipp_L_2_1 in the hippocampus decreased significantly in AD. We also found that with progression, significantly different regions in the frontal lobe decreased, while some regions in the occipital lobe increased significantly in AD. The regions with significantly different BC values are listed in Supplementary Table 3.

3.6 Altered connections in CBF correlation networks

We did not find a connection with significant differences between CN and MCI. While 27 connections were found with significant differences between CN and AD, they were distributed in the frontal lobe (middle and inferior frontal gyrus, orbital gyrus, precentral gyrus), temporal lobe (superior and

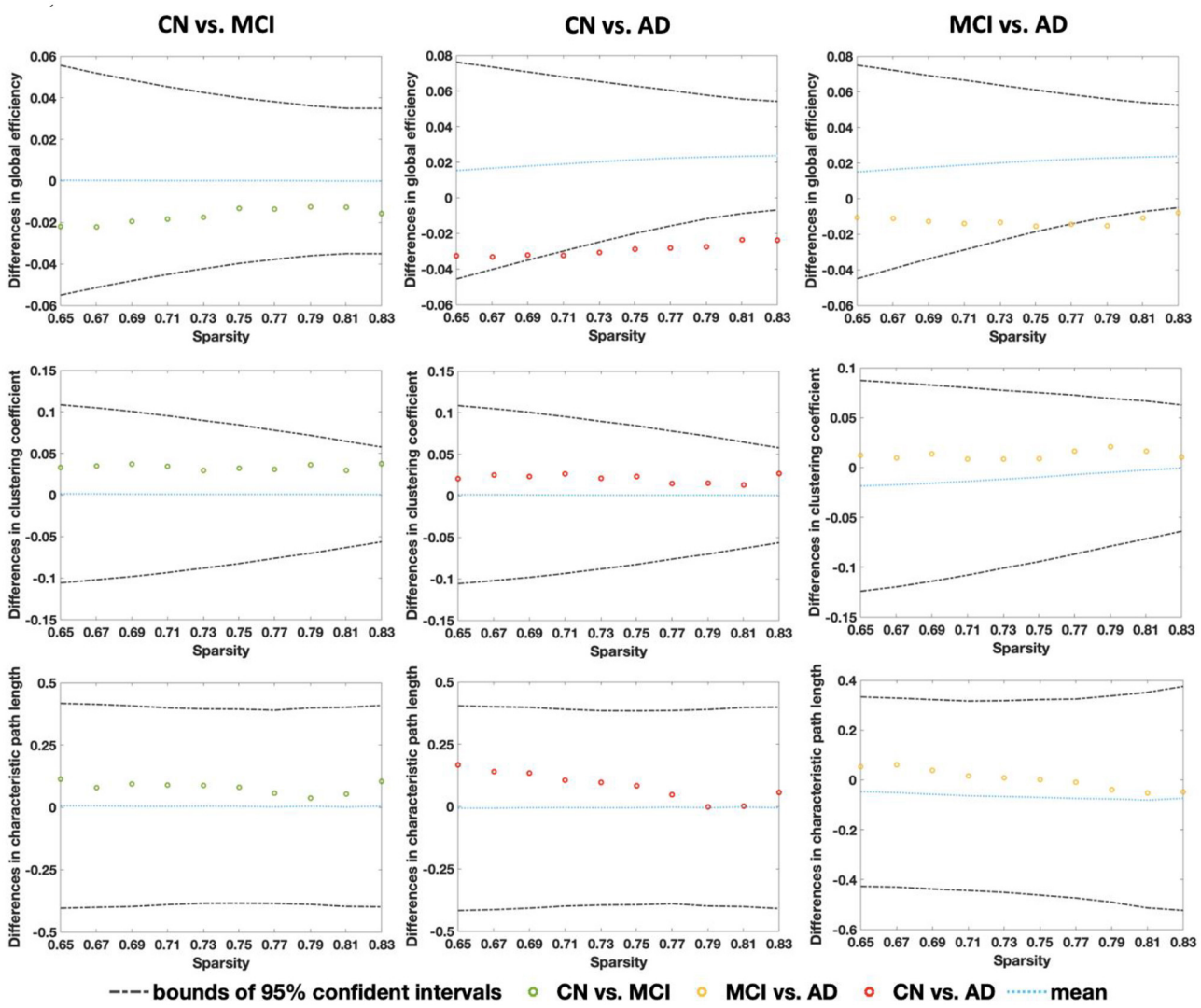

FIGURE 4
Relative differences in global properties of CBF correlation networks (global efficiency, clustering coefficient, and characteristic path length) between CN-MCI, CN-AD, and MCI-AD across the sparsity from 0.65 to 0.83. The non-parametric permutation tests (1,000 permutations) were conducted showing the results of the mean value (blue lines) and 95% confidence intervals (dashed lines).

middle temporal gyrus, parahippocampal gyrus, posterior superior temporal sulcus), parietal lobe (superior parietal lobule, angular gyrus, supramarginal gyrus, precuneus, postcentral gyrus), insular lobe (rostrodorsal posterior insula), limbic lobe (cingulate gyrus), occipital lobe (cuneus, superior occipital gyrus), and subcortical nuclei (hippocampus), and those spatial distributions mentioned above are shown in Figure 8 (left). From Figure 9 (top), we found most of the connections were significantly decreased, except for seven connections in the frontal, parietal limbic, and occipital lobes were