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Recent advances in research on cognitive frailty and related conditions

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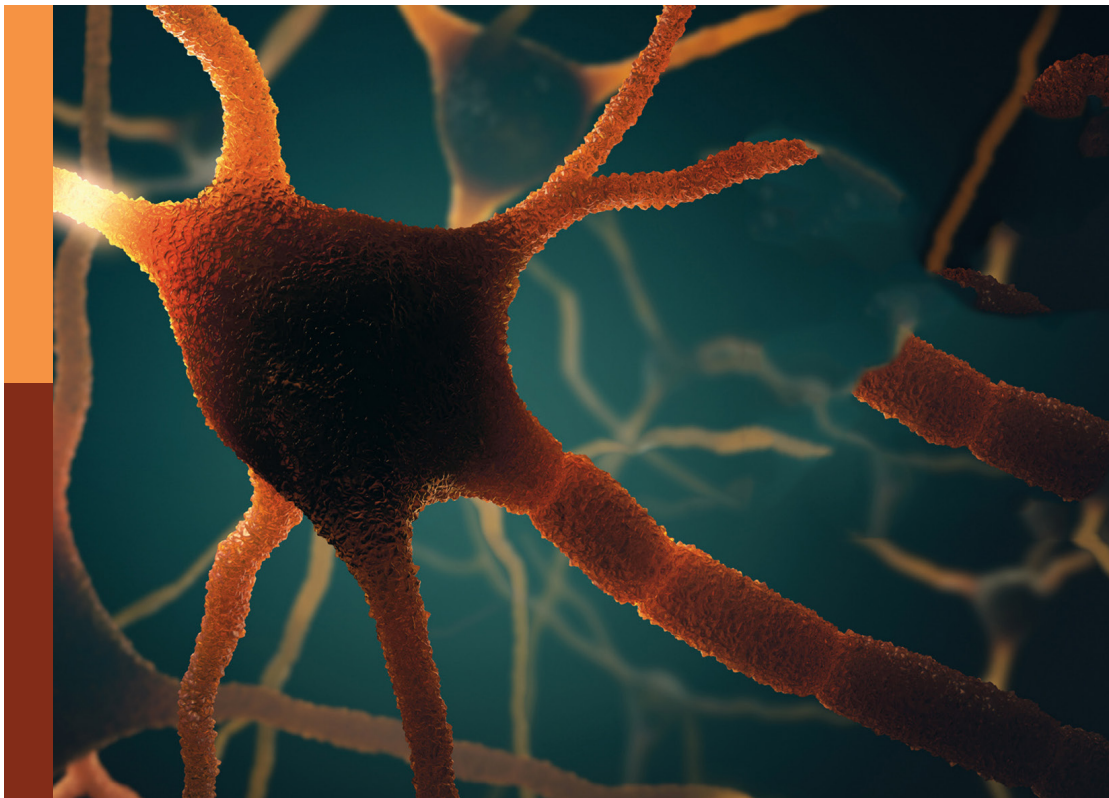

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Recent advances in research on cognitive frailty and related conditions

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Editorial: Recent advances in research on cognitive frailty and related conditions

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Editorial on the Research Topic
Recent advances in research on cognitive frailty and related conditions

1 Introduction

Cognitive frailty (CF) is an age-related condition that combines physical frailty and cognitive impairment without dementia (Kelaiditi et al., 2013). Conversely, physical frailty includes unintentional weight loss, exhaustion, weakness, slow walking speed, and low physical activity (Fried et al., 2001). This dual vulnerability significantly increases the risk of dementia, functional disability, reduced quality of life, hospitalization, and mortality (Chen et al., 2022).

Frailty encompasses other phenotypes, such as social and oral frailty. Social frailty refers to declining social resources critical for basic human needs (Bunt et al., 2017), whereas oral frailty involves the deterioration of oral functions among older adults (Tanaka et al., 2018). Moreover, both increase the risk of dementia (Choi and Ko, 2024; Nagatani et al., 2023).

Other dementia-related high-risk states include subjective cognitive decline (SCD), mild cognitive impairment (MCI), motoric cognitive risk syndrome (MCR), and sarcopenia (Yamasaki and Ikeda, 2024). SCD is characterized as a self-perceived cognitive decline without objective deficits (Jessen et al., 2020), whereas MCI involves measurable deficits but intact daily functioning (Alzheimer's Association., 2024). Both progress along the Alzheimer's disease continuum (Yamasaki and Ikeda, 2024).

MCR is another pre-dementia condition characterized by subjective cognitive complaints and slow gait (Verghese et al., 2014). Sarcopenia, which is defined as age-related skeletal muscle loss and diminished function, is recognized as a risk factor for both cognitive decline and dementia (Cruz-Jentoft et al., 2019; Amini et al., 2024).

Since these conditions are partially reversible, early risk identification and interventions could delay adverse outcomes. Therefore, the aim of this Research Topic is to collect research on advances in understanding high-risk dementia states, focusing on risk factors, innovative interventions, and biomarkers.

2 New insights into risk factors for cognitive decline and its prevention

Dementia risk is significantly influenced by 14 modifiable factors, including low education, traumatic brain injury, physical inactivity, smoking, excessive alcohol consumption, hypertension, obesity, diabetes, hearing loss, depression, social isolation, air pollution, poor vision, and high low-density lipoprotein cholesterol. Addressing these factors could prevent up to 45% of dementia cases globally (Livingston et al., 2024). This Research Topic encompasses five studies evaluating the risk factors contributing to high-risk states of dementia, focusing on 14 identified factors as well as additional potential risks.

By leveraging group-based dual trajectory modeling, Ji et al. identified a subgroup of older adults characterized by poor cognitive function and higher levels of frailty. This group was significantly associated with several factors, including being female, older age, low levels of education, residing in rural areas, being unmarried, and having comorbidities such as hypertension, diabetes, complete tooth loss, vision impairment, and hearing impairment.

Dong Q. et al. conducted a latent profile analysis to categorize community-dwelling older adults based on cognitive function, physical frailty, and social frailty, revealing two distinct subgroups: one characterized by high cognitive function and low frailty, while the other by low cognitive function and high frailty. Individuals in the latter group were predominantly aged 80 years, had lower income levels, faced multiple chronic conditions, and exhibited moderate to poor health status.

Qin et al. suggested that age, lower educational attainment, malnutrition, and depression are significant risk factors for CF. Moreover, their findings emphasized a significant correlation between mitochondrial dysfunction and CF, suggesting that mitochondrial dysfunction in the peripheral blood could serve as a potential phenotype of CF.

Dong X. et al. also investigated the relationship between sarcopenia and cognitive function, with a particular focus on the cognitive subdomains impacted by sarcopenia. Their findings revealed a clear correlation, as individuals with sarcopenia exhibited diminished performance in overall cognitive function as well as specific subdomains. Of note, cognitive abilities such as fluency declined progressively with the increasing severity of sarcopenia.

In a community-based prospective cohort study, Li S. et al. revealed a compelling connection between baseline cognitive decline and all-cause mortality among individuals aged 60 years. Their findings emphasized that both mild and moderate-to-severe cognitive impairments, as well as rapid cognitive decline, significantly increased the risk of mortality from all causes.

By synthesizing the findings of these five studies, two key strategies have been established. First, preventing high-risk states for dementia requires regular health monitoring and timely intervention to address modifiable risk factors. Second, the early detection of cognitive decline through consistent cognitive assessments is essential. Moreover, targeted interventions can then be used to delay cognitive impairment progression and mitigate the associated mortality risks.

3 Innovative approaches for preventing cognitive decline

Preventive strategies for cognitive impairment include both pharmacological and non-pharmacological therapies. Non-pharmacological approaches include cognitive training, physical exercise, dietary interventions, art-based therapy, reminiscence therapy, and aromatherapy (Maneemai et al., 2024). This Research Topic also emphasized three promising preventive interventions.

For research on pharmacological therapy, Wang and Li investigated a cohort of community-dwelling individuals with dyslipidemia and found that sustained statin use was associated with better cognitive outcomes compared with non-use. The benefits were particularly pronounced in individuals aged 65 years, suggesting that statins could play a protective role in preserving cognitive function in the elderly.

Jhan et al. investigated the effects of light-intensity physical activity on cognitive function among community-dwelling older adults as part of their research on non-pharmacological therapy. Their findings suggested that engaging in at least 3 h of light-intensity physical activity per day plays a crucial role in preserving and enhancing orientation-related cognitive function over the long term.

Meanwhile, repetitive transcranial magnetic stimulation (rTMS), a non-invasive and widely regarded safe treatment, is gaining traction for its applications in neurological and psychiatric conditions. Li H. et al. have shown that rTMS not only improved cognitive performance but also increased the T3 hormone levels among elderly post-stroke patients with low thyroid hormone levels. Furthermore, their findings revealed a positive correlation between increased T3 levels and improved cognitive function, suggesting that rTMS may serve as an effective rehabilitative intervention for post-stroke cognitive impairment.

These studies emphasize the potential of both pharmacological and advanced non-pharmacological therapies in addressing cognitive decline, paving the way for more comprehensive and targeted preventive strategies.

4 Biomarkers of dementia risk states: advances in detection and risk assessment

The biomarkers for dementia risk states span a wide array of categories, including behavioral, neurophysiological, neuroimaging, biological, and statistical approaches (Shah et al., 2023; Yamasaki and Ikeda, 2024). Seven studies also provided insights into the early detection and risk assessment of high-risk conditions associated with dementia.

Gao et al. investigated the risk factors for CF among older adults in nursing homes, applying both logistic regression and decision tree modeling to assess their predictive performance. Their findings revealed that while both methods delivered comparable accuracy, each offered unique strengths. By integrating these approaches, predictive precision can be further improved, providing valuable insights to inform clinical practice and guide policy development.

Bai et al. have suggested that integrating handgrip strength into the concept of MCR was shown to improve the predictions of dementia and all-cause mortality. The authors concluded that a modified MCR, incorporating handgrip strength, holds significant potential as an effective screening tool for detecting individuals at risk of dementia and mortality in national health examinations.

Yuan et al. further advanced predictive tools by identifying education, physical exercise, hyperlipidemia, osteoarthritis, depression, and Timed Up and Go test time as independent risk factors for MCR syndrome. They developed a nomogram model that demonstrated high accuracy, making it a valuable resource for early detection.

Ye et al. revealed a strong association between oral health-related quality of life and MCI in older adults, emphasizing its potential role in cognitive decline. The Geriatric Oral Health Assessment Index provides a practical tool for evaluating oral health in older adults, enabling the timely detection of poor oral conditions to help mitigate cognitive decline.

Tanaka et al. conducted a comprehensive review of studies on electroencephalography (EEG) markers for the early detection of dementia-related precursors, such as SCD and CF. The review emphasized advanced EEG techniques, including event-related potentials, quantitative EEG, microstate analysis, functional connectivity approaches, and the integration of artificial intelligence. Their findings suggested the potential of EEG as a non-invasive, cost-effective tool to identify individuals at risk, paving the way for timely interventions and personalized therapeutic strategies.

Frailty and increased serum neurofilament light chain (sNfL) levels are both closely associated with cognitive impairment. Yang et al. found a significant association between frailty and increased sNfL levels in a representative US population, with the estimated glomerular filtration rate partially mediating this relationship. These findings indicate that sNfL is a promising biomarker for frailty-related neuronal damage and emphasize the critical role of kidney function in this interplay.

Non-alcoholic fatty liver disease (NAFLD) has been associated with a heightened risk of dementia and cognitive decline. Wu et al. revealed a positive correlation between higher serum klotho levels and better cognitive performance in patients with NAFLD, suggesting that routine klotho testing can be used as a valuable tool for the early detection of cognitive decline in this population.

These studies collectively emphasize the importance of integrating diverse biomarkers and risk factors into innovative predictive frameworks, providing new opportunities for early detection and intervention in high-risk dementia states.

5 Unveiling research trends through bibliometric analysis

Bibliometric analysis is a systematic approach to studying scientific literature, along with identifying patterns, trends, and impacts within a field by applying quantitative methods to data collected and refined from relevant databases (Passas, 2024). This Research Topic encompasses two key bibliometric studies, each offering significant contributions to their respective fields.