increased. Compared with MCI, we found 20 connections with significant differences in the AD group, which were distributed in the frontal lobe (superior, middle and inferior frontal gyrus, orbital gyrus, precentral gyrus, paracentral lobule), temporal lobe (superior and middle temporal gyrus), parietal lobe (supramarginal gyrus, postcentral gyrus), insular lobe (dorsal anterior insula, ventral posterior insula, rostrodorsal posterior insula, caudoventral anterior insula), limbic lobe (cingulate gyrus), occipital lobe (cuneus), and subcortical nuclei (striatum, thalamus). The spatial distributions of these connections are shown in Figure 8 (right). From Figure 9 (bottom), three edges in the frontal, parietal, and insular lobe increased significantly, and the other edges reduced significantly in AD compared with MCI.

4 Discussion

We used a 3D PCASL technique to investigate the altered topological properties of CBF correlation networks in subjects identified as having CN, MCI, and AD. In earlier studies, correlation networks have been detected with different techniques for MCI or AD, including functional networks with SPECT data, fluorodeoxyglucose positron emission tomography (FDG-PET) data, blood oxygen level-dependent (BOLD) MRI, and cortical networks with T1-weighted MRI (Yao et al., 2010; Seo et al., 2013;

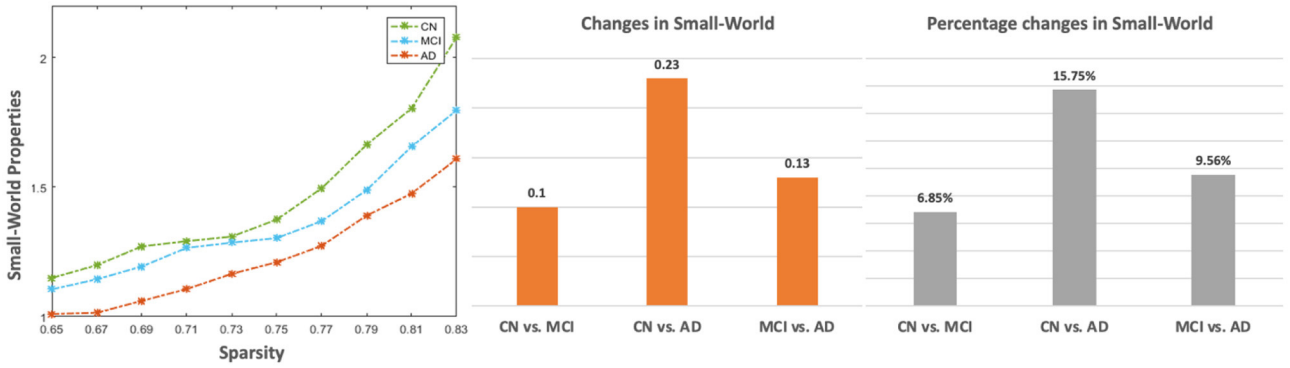

FIGURE 5
The small-world properties of the CBF correlation network in CN, MCI, and AD groups. The left sub-figure is the small-world values across the sparsity from 0.65 to 0.83. The two sub-figures on the right are absolute and percentage changes in mean small-world by averaging across all sparsity levels among CN, MCI, and AD, respectively.

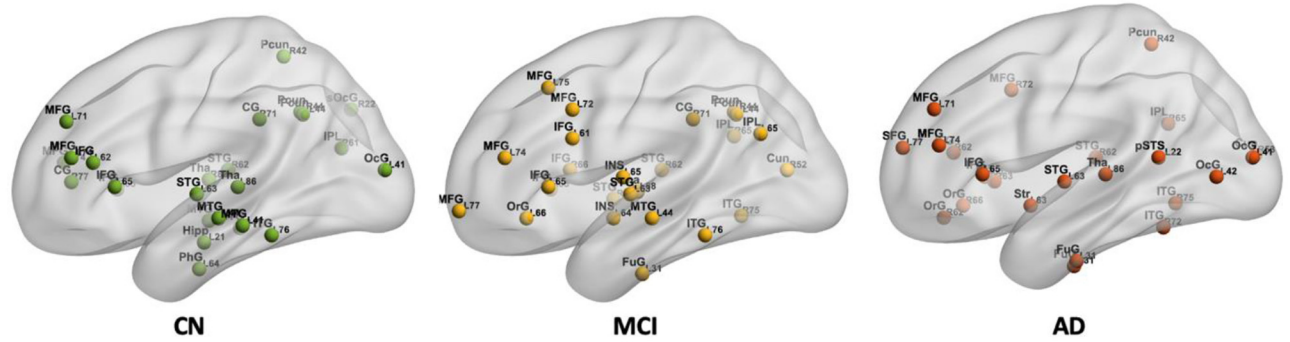

FIGURE 6
The spatial locations of hub regions in CN, MCI, and AD.

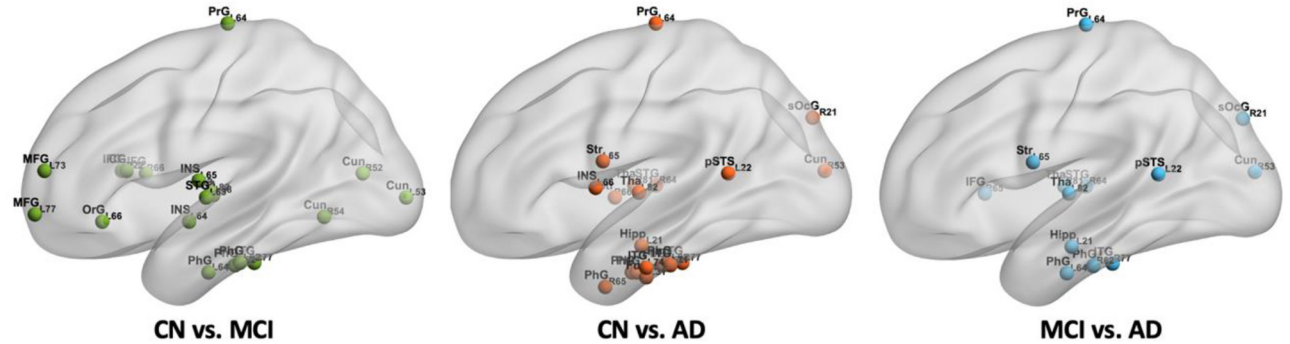

FIGURE 7
The spatial locations of regions with significant differences in nodal BC value in CBF correlation networks among CN, MCI, and AD groups.