Xiao et al. performed a bibliometric analysis to determine the key factors linking health behaviors to MCI. Their study emphasized five major research hotspots: exercise, diet, risk factors and preventive measures for dementia, cognitive decline-related biomarkers, and clinical trials.

Moreover, Wang et al. conducted a bibliometric analysis to investigate the research trends and key topics on social frailty among older adults. The key research hotspots in this field include social vulnerability, health, frailty, mortality, and older adults, while emerging trends emphasize dementia, Alzheimer's disease, population, and COVID-19 in the context of social frailty among older adults.

These findings provide valuable perspectives for researchers, aiding in the identification of critical contributions and shaping future investigations in this domain.

6 Conclusion

This Research Topic brings together pivotal studies on the risk factors for dementia-related high-risk conditions, innovative prevention and treatment strategies, emerging biomarkers, and bibliometric analyses. Collectively, these findings emphasize the critical importance of multidisciplinary approaches for early intervention and comprehensive management to mitigate cognitive decline. We believe the findings of these studies serve as a valuable resource, guiding clinicians in their practice and inspiring researchers in their pursuit of future advancements.

Author contributions

TY: Writing – original draft, Writing – review & editing. MT: Writing – review & editing. SK: 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 bibliometric analysis on the health behaviors related to mild cognitive impairment

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Background: Mild cognitive impairment (MCI) is commonly defined as a transitional subclinical state between normal aging and dementia. A growing body of research indicates that health behaviors may play a protective role against cognitive decline and could potentially slow down the progression from MCI to dementia. The aim of this study is to conduct a bibliometric analysis of literature focusing on health behaviors and MCI to summarize the factors and evidence regarding the influence of health behaviors on MCI.

Methods: The study performed a bibliometric analysis by retrieving publications from the Science Citation Index and Social Sciences Citation Index sub-databases within the Web of Science Core Collection. Utilizing VOSviewer and CiteSpace software, a total of 2,843 eligible articles underwent co-citation, co-keywords, and clustering analyses. This methodology aimed to investigate the current status, trends, major research questions, and potential future directions within the research domain.

Results: The bibliometric analysis indicates that research on healthy behaviors in individuals with MCI originated in 2002 and experienced rapid growth in 2014, reflecting the increasing global interest in this area. The United States emerged as the primary contributor, accounting for more than one-third of the total scientific output with 982 articles. Journals that published the most articles on MCI-related health behaviors included "Journal of Alzheimer's Disease," "Neurobiology of Aging," "Frontiers in Aging Neuroscience," and other geriatrics-related journals. High-impact papers identified by VOSviewer predominantly cover concepts related to MCI, such as diagnostic criteria, assessment, and multifactorial interventions. Co-occurrence keyword analysis highlights five research hotspots in health behavior associated with MCI: exercise, diet, risk factors and preventive measures for dementia, cognitive decline-related biomarkers, and clinical trials.

Conclusion: This study provides a comprehensive review of literature on health behavior in individuals with MCI, emphasizing influential documents and journals. It outlines research trends and key focal points, offering valuable insights for researchers to comprehend significant contributions and steer future studies.

KEYWORDS

mild cognitive impairment, health behavior, exercise, bibliometric analysis, cognitive impairment

1 Introduction

With the increasing global trend of population aging, cognitive health issues have emerged as a significant social challenge. In 1997, American researcher Ronald C. Petersen first introduced the concept of mild cognitive impairment (MCI) in a paper titled "Mild Cognitive Impairment: Transition Between Aging and Alzheimer's Disease (AD)." MCI acts as a precursor stage of AD, characterized by mild memory decline or slight impairment of other cognitive functions while maintaining basic daily life functioning. Since then, MCI has become a widely studied field, with a growing body of related research (Petersen, 2000).

Mild cognitive impairment, as a precursor to cognitive diseases like Alzheimer's, not only negatively affects an individual's quality of life but can also progress to more severe cognitive disorders, placing a significant burden on patients and their families. Statistics indicate that the prevalence of MCI among the global population over 65 ranges from 3% to 42%, with an annual progression rate to AD of 8%–25%, which is 10 times higher than in the normal population (Anderson, 2015). Recent estimates from the HRS HCAP study suggest a 22% prevalence of MCI in individuals aged 65 and above (Manly et al., 2022). Extensive research shows that MCI can be effectively prevented and managed through active lifestyles and cognitive training (Qi et al., 2023; Xing et al., 2024). Scientific evidence demonstrates that adopting good living habits and proper nutrition can significantly slow the progression of MCI (Castro et al., 2023). Preventing MCI relies not only on scientific evidence but also on healthy choices and actions in daily life. A growing body of literature provides evidence that improvements in health behaviors can enhance cognitive function, with common healthy behaviors including physical activities, social interactions, quality sleep, and cognitive training (Livingston et al., 2017). In recent years, research on health behavior interventions for the MCI population has gradually become a prominent topic in the fields of health promotion and disease prevention (Farias et al., 2023).

Bibliometric analysis, a popular and rigorous method, has experienced significant growth in recent years in scientific research, providing a powerful tool for the in-depth exploration and analysis of large volumes of scientific data. Discussions on bibliometrics date back to the 1950s, and over time, this method has become increasingly crucial in interpreting and mapping accumulated scientific knowledge and subtle differences in mature fields (Ellegaard and Wallin, 2015). This study aims to utilize bibliometric analysis to investigate the potential impact of health behaviors on MCI prevention. Through a comprehensive bibliometric analysis, we will examine aspects such as the volume of literature, collaboration trends, research collaboration networks, keyword contribution analysis, and citation network analysis to gain a profound understanding of the relationship between health behaviors like exercise, diet, lifestyle habits, and cognitive function. By deeply comprehending the literature in the field of MCI prevention, this study seeks to provide a scientific basis for the development of more effective cognitive health intervention strategies in the future.

2 Research methodology

2.1 Data source and processing

To ensure the authority and comprehensiveness of the study data, the Web of Science Core Collection (WoSCC) was utilized as the data source, specifically drawing from the Science Citation Index Expanded (SCI-EXPANDED) and Social Sciences Citation Index (SSCI) databases. The rationale behind selecting WoSCC over Scopus was its inclusion of a wide range of influential and high-quality journals from around the globe (You et al., 2021).

When selecting the primary subject term, "mild cognitive impairment" was identified as a clear medical term, with "MCI" serving as its abbreviation. However, upon conducting literature retrieval and analysis, it was discovered that "MCI" had alternative meanings, such as "maximum cardiac index" and "millicurie." To prevent data interference, the search term for MCI was specified as "mild cognitive impairment." In terms of determining subject terms related to "health behavior," using solely "Health Behavior" produced limited search outcomes and failed to encompass all literature on the topic. After reviewing a substantial number of relevant articles (Lee et al., 2010), the subject terms for health behavior were eventually established to include "Health Behavior," "Lifestyle," "Physical Activity," "Exercise," and "Diet." The search query was configured as "TS = 'mild cognitive impairment' AND TS = ('Health Behavior' OR 'Lifestyle' OR 'Physical Activity' OR 'Exercise' OR 'Diet')." The publication type was restricted to "article" and "review article," with no constraints on publication date. The search was executed on 21 November 2023, resulting in the retrieval of a total of 2,843 pertinent articles as the data source for this study. Relevant articles were extracted and downloaded on the same day to prevent bias stemming from

frequent database updates. Basic information for each research piece was obtained as "full record and cited references" for further analysis.

2.2 Analytical methods and tools

The research methodology employed in this article utilized bibliometric strategies. Two Java-based visualization tools, namely VOSviewer and CiteSpace, were utilized to present the findings from the bibliometric analysis. VOSviewer, developed by the Quantitative Studies group at Leiden University in the Netherlands, is a tool designed for visualizing and analyzing scientific literature. It boasts advanced graphical representation capabilities and can generate knowledge maps depicting units and their relationships within research literature (van Eck and Waltman, 2010).

For the bibliometric analysis of the knowledge base and research trends on health behavior and MCI, this study employed VOSviewer for knowledge mapping analysis, utilizing VOSviewer version 1.6.19. Initially, all records and citation data from the retrieved 2,843 articles were imported into VOSviewer for co-citation analysis, co-word analysis, and cluster analysis. The co-occurrence function of VOSviewer was utilized to investigate keyword associations, with the counting method set to full counting and the unit of analysis focused on author keywords (AKs). Node size variations indicated the strength of the connection effect for each node, while association strength was used to normalize the links' strength between items (Chen et al., 2022).

The version of CiteSpace used was 6.1R1, which facilitated the creation of a dual-map overlay of journals within the research field. The research structure of this review is depicted in **Figure 1**.

3 Results

3.1 Status of literature publications

From **Figure 2**, it is evident that there were no publications before 2002. The first research focusing on the prevention and treatment of MCI through the lens of health behavior emerged in 2002. Subsequently, there was a gradual increase in publications

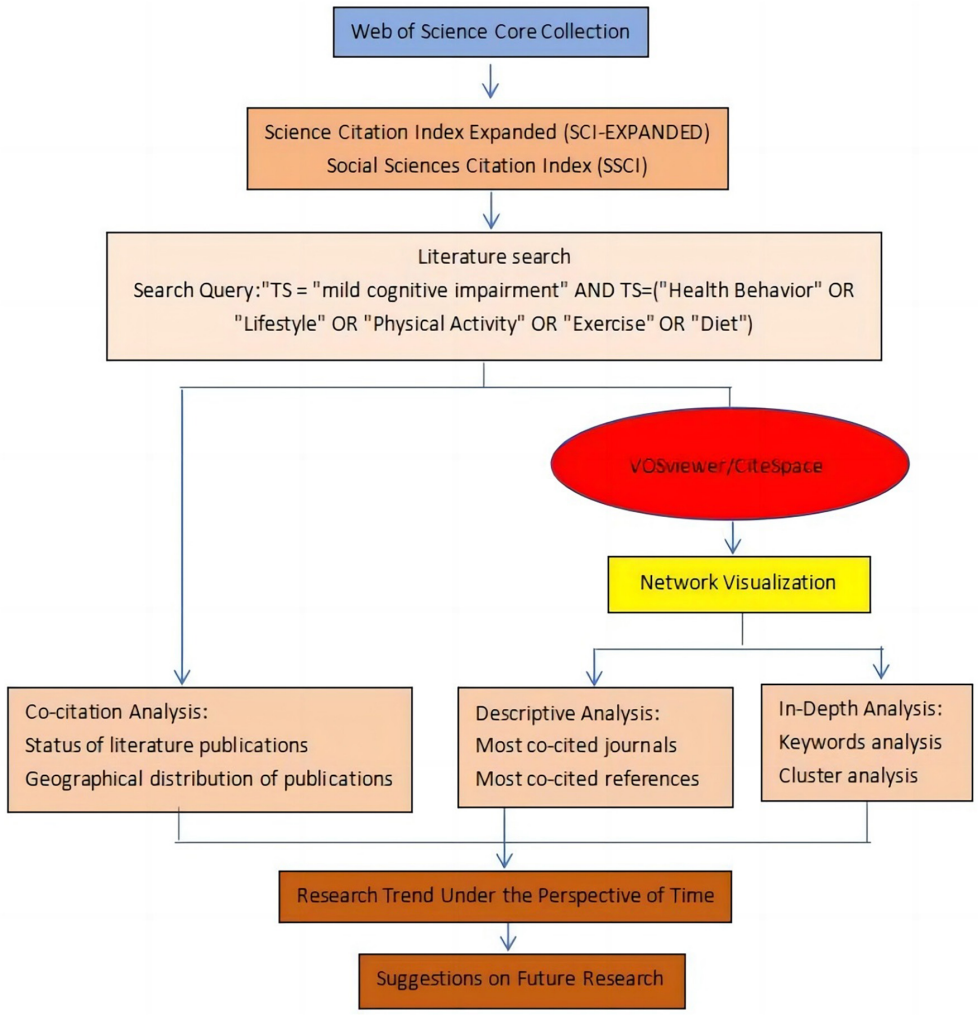

FIGURE 1
The structure of this review.

over the years, with a notable surge in 2014. The number of published articles reached 138 in 2014, peaked at 380 in 2021, and has consistently hovered around 300 in both 2022 and 2023. The majority of the research literature consists of articles, comprising 71%, while review articles account for 29%.