Dai and He, 2014; Sanchez-Catasus et al., 2018). However, CBF correlation networks were only analyzed in MCI with SPECT (Sanchez-Catasus et al., 2018), where the global efficiency of MCI was found to be reduced compared to the control group. Although FDG-PET, SPECT, and ASL are widely applied to measure cerebral metabolism, ASL has the advantages of rapid imaging, non-invasive, and low costs compared with the others. BOLD and ASL are both commonly used to estimate functional networks calculated by interregional correlation coefficients. Using BOLD, time series were used to examine the connectivity at the individual level, which can reflect temporal synchronization of the inter-regional neural activity (Biswal et al., 1995), while the interregional CBF-related networks are obtained at the group level and cannot be compared between individuals. Moreover, CBF connectivity

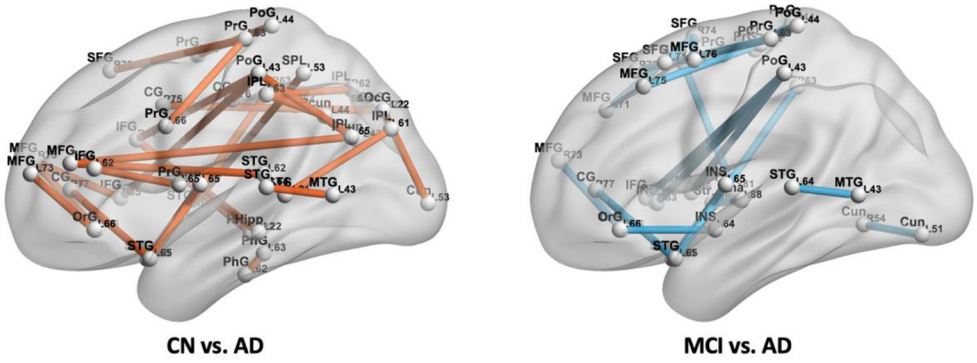

FIGURE 8
Connections with significant difference ($P < 0.001$) between CN and AD, MCI and AD.

as a single physiological parameter might be more relevant for characterizing cerebral metabolism, whereas BOLD connectivity is influenced by several parameters including CBF, cerebral blood volume, cerebral metabolic rate of oxygen, and oxygen metabolism (Buxton et al., 2004).

There are five main findings revealed in this study: (1). The CBF correlation networks of CN, MCI, and AD showed small-world properties. (2). Compared with CN, global efficiency showed a significant decrease in AD. (3). A loss of hub regions in the middle temporal lobe was found in MCI and AD. (4). Significant differences in the nodal properties of BC are observed in both MCI and AD in the middle temporal lobe; in addition, in the frontal lobe, BC was found to be reduced in MCI while it increased in the occipital lobe in AD. Both regional CBF values and BC decreased in the entorhinal cortex and hippocampus in AD. (5). Connections in AD showed significant differences compared to those in CN and MCI. The findings mentioned above are discussed in the following subsections.

4.1 Global properties of CBF correlation networks

Compared with matched random networks, small-world networks have higher local clustering and similar path lengths, thus improving the communication efficiency of the brain (Bullmore and Sporns, 2009). In this study, the CN, MCI, and AD groups all exhibited small-world properties, which are consistent with other studies including FDG-PET-based functional and cortical networks in MCI and AD (Supekar et al., 2008; Yao et al., 2010; Seo et al., 2013; Xu et al., 2020), indicating that the 3D PCASL-based CBF correlation networks of CN, MCI, and AD present an optimal balance between local specialization and global integration processes.

In comparison with CN and MCI, the global efficiency was reduced in AD, which is consistent with a prior study (Liu et al., 2014), where the lower global efficiency of BOLD functional MRI networks in AD was reported. While in other studies, significantly reduced global efficiency or the clustering coefficient of networks were found (Berlot et al., 2016; Sanchez-Catasus et al., 2018; Zhou, 2020), in this study, MCI shows no apparent differences in properties of global efficiency, clustering coefficient, and characteristic path length over the entire range of sparsity thresholds. The intermediate state of MCI of the small-world in CBF correlation networks between CN and AD is consistent with prior studies (Liu et al., 2012; Dai and He, 2014).

4.2 Hub regions in CBF correlation networks

The hub regions identified in our study are largely consistent with previous reports. For instance, in CN, hub regions in the middle temporal gyrus, inferior frontal gyrus, and orbital gyrus occurred in a previous study in which cortical networks were characterized by gray matter volumes (Yao et al., 2010). Hub regions in the precuneus, medial frontal gyrus, inferior parietal cortex, and thalamus in current findings are consistent with the results in a study where nodal strength was used to identify hubs in functional networks (Dai et al., 2015). For the altered hub regions in brain connectivity in MCI and AD, some of our results are consistent with previous studies. Hub regions in the right precuneus were defined in all three groups, with left parahippocampal gyrus (e.g., entorhinal cortex) only appearing in the CN but missing in MCI and AD (Seo et al., 2013; Khazaee et al., 2017). In agreement with earlier studies (Seo et al., 2013; Grajski et al., 2019; Hrybouski et al., 2023), hub regions were found in the left precuneus and PCC only in CN and MCI, while in MCI and AD, hub regions occurred in the right angular gyrus (right inferior parietal lobe). Moreover, hub regions in the middle temporal gyrus in CN disappearing in MCI an AD was also proved. Of note, the loss of hubs in the hippocampus and entorhinal cortex in MCI and AD are subregions of the core memory-associated middle temporal lobe, which might be related to the dysfunction of the memory (Fjell et al., 2015; Hrybouski et al., 2023).

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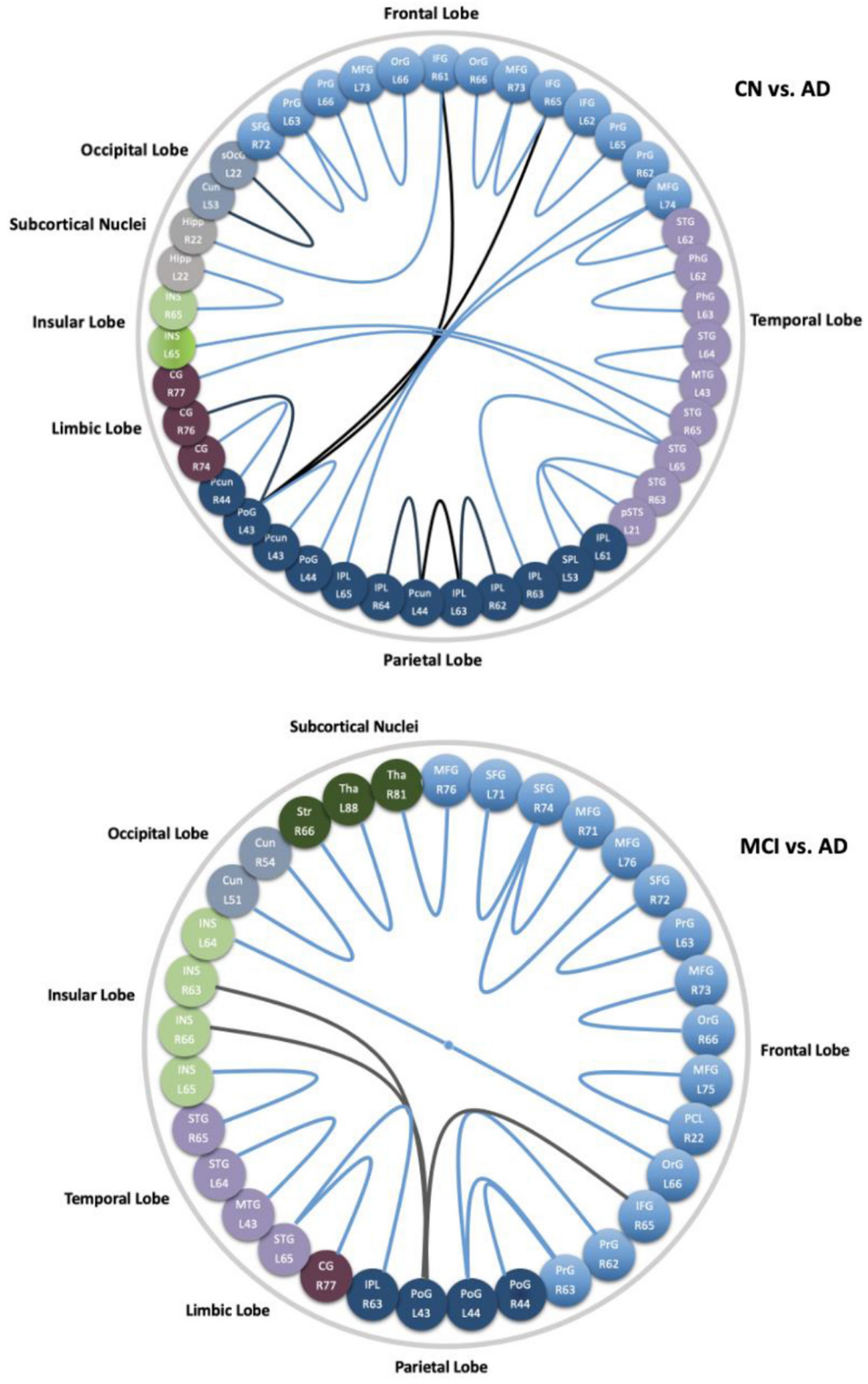