These findings suggest that as the global population ages and the prevalence of MCI rises, there is a growing emphasis on enhancing the cognitive wellbeing of older adults. The increasing number of studies in this area aims to develop more comprehensive and sustainable solutions for cognitive health issues in the elderly, ultimately contributing to improved societal health and wellbeing.

3.2 Geographical distribution of publications

According to Table 1, research on health behaviors associated with MCI is predominantly concentrated in the top 10 countries or regions, including the United States, China, Australia, England, Canada, among others. Over the past two decades, 84 countries or regions have been actively engaged in researching health behaviors linked to MCI. The United States leads with a total of 982 publications, representing 34.541% of the research output. Following closely is China with 431 articles, accounting for 15.16% of the total publications. Significant contributions have also been made by countries such as Australia, England, and Canada. The top 10 countries collectively contribute to 107.174% of the total publications, indicating a clear trend of concentration. (Due to collaborative research efforts, such as joint publications between the United States and China totaling 82 articles, there is an overlap in counting, resulting in a total percentage of 151.597%.)

Figure 3 visually illustrates the collaboration patterns among countries or regions in terms of research output through co-authorship analysis conducted using VOSviewer. Countries or regions with more than 10 publications were included, leading to 43 out of 84 entities meeting the criteria. The visualization highlights frequent collaborations between countries or regions, particularly between the United States and China, the United States and Australia, and the United Kingdom and Australia, among others.

As depicted in Figure 4, the annual distribution of research publications concerning MCI and health behavior in the top 10 countries or regions over the past two decades is presented. It is evident that the United States and Canada were among the earliest countries to explore the relationship between health behavior and MCI, with the United States maintaining a leading position in research in this field. China's research contributions have gained prominence since 2020, with a significant increase in research output observed over the past 3 years from China, Australia, and England.

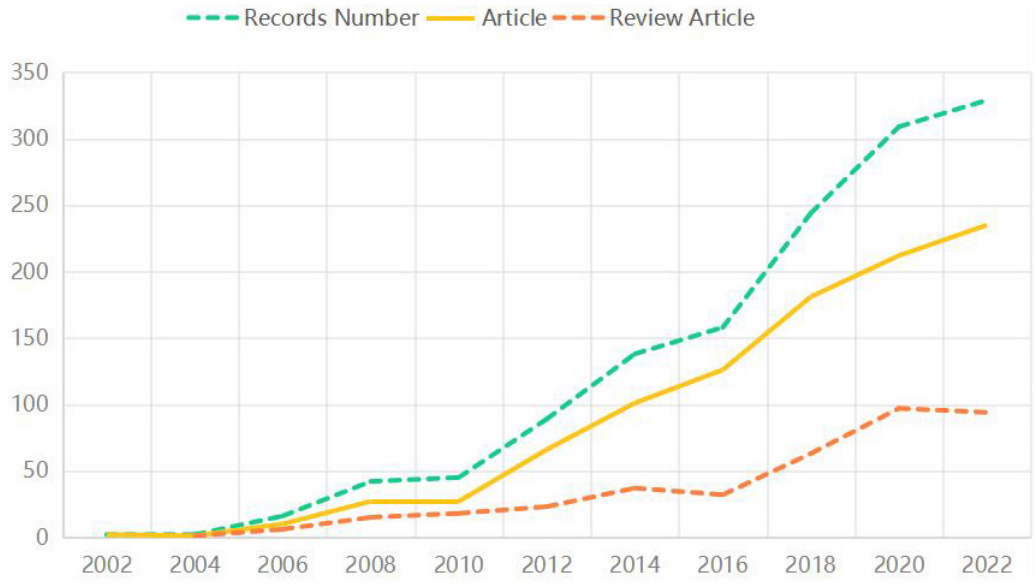

FIGURE 2
The status of literature publications (2000–2023).

TABLE 1 The geographical distribution (top 10).

Country/region	Count	Percentage	Country/region	Count	Percentage
United States	982	34.541	Italy	219	7.703
China	431	15.160	Japan	174	6.120
Australia	322	11.326	Germany	173	6.085
England	249	8.758	Spain	166	5.839
Canada	220	7.738	South Korea	111	3.904

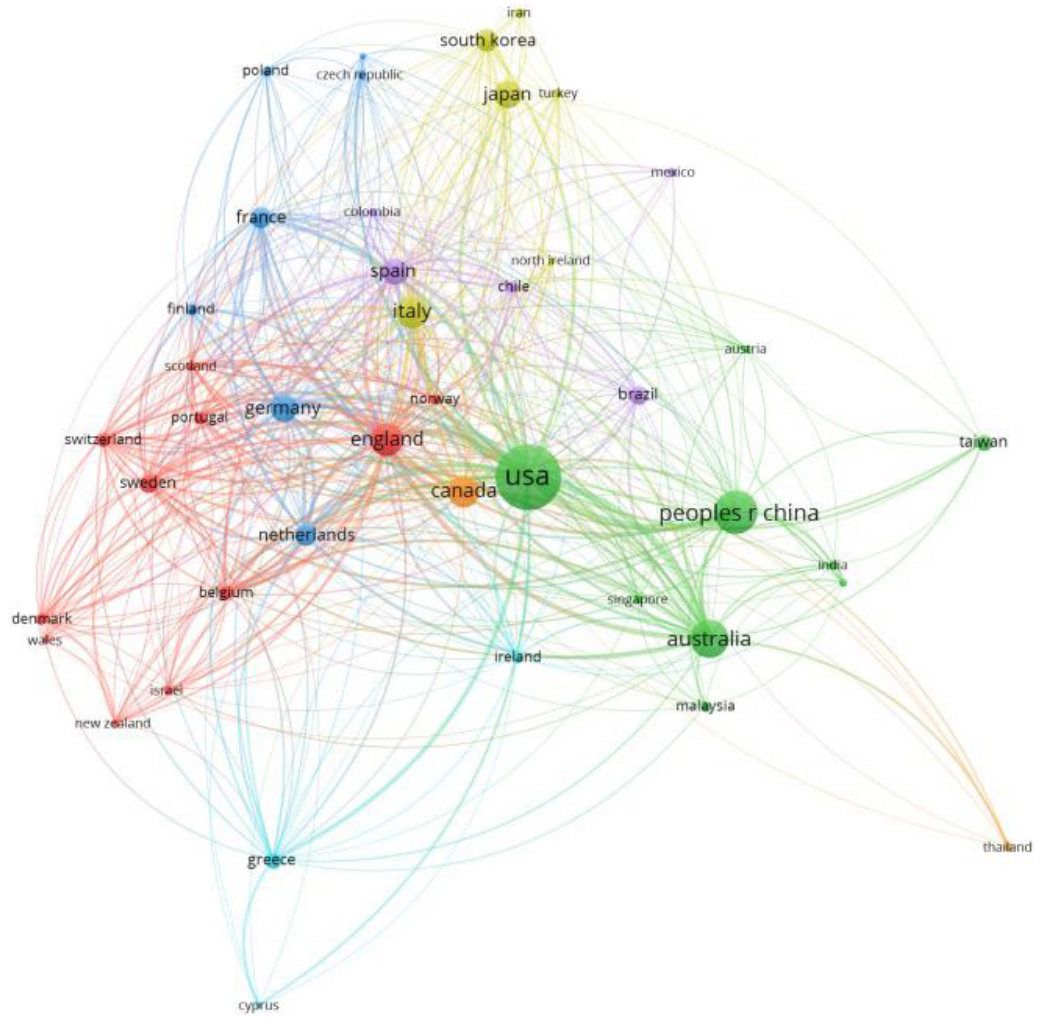

FIGURE 3
The mapping of countries' collaboration analysis (2000–2023).

3.3 Most co-cited journals

Figure 5A depicts a visualization of citation references generated by the VOSviewer tool using co-citation analysis. Nodes in the figure represent the sources of literature, while links indicate co-citation relationships between the literature pieces. Literature pieces sharing the same color indicate a close relationship between them. For this study, literature with citation frequencies exceeding 600 times was selected, resulting in a total of 71 literature pieces meeting this criterion, while the dataset consisted of 14,154 cited literature pieces.

Table 2 lists the top 10 cited journals during the study period, ranked by total link strength (TLS). Notably, "Neurology" emerges as highly influential, with both its local citation score (LCS) and TLS significantly surpassing other journals, underscoring its authority in the realm of health behavior and MCI research. Among the top 10 journals, 8 are based in the United States, indicating the concentration of MCI research within the country. The JCR categories of these top 10 cited journals suggest a diverse disciplinary coverage, encompassing Clinical Neurology, Neurosciences, and Geriatrics/Gerontology. These journals have played a pivotal role in advancing research on health behavior and MCI, offering varied perspectives on the subject.

Similar to Table 2 and Figure 5A also highlights the most influential research categories in the domain of health behavior and MCI. Notably, the green cluster dominated by Geriatrics-related journals such as "Journal of Alzheimer's Disease," "Neurobiology of Aging," and "Frontiers in Aging Neuroscience" is prominently featured. The red cluster comprises interdisciplinary journals like "Archives of Neurology," "JAMA – Journal of the American Medical Association," and "Lancet," while the blue cluster is predominantly composed of neurology journals such as "Neurology" and "Lancet Neurology." The co-citation relationships among journals in these clusters underscore the interdisciplinary and cross-integrative nature of research on MCI and health behavior.

Figure 5B showcases a dual-map overlay of journals that have published literature related to MCI and health behavior fields using CiteSpace. This visualization method employs two graphs simultaneously, with the left graph representing the categories of citing journals and the right graph indicating the disciplines of cited journals. Citation links reveal the flow of citations

10.3389/fnagi.2024.1402347

No.	Country/region	year																							Total
		2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	
1	USA	2	1	1	4	10	14	18	23	20	27	35	40	51	58	57	74	71	95	85	113	99	84		982
2	Peoples R China	0	0	0	0	0	0	1	2	2	3	2	8	10	11	24	12	32	38	57	64	97	67	1	431
3	Australia	0	0	0	0	2	2	1	5	6	5	16	22	22	24	18	24	24	29	28	46	28	20		322
4	England	0	0	0	1	0	0	1	3	3	2	5	7	11	13	13	16	26	35	40	39	18	16		249
5	Canada	1	0	0	1	1	2	8	2	1	3	7	10	14	9	13	15	23	21	32	22	22	13		220
6	Italy	0	1	1	2	2	2	5	2	9	3	4	3	5	12	17	17	31	24	31	24	16	8		219
7	Japan	0	0	0	0	2	3	1	0	1	1	9	8	4	7	10	10	13	19	22	25	27	12		174
8	Germany	0	0	1	1	1	1	1	1	4	2	6	7	7	12	8	16	11	19	17	24	20	14		173
9	Spain	0	0	0	0	0	0	1	0	0	1	3	5	8	6	6	10	20	17	27	26	25	11		166
10	South Korea	0	0	0	0	0	0	0	3	1	3	0	0	4	0	3	8	14	13	10	17	21	14		111

FIGURE 4
Top 10 country/region and their annual distribution of publications.

within datasets. By juxtaposing citing and cited journals, this map offers insights into the citation relationships between disciplines (You et al., 2021). Three main citation paths are discernible: the yellow path suggests that literature from "Molecular Biology, Immunology" journals tends to cite journals in the "Molecular Biology, Genetics" domain, the green path indicates that articles from "Medicine, Medical, Clinical" journals predominantly cite journals in the "Health, Nursing, Medicine" domain, and the blue path signifies that literature from "Psychology, Education, Health" journals leans toward citing journals in the "Psychology, Education, Social" domain.

3.4 Most co-cited references

Figure 6 displays the outcomes of co-citation analysis of cited references visualized using VOSviewer. Cited literature pieces with local citation scores (LCS) exceeding 100 were chosen, resulting in the identification of 37 cited references from a dataset of 123,962 cited literature pieces. In this visualization, nodes represent the cited references, while links signify the co-citation relationships between them. A consistent color scheme is utilized to denote the close relationships among the cited references.

Table 3 showcases the top 22 highly cited literature pieces identified based on LCS and TLS metrics using VOSviewer within the dataset. These literature pieces span from 1969 to 2020 and predominantly comprise "articles" and "reviews," sorted by TLS. Additionally, the table presents the Global Citation Score (GCS) calculated by Google Scholar and the LCS calculated by VOSviewer. The GCS reflects the total number of citations of the literature in Google Scholar, whereas the LCS measures the number of citations between literature pieces within the locally retrieved set, offering insights into peer attention within the specific field of research on MCI and health behavior.

Figure 6 and Table 3 delineate the highly cited papers identified based on the VOSviewer LCS metric, categorizing the knowledge base of research on MCI and health behavior into four primary clusters. These clusters encompass topics such as MCI, diagnostic criteria and assessment, the impact of multifactorial interventions on cognitive function in older adults (including physical exercise, diet, leisure activities, interventions targeting potential risk factors), and more.

The first cluster, focusing on the concept of MCI, diagnostic criteria, and cognitive assessment, is depicted by the red section in Figure 6 and encompasses articles 1, 2, 3, 6, 8, 11, 14, and 15 in Table 3. These articles address various facets of cognitive function, cognitive impairment, and neurodegenerative conditions like AD within the domain of neuroscience. Some literature delves into the concept and diagnostic criteria of early cognitive decline, particularly the discourse surrounding MCI, situated between normal aging and dementia. Conversely, certain studies aim to enhance existing assessment tools, such as the Mini-Mental State (MMS) examination, for a more convenient and effective evaluation of patients' cognitive status. For instance, Folstein et al. (1975) introduced a simplified cognitive assessment tool, the MMS, which can be administered in just 5–10 min, making it more suitable for elderly patients. Petersen et al. (1999) offer a clinical characterization of patients with MCI, highlighting that MCI patients demonstrate less impairment in cognitive domains other than memory compared to those with AD. McKhann et al. (1984, 2011), Albert et al. (2011), and Sperling et al. (2011), drawing on the most recent revisions of AD diagnostic criteria by the National Institute on Aging and Alzheimer's Association workgroup, categorize the diagnostic criteria into

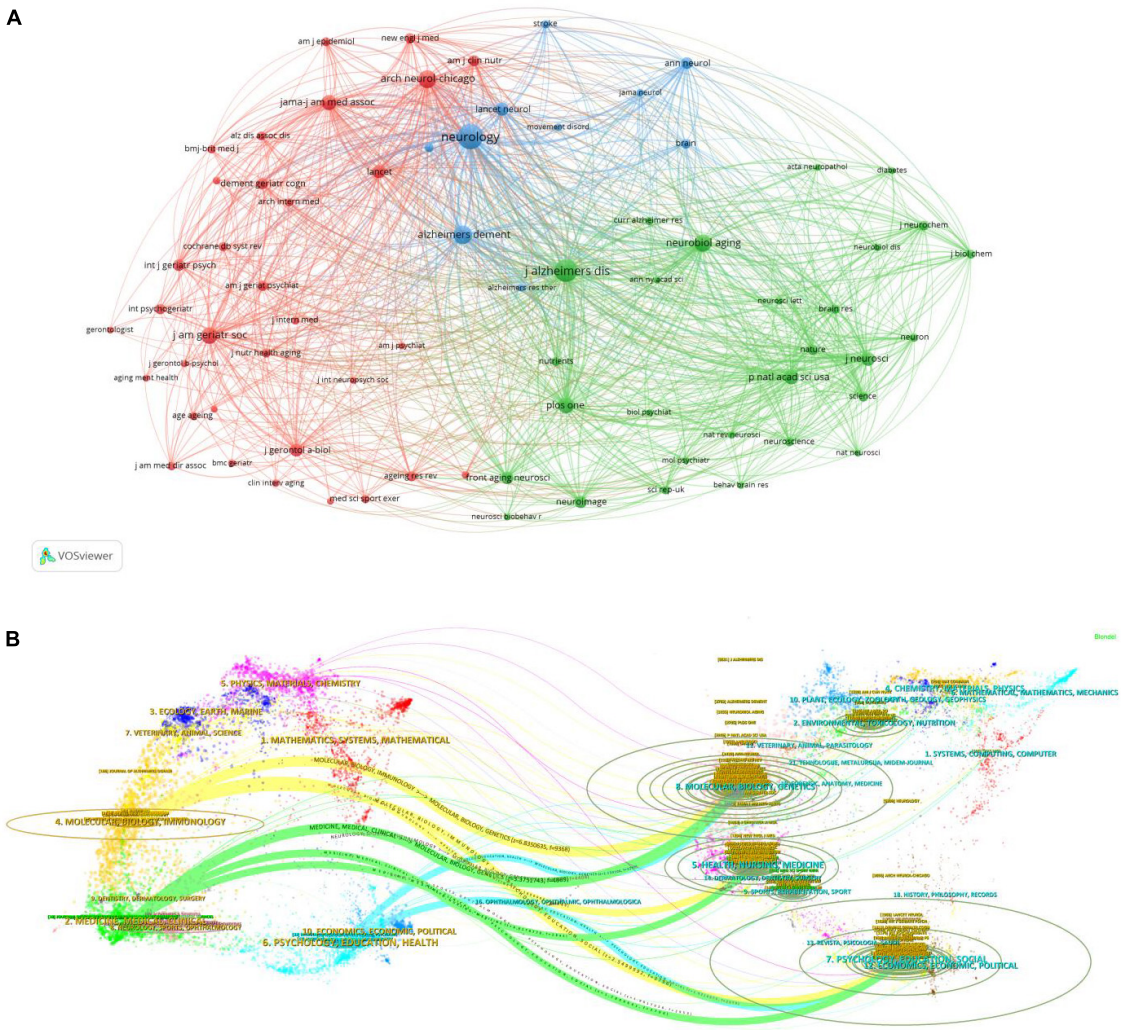

FIGURE 5
(A) The mapping of cited sources co-citation analysis. **(B)** A dual-map overlay of journals.

TABLE 2 **Highly total link strength cited journals (top 10).**

Journal	JCR category	Host country	LCS	TLS
Neurology	Clinical Neurology	United States	7,858	452,443
Journal of Alzheimer's Disease	Neurosciences	Netherlands	6,244	374,292
Neurobiology of Aging	Geriatrics/Gerontology	England	3,797	263,533
Archives of Neurology	Clinical Neurology	United States	4,074	228,398
Alzheimers & Dementia	Clinical Neurology	United States	4,240	226,375
Proceedings of the National Academy of Sciences of the United States of America	Multidisciplinary Sciences	United States	2,629	192,563
PLoS One	Multidisciplinary Sciences	United States	3,213	191,532
Journal of Neuroscience	Neurosciences	United States	2,293	181,407
JAMA – Journal of the American Medical Association	Medicine, General & Internal	United States	2,971	173,509
Journal of the American Geriatrics Society	Geriatrics & Gerontology	United States	3,517	166,125

core clinical and research criteria. They propose the concept of a "preclinical" stage that presents a crucial opportunity for therapeutic interventions for MCI. Additionally, Petersen (2004) and Winblad et al. (2004) discuss the concept and understanding of MCI, addressing controversies surrounding its implementation in diverse clinical settings.

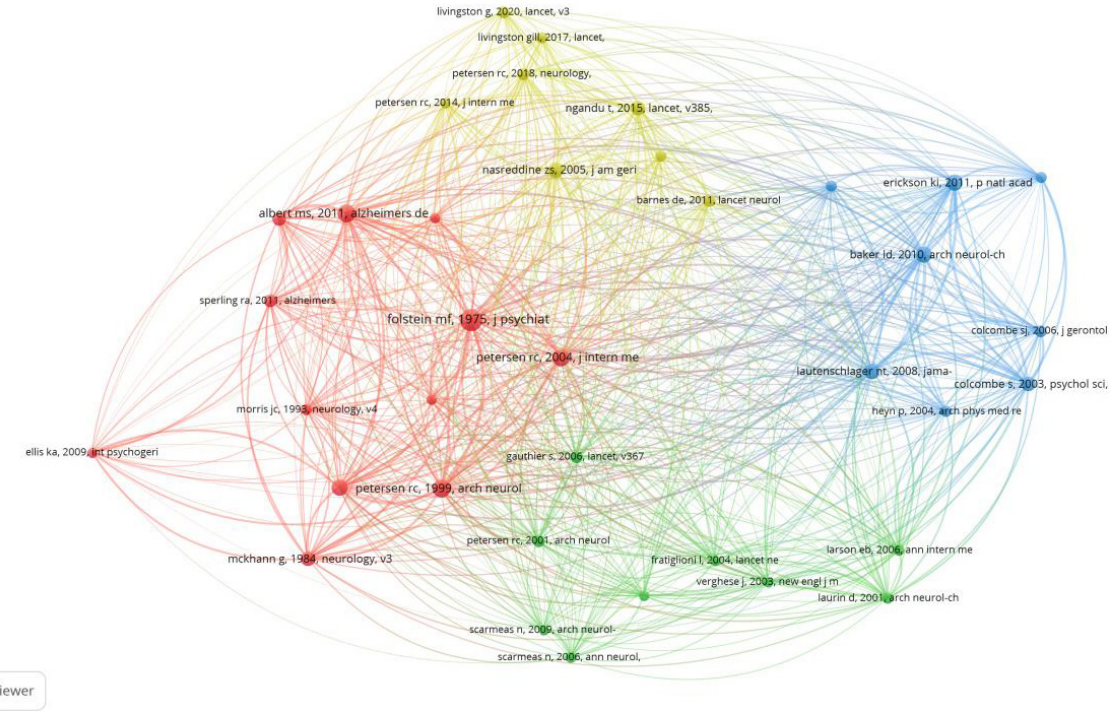

FIGURE 6
The mapping of cited references co-citation analysis.

The second cluster highlights the positive impact of physical exercise, specifically aerobic exercise, in safeguarding and enhancing cognitive function in elderly individuals with MCI. In **Figure 6**, this cluster is denoted in blue and comprises articles 4, 5, 7, 9, 12, 18, and 20 in **Table 3**. These studies all conducted pertinent randomized controlled trials, with findings indicating that aerobic exercise can reverse hippocampal volume loss in elderly individuals, enhance spatial memory, significantly increase gray matter volume, and improve executive control processes in older adults.

Lautenschlager et al. (2008) demonstrated, through a randomized controlled trial, that 6 months of physical exercise had a moderate positive impact on cognition in elderly individuals with MCI, with effects persisting for up to 18 months. Colcombe and Kramer (2003), Heyn et al. (2004), and Smith et al. (2010), utilizing randomized controlled trials and meta-analyses, discovered that aerobic exercise can enhance executive control processes in older adults, particularly attention and processing speed. Moreover, physical exercise has been shown to enhance physical fitness, bodily functions, cognitive function, and behavior in dementia patients. Aerobic exercise is also linked to improvements in executive function, attention, processing speed, and memory.

The third cluster, highlighted in green in **Figure 6**, delves into the role of diet, leisure activities, and other factors in preventing cognitive impairment and dementia. This cluster encompasses articles 16, 17, 19, 21, and 22 in **Table 3**. Collectively, these studies underscore the significance of early detection of cognitive impairment, the impact of lifestyle elements like exercise, diet, and leisure activities on cognitive wellbeing, and the necessity of global research endeavors to comprehend and prevent cognitive decline.

Scarmeas et al. (2009), in a prospective study involving 469 elderly individuals, discovered that engaging in leisure activities such as reading, playing board games, musical instruments, and dancing was linked to a reduced risk of dementia in older adults. Additionally, Scarmeas et al. (2006) explored the correlation between the Mediterranean diet (MeDi) and MCI and cognitive decline. The findings suggest that high adherence to the MeDi is associated with a decreased risk of MCI and the progression from MCI to AD.

The fourth cluster concentrates on the effects of multifactorial interventions on cognitive function in older adults, primarily targeting modifiable risk factors for cognitive decline and impairment, including monitoring vascular risks, diabetes, hypertension, obesity, depression, among others. Represented in yellow in **Figure 6**, this cluster includes articles 10 and 13 in **Table 3**. Ngandu et al. (2015), through the randomized controlled trial of the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), suggests that multifaceted interventions such as cognitive training and monitoring vascular risks could potentially enhance or sustain cognitive function in older adults at risk.