FIGURE 9
Subregions and lobes to which the corresponding connections with significant differences of CN vs. AD (**top**), and MCI vs. AD (**bottom**). Connections in blue decrease significantly in AD, while the black ones are increased edges in AD.

4.3 Altered CBF values and nodal properties in CBF correlation networks

Brain regions with abnormal nodal properties (in terms of BC) and regional CBF values in AD are mainly distributed in the parahippocampal gyrus (e.g., entorhinal cortex), temporal gyrus, and hippocampus. The regions with significant differences in the entorhinal cortex and hippocampus are also identified as the loss hub regions, which is consistent with prior research and related to the impairment of memory (Seo et al., 2013; Hrybouski et al., 2023). Compared with CN, altered BC was found in the inferior frontal gyrus in MCI, which was revealed in a prior study (Seo et al., 2013). The superior temporal gyrus was found to decrease significantly in BC in MCI and AD, which was also marked in a previous study (He et al., 2008; Zhang et al., 2021), which involved auditory (e.g., language) processing and social cognition (Bigler et al., 2007). Additionally, significant BC increased in the occipital gyrus (e.g., cuneus). The increased hub region in AD, is consistent with a study in which structural connectivity was applied to understanding the association between disrupted integrity of the network and the underlying cognition (He et al., 2008), and which may serve as a compensatory system.

A previous study proved that regional CBF values decreased in patients with AD, and they were mainly distributed in the entorhinal cortex and hippocampus. The regional CBF values in the parietal cortex and precuneus were reduced in MCI when compared with CN, and our findings are consistent with these results (Binnewijzend et al., 2013; Mattsson et al., 2014). Moreover, a higher amyloid-β load was considered to have associations with those lower regional CBF values mentioned above (Maier et al., 2014; Mattsson et al., 2014). Although we did not estimate the association between the amyloid-β load and network-based changes of CBF, the abnormality of hub regions and connections in the entorhinal cortex and hippocampus in AD in this study may be related to the high load of amyloid-β.

4.4 Altered connections in CBF correlation networks

In Figure 9, details of the changes with significant differences ($P<0.001$) of groups with CN-AD and MCI-AD are shown. Compared with CN, the decreased correlations in AD are mainly distributed in the frontal lobe, temporal lobe (e.g., middle temporal gyrus and parahippocampus), parietal lobe (e.g., precuneus and cingulate gyrus), and subcortical nuclei (e.g., hippocampus). The disrupted hub regions with apparently reduced BC are also linked by significantly decreased edges. They occurred in parahippocampus, precuneus, and hippocampus. Most of the altered connections in the hippocampus, middle temporal gyrus, cingulate gyrus, and precuneus in current CBF correlation networks are consistent with changes in the functional networks of AD in earlier studies (Wang et al., 2006; Zhou et al., 2008; Seo et al., 2013). Specifically, the alteration of the hippocampal–cortical (e.g., hippocampal-inferior frontal gyrus) connectivity is consistent with previous studies (Wang et al., 2006; Allen et al., 2007) and may link the decline of memory and cognitive function in AD since the hippocampal-cortical memory system contains interacting brain regions that are activated during episodic memory retrieval (Vincent et al., 2006; Buckner et al., 2008). In addition, the connection of the hippocampus to the right insular reduced in AD is in agreement with a prrevious study (Wang et al., 2011) and the changes in connections may underlie memory impairment. In earlier studies, the inferior parietal gyrus and/or precuneus were proved to have an association with mental orientation in CN and aMCI (Peer et al., 2015; Oishi et al., 2018). Our findings in this study showed the connection of the precuneus to the inferior parietal lobe decreased significantly, which may be the underlying reason for cognitive dysfunction of disorientation.