3.5 Emerging themes from the literature

In this study, we employed VOSviewer to perform a co-occurrence analysis of author keywords extracted from 2,843 articles focusing on research related to MCI and health behavior. The aim of this analysis was to pinpoint research hotspots and trends within this domain. The connections between

TABLE 3 Highly total link strength cited references (top 22).

No.	Literature title	Type	Year	LCS	GCS	TLS
1	"Mini-mental state": A practical method for grading the cognitive state of patients for the clinician	Article	1975	486	105,521	1,373
2	Mild cognitive impairment: Clinical characterization and outcome	Article	1999	317	12,128	1,216
3	The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease	Article	2011	308	10,428	1,072
4	Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease	Article	2008	243	2,223	1,053
5	Effects of aerobic exercise on mild cognitive impairment	Article	2010	271	1,506	1,032
6	Mild cognitive impairment as a diagnostic entity	Article	2004	301	8,864	971
7	Exercise training increases size of hippocampus and improves memory	Article	2011	273	5,335	937
8	Mild cognitive impairment – beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment	Article	2004	258	5,538	922
9	Fitness effects on the cognitive function of older adults: A meta-analytic study	Article	2003	207	5,358	848
10	The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment	Article	2005	240	22,285	655
11	Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease	Review	1984	212	33,218	650
12	Aerobic exercise training increases brain volume in aging humans	Article	2006	143	2,833	613
13	A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): A randomised controlled trial	Article	2015	199	3,043	607
14	The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease	Article	2011	178	14,754	589
15	Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease	Article	2011	161	7,613	552
16	Current concepts in mild cognitive impairment	Article	2001	150	6,405	549
17	Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older	Article	2006	117	2,290	540
18	The effects of exercise training on elderly persons with cognitive impairment and dementia: A meta-analysis	Article	2004	125	1,879	510
19	Physical activity and risk of cognitive impairment and dementia in elderly persons	Article	2001	129	2,332	505
20	Aerobic exercise and neurocognitive performance: A meta-analytic review of randomized controlled trials	Review	2010	131	1,979	495
21	Mediterranean diet and mild cognitive impairment	Article	2009	115	933	319
22	Mediterranean diet and risk for Alzheimer's disease	Article	2006	123	1,379	315

keywords indicate the strength of their co-occurrence, with thicker lines denoting higher co-occurrence strength and shorter lines indicating closer relationships. Keywords that are closely related are depicted in the same color.

Prior to the analysis, the data underwent a cleaning and term merging process using VOSviewer. This merging process involved consolidating keywords with similar meanings and standardizing different spellings of words that convey the same meaning. For instance, various terms related to Alzheimer's disease, such as "alzheimer-disease," "alzheimers-disease," "alzheimer disease," and "alzheimer's," were standardized to "alzheimer's disease." Similarly, phrases associated with Parkinson's disease, such as "parkinsons-disease" and "parkinsons disease," were merged into "parkinson's disease." The process of term merging and data cleaning is essential for maintaining term consistency and ensuring accurate analysis.

Subsequently, a co-occurrence frequency analysis of author keywords was conducted in VOSviewer, focusing on keywords with frequencies exceeding 20. Out of the 4,491 keywords in the dataset, 66 keywords met these criteria. The co-occurrence analysis of author keywords in the realm of MCI and health behavior research is illustrated in Figure 7, highlighting five

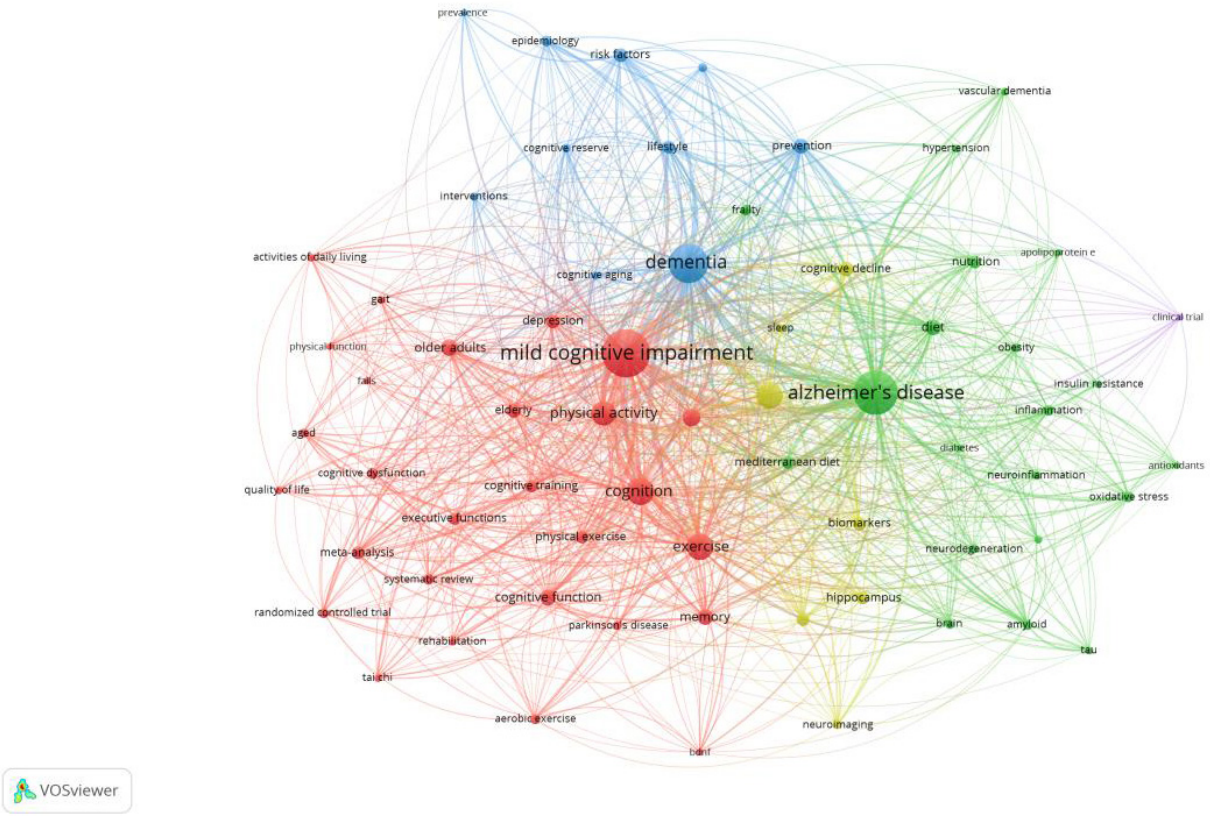

FIGURE 7
The mapping of author keywords co-occurrence analysis.

clusters of different colors. Table 4 provides a summary of the primary research concepts and key topics within the five clusters identified through the co-occurrence analysis of author keywords in this field.

4 Discussion

This study has conducted a comprehensive bibliometric analysis focusing on the preventive and therapeutic roles of healthy behaviors in MCI. Our findings reveal a substantial increase in related publications since 2002, with a significant surge post-2014, indicating the growing global interest in this area. The United States emerges as a leading contributor in this field, accounting for over one-third of the publications, followed by China, Australia, England, and Canada. This geographical distribution underscores the global acknowledgment of healthy behaviors in addressing cognitive decline. Additionally, our study demonstrates a multidisciplinary approach in the literature, encompassing fields such as neurology, geriatrics, and neuroscience, indicating a comprehensive understanding of MCI and its intervention strategies. The rise in collaborative efforts, especially between the United States and China, underscores the importance of international cooperation in tackling this public health issue. These insights lay the foundation for future research directions and stress the necessity for a united global endeavor in exploring and implementing effective interventions for MCI.

Having established the increasing global interest and multidisciplinary nature of research on healthy behaviors and MCI, we now transition to examining the five key research hotspots that have emerged. These focal areas not only signify the most significant trends in the field but also showcase the diverse approaches and theories being explored by researchers worldwide. The co-occurrence frequency analysis in this study has broadly classified the themes into five clusters: exercise, Alzheimer's disease, dementia, aging, and clinical trials. This information offers valuable insights into the current status and trajectory of research concerning MCI and healthy behaviors, unveiling the prominent topics in the realm of MCI and health behavior research.

The first cluster in our study, "Exercise," comprises 28 keywords, with "Exercise" and "Mild Cognitive Impairment" as the key terms, supported by secondary keywords like "physical activity" and "older adults." Researchers have conducted extensive randomized controlled trials and meta-analyses, particularly focusing on cognitive function training in the elderly, especially individuals aged 60 and above. These studies have shown that structured, purposeful physical activities and exercises, especially aerobic exercises and physical labor, play a significant role in assisting and safeguarding against MCI in older populations. Meta-analyses from various sources suggest that among all comprehensive or single-component interventions, multimodal exercise combined with cognitive training demonstrates the most significant improvement in overall cognitive function (Xue D. et al., 2023). The research indicates that mind-body interventions

TABLE 4 Research concepts and hot topics.

Cluster	Concept	Nodes (n = 67)
1	Exercise	Cognition, exercise, mild cognitive impairment, memory, older adults, cognitive impairment, cognitive function, depression, meta-analysis, elderly, physical exercise, physical activity, systematic review, cognitive training, executive functions, cognitive dysfunction, randomized controlled trial, Parkinson's disease, aged, aerobic exercise, Tai Chi, gait, activities of daily living, quality of life, physical function, BDNF, rehabilitation, and falls (n = 28)
2	Alzheimer's disease	Diet, nutrition, Mediterranean diet, oxidative stress, amyloid, inflammation, frailty, vascular dementia, Alzheimer's disease, brain, obesity, tau, neurodegeneration, diabetes, neuroinflammation, insulin, hypertension, antioxidants, apolipoprotein E, and insulin resistance (n = 20)
3	Dementia	Prevention, risk factors, lifestyle, dementia, epidemiology, subjective cognitive decline, cognitive reserve, interventions, cognitive aging, and prevalence (n = 10)
4	Aging	Biomarkers, cognitive decline, aging, hippocampus, magnetic resonance imaging, neuroimaging, and sleep (n = 7)
5	Clinical trial	Clinical trial (n = 1)

The background colors are primarily used to highlight the publication trends of countries or regions more clearly. Yellow, orange, and red respectively represent the number of documents published by a country or region exceeding 20, 30-40, and over 50 in the current year.

have the strongest supporting evidence (Veronese et al., 2023), and multi-component exercises provide significant benefits in alleviating depression in older adults with MCI (Liu et al., 2023).

The second cluster, Cluster 2 (green), primarily focuses on diet, inflammation, and Alzheimer's disease, incorporating 20 keywords such as "diet," "nutrition," "Mediterranean diet," "oxidative stress," "amyloid," and "inflammation." Studies have emphasized the role of gut microbiota in neuroinflammation and synaptic dysfunction, particularly in AD. Dysbiosis in the gut microbiota can result in gut products like amyloid and lipopolysaccharides (LPS) entering the circulatory system and affecting the central nervous system, thereby influencing brain-related cognitive functions (Bairamian et al., 2022). Diet can modulate the composition of the gut microbiota, serving as a crucial mediator of dietary effects on the host and impacting cognitive functions through the "gut-brain axis" (Cutuli et al., 2023). Current dietary interventions for MCI primarily include the Mediterranean diet (Ballarini et al., 2021), dietary approaches to stop hypertension (DASH) diet (Xu et al., 2018), Mediterranean-DASH Intervention for Neurodegenerative Delay (Hosking et al., 2019), and the ketogenic diet (An et al., 2018).