Moreover, the disruption of hub regions with altered connections occurred in the middle temporal gyrus, middle frontal gyrus, and cingulate gyrus. Of note, connectivity between precuneus and PCC decreased significantly in AD, which is consistent with prior studies (Rami et al., 2012; Yokoi et al., 2018). The functional connectivity with significantly decreased precuneus/PCC was assumed to have an association with cognitive function and plays a key role in developing AD (Yokoi et al., 2018).

4.5 Limitations

This study has several limitations. First, the modest sample size of 3D PCASL data from the ADNI database may limit its statistical power. Second, the results of the CBF map calculations were affected by the parameters selected. Third, in this study, we only studied the group-level correlation networks due to the limitations of time series with current GE ASL data, and the individual-level networks were not analyzed. Finally, we found significant differences in cognitive scores (MMSE, MoCA, and ADAS13) among the three groups, while no correlation analysis of cognitive scores and network parameters of CN, MCI, and AD was performed in this study.

5 Conclusion

In this study, we estimated the abnormality of the topological organization of 3D PCASL-based CBF correlation networks in subjects with MCI and AD. The CBF correlation networks of CN, MCI, and AD all showed small-world properties. Compared with CN, global efficiency decreased significantly in AD. Significant differences in nodal properties and a loss of hub regions were observed in the middle temporal lobe in both MCI and AD. In the frontal lobe, BC was reduced in MCI while it increased in the occipital lobe in AD. The identified altered hub regions with significant differences in MCI and AD were mainly distributed in the hippocampus and entorhinal cortex. In addition, disrupted hub regions in AD with significantly decreased connections were mainly found in the precuneus/PCC and hippocampus-cortical cortex. The observed disruptions in the topological organization of 3D PCASL-based CBF correlation networks may underlie the cognitive decline and provide new insight into understanding the mechanism of MCI and AD.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: Alzheimer's Disease Neuroimaging Initiative (ADNI) database (www.adni-info.org).

Ethics statement

The studies involving humans were approved by according to Good Clinical Practice guidelines, US 21Code of Federal Regulations Part 50– Protection of Human Subjects, and Part 56 –Institutional Review Boards/Research Ethics Boards, and under state and federal HIPAA regulations. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

ML: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Writing – original draft. TZ: Investigation, Writing – review & editing. YK: Conceptualization, Supervision, Writing – review & editing. SQ: Conceptualization, Funding acquisition, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2024.1345251/full#supplementary-material

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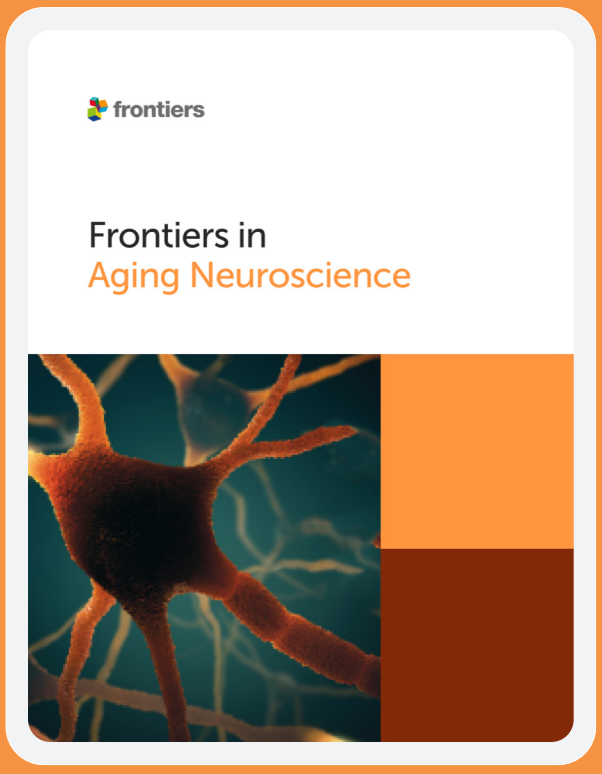

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