Cluster 3 (blue) focuses on the factors influencing dementia and intervention measures, encompassing 10 keywords. The National Institutes of Health (NIH) in the United States highlights the active identification of high-evidence-level risk factors for AD to promote primary prevention and reduce its incidence and prevalence (Daviglus et al., 2010). A systematic review and meta-analysis have resulted in the development of the first global evidence-based guidelines for AD prevention (Yu et al., 2020). These guidelines provide level I recommendations for ten factors/interventions, including maintaining a healthy body mass index, engaging in stimulating mental activities, adopting a healthy lifestyle to prevent diabetes, and preventing head trauma. Research supports that a multifactorial intervention approach can enhance cognitive functions, incorporating physical exercise and homocysteine-lowering treatment (Chen et al., 2024). Sustaining a healthy lifestyle, which includes healthy dietary habits, regular physical activity, active social involvement, engaging in positive cognitive activities, avoiding smoking or quitting smoking, and refraining from alcohol consumption, can postpone memory decline, even in the presence of genetic risk factors like the APOE ε4 genotype (Jia et al., 2023). Furthermore, traditional Chinese medicine and acupuncture are gaining recognition (Yee et al., 2018; Xue H. et al., 2023), with studies indicating that practices such as Tai Chi (Jasim et al., 2023; Xue H. et al., 2023; Chen et al., 2024), acupoint massage (Sun et al., 2021), and other traditional Chinese health behaviors can effectively deter cognitive decline.

Cluster 4 (yellow) focuses on biomarkers associated with cognitive decline, incorporating seven key terms. Researchers, utilizing biomarkers and advanced neuroimaging techniques such as magnetic resonance imaging (MRI) and neuroimaging, are dedicated to comprehending the biological, neurological, and behavioral mechanisms through which healthy behaviors mitigate MCI (Sørensen et al., 2017). The analysis of serum biomarkers, particularly those associated with neuroinflammation, oxidative stress, and metabolism, offers biological indicators of cognitive decline (De Felice and Lourenco, 2015). In recent years, researchers have started employing new methods, like machine learning algorithms, to investigate biomarkers for AD, enabling the quantitative evaluation of the effectiveness of healthy behaviors (Xu et al., 2023). Neuroimaging, especially MRI, plays a crucial role in this research. MRI allows researchers to observe changes in brain structure, especially in regions linked to cognitive functions such as the hippocampus and prefrontal cortex (Sorensen et al., 2016; Bast et al., 2017). This is crucial in unveiling the impact of healthy behaviors on brain structure, providing concrete evidence for the enhancement of cognitive function. Additionally, sleep plays a vital role in influencing the connection between health behaviors and MCI (Künstler et al., 2023). Sufficient sleep duration and quality are fundamental for cognitive function and overall brain health (You et al., 2023, 2024). Studies have indicated that sleep disorders and disruptions in circadian rhythms can heighten the risk of developing MCI by facilitating the accumulation of amyloid-beta (Aβ) and tau proteins. This, in turn, raises the risk of cognitive impairments (Barthélemy et al., 2020; Posner et al., 2021). Furthermore, sleep disturbances and deprivation can impair critical cognitive processes in MCI, such as memory consolidation, attention, and executive function (Kong et al., 2023). A study has shown that implementing Cognitive Behavioral Therapy for Insomnia (CBT-I) in elderly individuals with MCI significantly enhances participants' sleep quality and executive functions in cognition (Cassidy-Eagle et al., 2018). This implies that health behavior interventions targeting sleep could potentially boost cognitive function in elderly individuals with MCI.

Cluster 5 (purple) primarily delves into empirical studies on the impact of healthy behaviors on MCI, with "clinical trial" as its sole keyword. One study employed an integrative

intervention approach for MCI patients, incorporating risk factors like healthy lifestyle habits and physical activity into cognitive training (Gong and Tao, 2021). The findings suggested that this socio-psychological comprehensive care model could enhance cognitive function and quality of life in MCI patients. Another study showcased that cognitive-physical dual-task training yields clinical benefits by improving executive function and instrumental activities of daily living in older adults with MCI. Cognitive-physical dual-task training emerges as a promising intervention for older adults with MCI (Kim and Park, 2023). Nonetheless, challenges persist in clinical interventions for the MCI population, such as high participant dropout rates, low overall participation, and short follow-up durations. Future research should prioritize conducting larger-scale, high-quality clinical studies to explore more modifiable risk factors and their association with the onset of MCI, thus presenting promising avenues for MCI prevention.

The analysis from the aforementioned clusters highlights the research trends in the prevention and treatment of MCI through healthy behaviors. Lifestyle factors, including physical activity engagement, sleep quality, and nutritional habits, play a crucial role in the potential prevention of MCI (Dominguez et al., 2021). These factors often interact synergistically, influencing cognitive health and resilience against cognitive decline. Quality sleep is essential for memory consolidation, neuronal repair, and overall brain health, with disruptions in sleep patterns linked to an increased risk of cognitive impairment (Künstler et al., 2023). Similarly, nutrition plays a vital role, with a balanced diet rich in antioxidants, omega-3 fatty acids, and vitamins supporting brain function and reducing inflammation, which are associated with MCI risk (Li et al., 2022). Understanding the intricate interplay between these lifestyle factors and their collective impact on cognitive health is crucial for developing effective preventive strategies against MCI and promoting successful aging.

5 Future research direction and limitations of this study

The increasing trend in publications since 2002, particularly the surge post-2014, reflects a growing interest that presents opportunities for further exploration through international collaborations. Collaborations between leading contributors like the United States and emerging researchers from other countries can facilitate a deeper understanding of the factors influencing cognitive function. Future research is likely to place greater emphasis on interdisciplinary collaboration and integrated research methods, drawing on knowledge and techniques from diverse fields such as biology, neurology, geriatrics, psychology, and sociology. This holistic approach aims to comprehensively unravel the preventive and therapeutic effects of healthy behaviors on MCI. Through interdisciplinary collaboration, researchers can delve into the intricate relationship between cognitive function and health behaviors, offering more comprehensive and effective guidance for future interventions and treatment strategies.

Advancements in biomarker research represent another crucial area of focus. By leveraging more sophisticated biomarker analysis and neuroimaging techniques, future studies can enhance our understanding of the biological mechanisms underpinning MCI and provide a more precise assessment of the impact of various healthy behaviors.

However, it is important to acknowledge the limitations of this study. Firstly, the accuracy and reliability of the bibliometric analysis depend on the quality and source of the data, and relying solely on the WoS database may have resulted in the exclusion of relevant studies. Secondly, the focus on English-language articles introduces potential linguistic bias, potentially overlooking valuable research conducted in other languages. Therefore, further exploration across multiple databases and languages is warranted.

Scientometric is an emerging approach that utilizes mathematical and statistical methods to quantitatively and qualitatively analyze research trends and investigate the status of specific topics (Chen et al., 2022). In comparison to traditional systematic reviews or meta-analyses, bibliometric analysis can swiftly summarize and identify trends across a vast number of publications. It visually represents the research landscape using data such as citation counts and network characteristics, illustrating the connections between studies and offering objective measures of influence and relevance. However, there are certain drawbacks to consider. Bibliometric analysis heavily relies on data sources and citation metrics, which can be influenced by publication biases and variations in citation practices among different fields (Weingart, 2005). Unlike systematic reviews, bibliometric analysis typically does not evaluate the quality or content of the research. It provides a macro-level perspective that may overlook nuanced findings and methodological quality (Zupic and Cater, 2015). Additionally, bibliometric analysis might overlook context-specific insights that systematic reviews are better suited to capture. In conclusion, our bibliometric analysis can delineate the scope and trends of research concerning health behaviors in MCI, furnishing more specific information for systematic reviews or meta-analyses.

6 Conclusion

This study, employing bibliometric analysis, discovered that research on the healthy behaviors of individuals with MCI originated in 2002 and experienced rapid growth starting in 2014. Over the past two decades, the United States has emerged as the leading country in terms of publications, contributing 982 articles, representing 34.54% of the total scientific output. Noteworthy journals that have published extensive research on MCI-related healthy behaviors include "Alzheimer's Disease Journal," "Journal of Neuroaging," and "Frontiers in Geriatric Neuroscience," alongside other publications focused on gerontology. Co-occurrence keyword analysis identified five research hotspots in MCI healthy behaviors. Future research endeavors could benefit from integrating multidisciplinary perspectives through international collaborations, advancing biomarker research, and employing sophisticated biomarker analysis and neuroimaging techniques to deepen our understanding of the biological mechanisms underlying MCI and to accurately evaluate the impact of healthy behaviors.

Data availability statement

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

Author contributions

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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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Research status and hotspots of social frailty in older adults: a bibliometric analysis from 2003 to 2022

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Background: Social Frailty is a significant public health concern affecting the elderly, particularly with the global population aging rapidly. Older adults with social frailty are at significantly higher risk of adverse outcomes such as disability, cognitive impairment, depression, and even death. In recent years, there have been more and more studies on social frailty, but no bibliometrics has been used to analyze and understand the general situation in this field. Therefore, by using CiteSpace, VOSviewer, and Bilioshiny software programs, this study aims to analyze the general situation of the research on social frailties of the older adults and determine the research trends and hot spots.

Methods: A bibliometric analysis was conducted by searching relevant literature on the social frailty of the older adults from 2003 to 2022 in the Web of Science core database, using visualization software to map publication volume, country and author cooperation networks, keyword co-occurrences, and word emergence.

Results: We analyzed 415 articles from 2003 to 2022. Brazil has the highest number of articles in the field of social frailty of the older adults, and the United States has the highest number of cooperative publications. Andrew MK, from Canada, is the most published and co-cited author, with primary research interests in geriatric assessment, epidemiology, and public health. "Social Vulnerability," "Health," "Frailty," "Mortality," and "Older Adult" are among the research hotspots in this field. "Dementia," "Alzheimer's disease," "Population," and "Covid-19" are emerging research trends in social frailty among the older adults.

Conclusion: This scientometric study maps the research hotspots and trends for the past 20 years in social frailty among the older adults. Our findings will enable researchers to better understand trends in this field and find suitable directions and partners for future research.

KEYWORDS

older adults, social frailty, research trends, research hotspots, visual analytics, bibliometric

1 Introduction

Frailty is a significant public health concern affecting the elderly, particularly with the global population aging rapidly. It was first proposed at the American Federal Conference on Aging in 1987. Fried et al. (2001) define frailty as a clinical syndrome that occurs when age-related factors lead to a decline in physiological reserve, causing an increase in the body's vulnerability and a decline in its ability to cope with pressure. The types of frailty mainly include physical frailty, cognitive frailty, and social frailty. Although research on frailty has mostly focused on physical decline, studies have shown that social frailty is an important dimension that is closely related to overall frailty. In fact, social frailty can precede and contribute to overall frailty (Andrew et al., 2008). Despite this, research on social frailty has not received as much attention as physical and cognitive frailty. Past research has demonstrated that social frailty is strongly associated with various negative health outcomes in the elderly, such as depression, anxiety, obesity, cardiovascular disease, and increased hospitalization, disability, mortality, and cognitive impairment rates (Makizako et al., 2018; Park et al., 2019; Tsutsumimoto et al., 2019). In 2017, Bunt introduced the comprehensive concept of social frailty based on the social demand of the social productive function theory, wherein an individual continuously loses one or more important resources to meet basic social needs, which results in a lack of social behavior, activities, and self-management ability (Bunt et al., 2017). Studies have shown that older adults with social frailty are at significantly higher risk of adverse outcomes such as disability, cognitive impairment, depression, and even death than other older adults (Teo et al., 2017).

A meta-analysis revealed a high prevalence of social frailty among the older adults, with an aggregate prevalence of 47.3% among hospitalized older adults individuals and 18.8% among those living in the community (Zhang et al., 2023). Notably, social frailty may occur earlier than physical frailty (Makizako et al., 2018), but its significance is often overlooked. Given the increasingly severe aging trend in China, where over 50% of older adults individuals are empty-nesters, it is estimated that by 2030, empty-nesters will account for 90% of the total number of older adults (Su et al., 2020). The lack of companionship from family and friends can reduce the degree of family care (Shamsikhani et al., 2023) and social participation (Su et al., 2020), potentially leading to social frailty among the older adults. Therefore, further exploration and prediction of social frailty in the older adults are crucial.

Bibliometrics, as a novel scientific measurement technique, offers a comprehensive qualitative and quantitative approach to studying publications. It focuses on the quantitative attributes of literature, conducting in-depth analyses to identify multidimensional features such as countries, institutions, journals, authors, and keyword distributions within specific fields over defined periods (Zhu et al., 2023). This systematic approach enables researchers to discern prevalent topics within a research domain, accurately depict academic trends, and anticipate future research frontiers (Chen et al., 2012). Bibliometrics not only provides robust data support for current research but also establishes a firm academic foundation for shaping future research directions and strategies. While traditional literature reviews, systematic reviews, and main path analyses can offer quantitative insights, bibliometrics uniquely enable simultaneous analysis of author, institution, country, and journal contributions and collaborations within the academic realm, facilitating precise assessments of knowledge bases and research focal points (Chen and Song, 2019). In recent years, there have been more and more studies on social frailty, but no bibliometrics has been used to analyze and understand the general situation in this field. Therefore, by using CiteSpace, VOSviewer, and Bilioshiny software programs, this study aims to analyze the general situation of the research on social frailties of the older adults and determine the research trends and hot spots in the past two decades from 2003 to 2022, to provide references for researchers to understand hot spots in related fields and seek cooperation.

2 Method

2.1 Design

This study used CiteSpace, VOSviewer and Biblioshiny software to conduct data analysis, and interprets the literature data on social frailty among the older adults from 2003 to 2022 by analyzing various aspects, such as the number of publications, national cooperation network, core authors, co-cited literature, keyword co-occurrence, and keyword emergence. By examining these dimensions of the literature, the study aims to identify the research hotspots and trends in this field over the past two decades.

2.2 Sample

A total of 482 articles were retrieved under the specified search conditions. However, 67 non-medical articles that did not fall under the subject classification were excluded (Figure 1). The outcome of this literature search resulted in the derivation of 415 publications.

2.3 Data collection

In this study, the Web of Science™ core collection database was utilized as the primary data source to conduct a literature search related to social frailty. The search strategy used was TS = ("aged" OR "elderly" OR "older people" OR "older adult*" OR "Aged, 80 and over" OR "Frail Elderly") AND TS = ("social frailty" OR "social vulnerability" OR "social frail*" OR "Social vulnerabilities"). The search was conducted within the timeframe of January 1st, 2003 to January 1st, 2023, and the retrieval of data was carried out on March 17, 2023. The retrieved literature was exported in plain text format, where the entirety of the text content, including referenced citations, was recorded and saved in the input folder with the file name download_*.txt.

Inclusion criteria: ① Published journal literature on social frailties in the older adults; ② The language is English. Exclusion criteria: ① non-academic documents such as conferences, news, and reports; ② Repeated publication of literature.

2.4 Data analysis

In this study, a range of software tools was employed for the analysis of literature data on the social frailty of the elderly from 2003 to 2022.

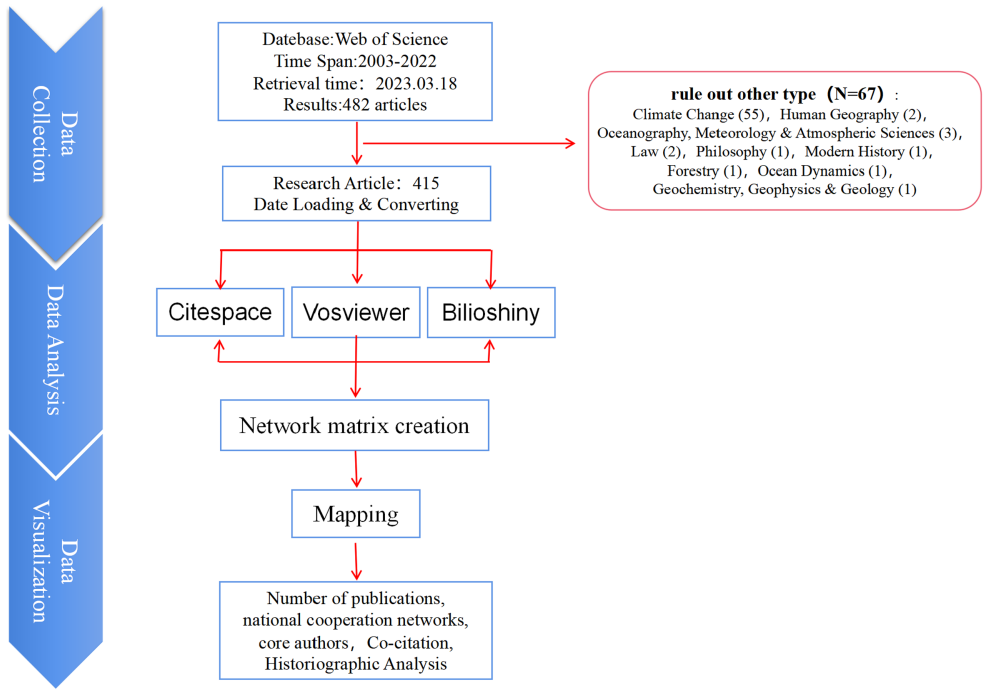

FIGURE 1
Literature screening and data analysis processes.

Specifically, Excel was used to create charts for the number of published documents and journal data retrieved. Web of Science was utilized for obtaining the journal impact factor and H index. Subsequently, CiteSpace, VOSviewer, and Biblioshiny were applied to analyze the data. This section mainly describes in the CiteSpace software, settings were adjusted for Time Slicing (2003–2022) and #Years Per Slice (1 year). The Node Types are offered different options such as Author, Country, Institution, and Keywords. The Selection Criteria was set to Top $N = 50$, and Pruning was chosen to include "Pathfinder" and "Pruning the sliced networks." After these Settings were established, the software was run to obtain the visual map.

2.5 Validity, reliability and rigidity

The data used in this study was sourced from high-quality journal publications. To ensure data accuracy and reduce duplication, two researchers carefully reviewed all articles retrieved for the study. Additionally, these researchers reviewed the titles, abstracts, and full texts of all selected literature, following strict inclusion and exclusion criteria aimed at excluding articles that were not relevant to our research topic.

3 Results

3.1 Number of publications

The quantity of literature is a significant indicator for measuring the developmental status of a research field and can provide insight into its future trends (Li and Song, 2022). As illustrated in Figure 2, the trend of the number of publications in international studies on the social decline of the elderly has fluctuated in recent years, but overall, there has been an upward trend. Based on the observed growth pattern, a regression model with a high degree of fitting ($R^2 > 0.7$) is obtained using the growth equation $y = 3.4802e^{0.2999x}$, $R^2 = 0.9574$. Particularly, the analysis reveals that the period from 2017 to 2022 shows the most significant growth in the number of published papers, suggesting that interest in the social frailty of the elderly has been increasing in recent years.

3.2 Cooperation map of country

In this study, we used VOSviewer and Biblioshiny software to create a geographical map of countries and a map of their collaborative publications. The nodes in Figure 3A represent each respective country, with the node size indicating the number of documents issued by the country. Wired connections between nodes indicate countries that collaborate, with more countries that engage in collaboration resulting in more connections. Additionally, the mediation centrality of a node indicates the strength of association and collaboration (Freeman, 1977). Based on the provided data, the top five countries in terms of the number of published articles are Brazil (96), the United States (48), Japan (33), the Netherlands (25), and China (23). On the other hand, the top five countries in terms of mediation centrality, are Brazil (0.62), followed by the United States and the Netherlands both tied with a score of 0.34, China (0.24), and Spain (0.22). In Figure 3B, "single country publications" (SCP) represent the volume of individual country publications; "Multiple Country Publications" (MCP) indicates that many countries have cooperated in publishing articles, of which the United States has the

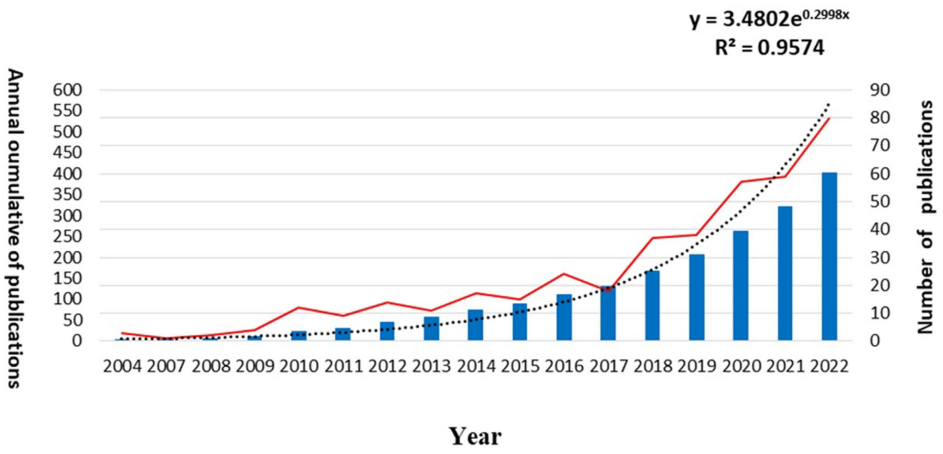

FIGURE 2
Number of articles published annually in the field of social frailty.

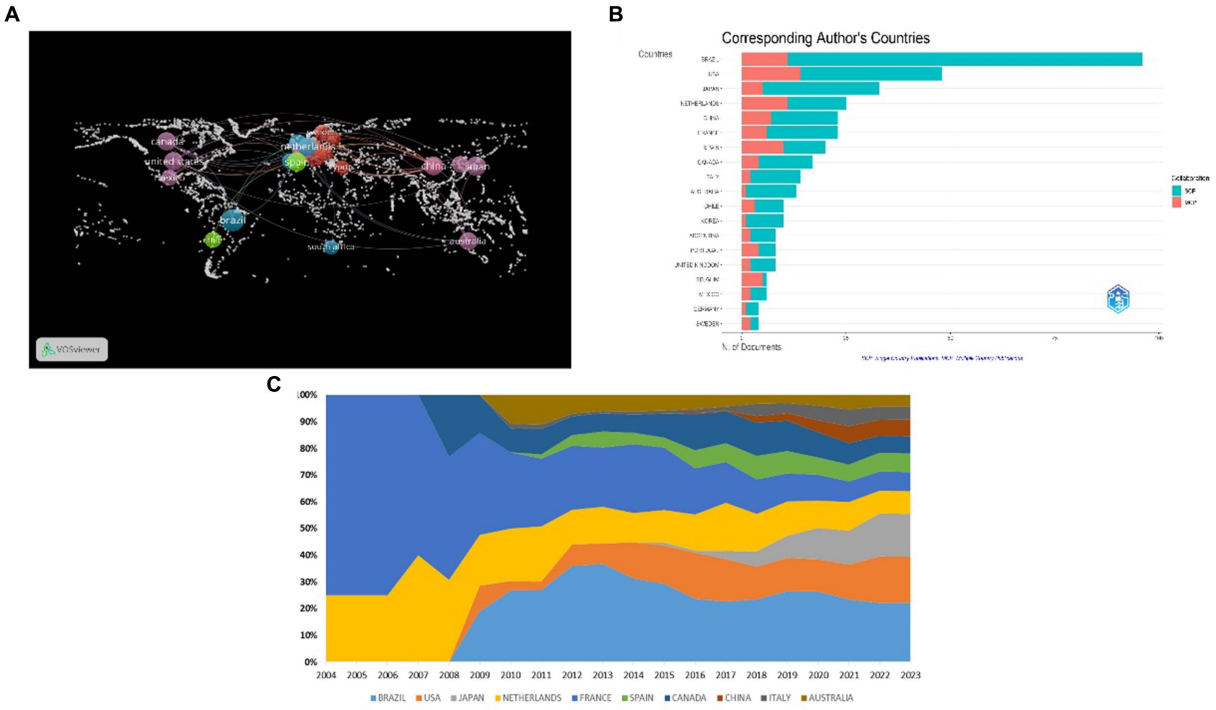

FIGURE 3
Analysis of national publications. **(A)** Collaboration WorldMap. **(B)** Corresponding author's countries. **(C)** the area chart of the proportion of national publications.

largest number of independent publications in the field of Social frailty, ranking second in total publications; Brazil has the largest number of cooperative publications and the total number of publications, which shows that Brazil and the United States not only have a high number of publications but also pay attention to cooperation, and are in a leading position in the field of Social frailty. Figure 3C shows the area chart of the proportion of national publications, and the results of the analysis are consistent that Brazil and the United States are generally dominant, especially in the early stage of social frailty research (before 2008), and in 2008, French scholars began to study social frailty, and continued to maintain research enthusiasm in the middle and late stages, and the proportion gradually caught up with Brazil.

3.3 Author analysis

Co-citation author analysis means that the literature of two authors is cited by the third author at the same time (Zhang et al., 2022), and through the analysis of the authors with the highest number of publications and co-citation frequency, it can intuitively reflect the research strength of the authors and the research hotspots

in the field of social weakness. Data analysis showed that there were 1943 authors in the field of social frailty of the older adults, of which 1,697 (87.3%) published one article; 160 (8.2%) published two papers; 33 (1.7%) published three papers; Twenty-five (1.3%) published four or more papers. Authors who have published multiple papers are considered "core" authors. The analysis of the top 10 authors in the field of social frailty found that Andrew MK (Dalhousie Univ, Div Geriatr Med, Halifax, NS, Canada) has the highest number of publications and H-index. Generally, the higher the H-index, the greater the author's influence in the field, as the H-index accurately and objectively evaluates scholars' academic influence based on the number of publications and citations (Esposito, 2010). It can also evaluate other academic entities such as countries, research institutions, and academic teams. As the H-index does not factor in the academic age of the author, which refers to the time since the author published their first paper, the *M*-index = (*H*-index/academic age) has been calculated. Additionally, the g-index was used to assess the authors' most cited papers.

Table 1 The top five most cited authors in the field of social frailty were Andrew MK (768), Rockwood K (660), Gobbens RJJ (609), Van Assen MALM (455), and Makizako H (386), indicating that Andrew MK has a high level of influence in both publication volume and co-citations. Figure 4A displays the author's collaboration network, which can be approximately classified into four different color-coded cooperative groups, namely Andrew MK, Machado De Jesus, IT, etc. (green), Makizako H, Tsutsumimoto K, etc. (blue), Gobbens RJJ, Inzerilli MC, etc. (red), and Iost Pavarini SC, Pereira De Brito TR, etc. (yellow). Furthermore, Figure 4B illustrates the average annual number of publications and contributions of influential authors in the field of social frailty. The figure reveals ANDREW MK as the author with the highest average citation per article, and they have maintained a high scientific impact in the area of social frailty from 2008 to 2022.

TABLE 1 Top 10 authors in the field of social frailty of older adults.

Rank	Author	*H*-index	*G*-index	*M*-index	Publications	Total citation	PY_start
1	Andrew MK	13	15	0.81	15	768	2008
2	Rockwood K	12	13	0.75	13	660	2008
3	Gobbens RJJ	10	15	0.71	15	609	2010
4	Makizako H	7	12	0.78	12	386	2015
5	Paiva SM	7	8	0.47	8	264	2009
6	Shimada H	7	9	0.78	9	372	2015
7	Vale MP	7	8	0.5	8	209	2010
8	Van Assen MALM	7	8	0.5	8	455	2010
9	Pavarini SCI	6	8	0.4	8	67	2009
10	Pordeus IA	6	6	0.4	6	234	2009

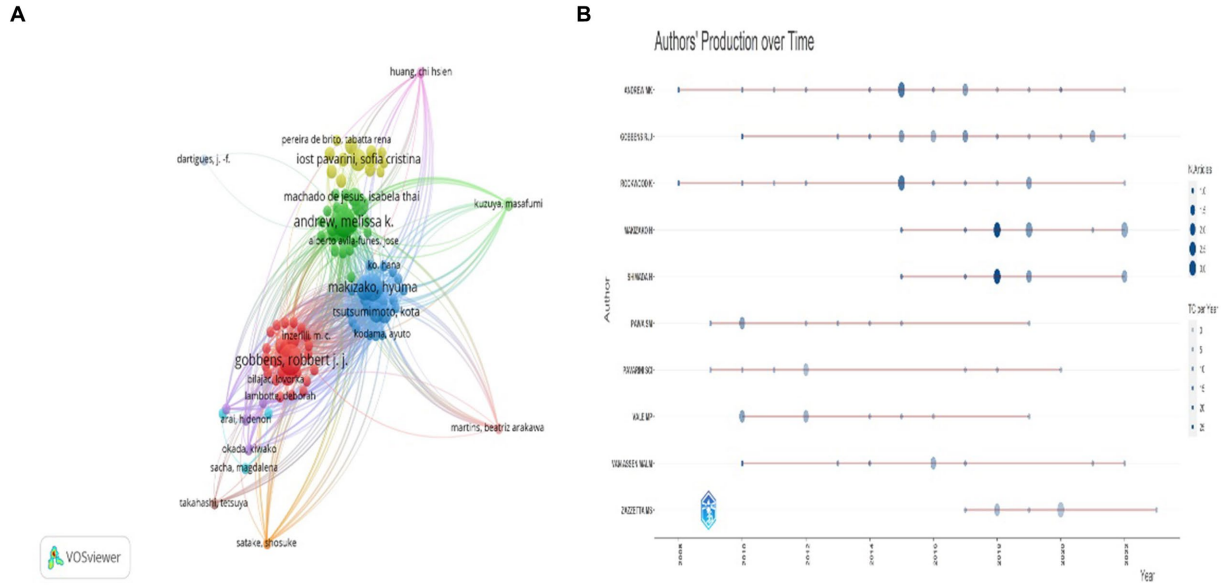

FIGURE 4
Analysis of the cited authors. **(A)** Co-cited author relationship network map, where nodes of different colors represent the group of authors who form cooperation. **(B)** Authors' Production Over Time, the node size represents the number of documents, and the color shade represents the average number of citations per year.

TABLE 2 Top 10 journals with publications related to social frailty.

Rank	Total publications	Year publication	Journal	Publications	Country	H-Index	Impact factor
1	59,389	2004	INT J ENVIRON HEAL R	19	Switzerland	113	4.614
2	7,854	1996	CIENCIA AND SAUDE COLETIVA	14	Brazil	78	1.917
3	4,845	1982	ARCH GERONTOL GERIAT	12	Netherlands	89	4.163
4	4,575	2001	BMC GERIATRICS	12	United Kingdom	89	4.07
5	5,025	2000	J AM MED DIR ASSOC	10	United States	114	7.802
6	2,920	1997	J NUTR HEALTH AGING	7	France	95	5.285
7	281,518	2006	PLOS ONE	7	United States	332	3.752
8	3,515	1967	REV ESC ENFERM USP	5	Brazil	42	1.123
9	2,944	2001	GERIATR GERONTOL INT	5	Serbia	71	3.387
10	10,202	1972	AGE AND AGEING	4	United Kingdom	143	12.782

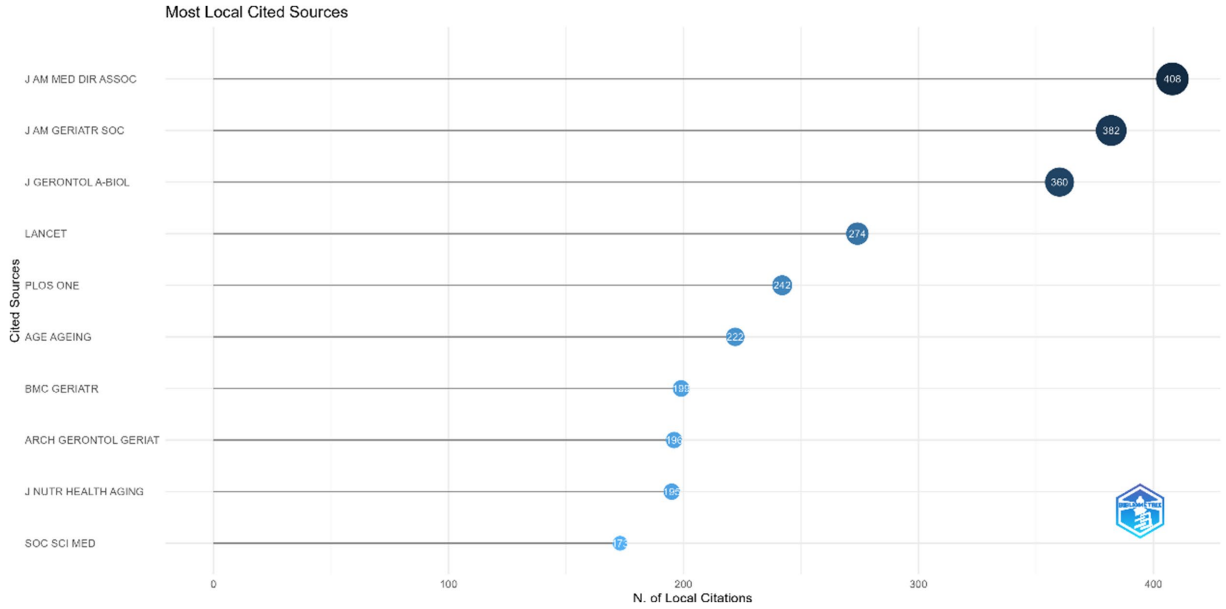

FIGURE 5
Top 10 journals by total citation.

3.4 Journal publication volume and co-citation analysis

Table 2 displays the top 10 journals with the most published publications in the field of social frailty. *The international journal of environmental research and public health* ranked first. In Figure 5, the top three most cited journals were *J Am Med Dir Assoc* (408 citations), *J Am Geriatr Soc* (382 citations), and *J Gerontol A-Biol* (360 citations). Journals with more citations suggest that they contain higher-quality articles with wider applicability.

3.5 Analysis of co-cited literature

the number of citations is often used as a measure to determine the quality and impact of scientific literature on the scientific community. It can reflect the attention and influence of a publication, indicating how frequently and widely other researchers reference it in their own work. Higher citation counts suggest that a publication is more impactful and valuable to the research community. Table 3 provides a list of the top 10 cited references in the field of social frailty, which include reviews, cross-sectional surveys, longitudinal studies, and systematic reviews. The main research content covers the definition of social frailty, theoretical frameworks, and influencing factors. The most cited article was a review published by Robertson DA et al. in 2013, with a total of 421 citations and an annual average of 38.27.

By using the Biblioshiny software and selecting "Historiograph" in the "Intellectual Structure" option for analysis, Figure 6A displays node size and label color related to the number of citations, while the lines between documents indicate citation relationships, and arrows point to the cited documents. By analyzing the relationship of references among 30 nodes, the historical process of social frailty

TABLE 3 Top 10 citation references.

Year	Author	Article Title	DOI	Total Citations	citations per year
2013	Robertson DA	Frailty and cognitive impairment--a review of the evidence and causal mechanisms	10.1016/j.arr.2013.06.004	421	38.27
2010	Gobbens RJJ	Determinants of frailty	10.1016/j.jamda.2009.11.008	225	16.07
2008	Andrew MK	Social vulnerability, frailty and mortality in elderly people	10.1371/journal.pone.0002232	214	13.38
2017	Bunt S	Social frailty in older adults: a scoping review	10.1007/s10433-017-0414-7	161	23.00
2018	Makizako H	Social Frailty Leads to the Development of Physical Frailty among Physically Non-Frail Adults: A Four-Year Follow-Up Longitudinal Cohort Study	10.3390/ijerph15030490	101	16.83
2015	Makizako H	Social Frailty in Community-Dwelling Older Adults as a Risk Factor for Disability	10.1016/j.jamda.2015.08.023	98	10.89
2014	Gobbens RJJ	The prediction of quality of life by physical, psychological and social components of frailty in community-dwelling older people	10.1007/s11136-014-0672-1	86	8.60
2013	Garre-Olmo J	Prevalence of frailty phenotypes and risk of mortality in a community-dwelling elderly cohort	10.1093/ageing/afs047	80	7.27
2014	Andrew MK	Social vulnerability from a social ecology perspective: a cohort study of older adults from the National Population Health Survey of Canada	10.1186/1471-2318-14-90	78	7.80
2010	Andrew MK	Social vulnerability predicts cognitive decline in a prospective cohort of older Canadians	10.1016/j.jalz.2009.11.001	78	5.57

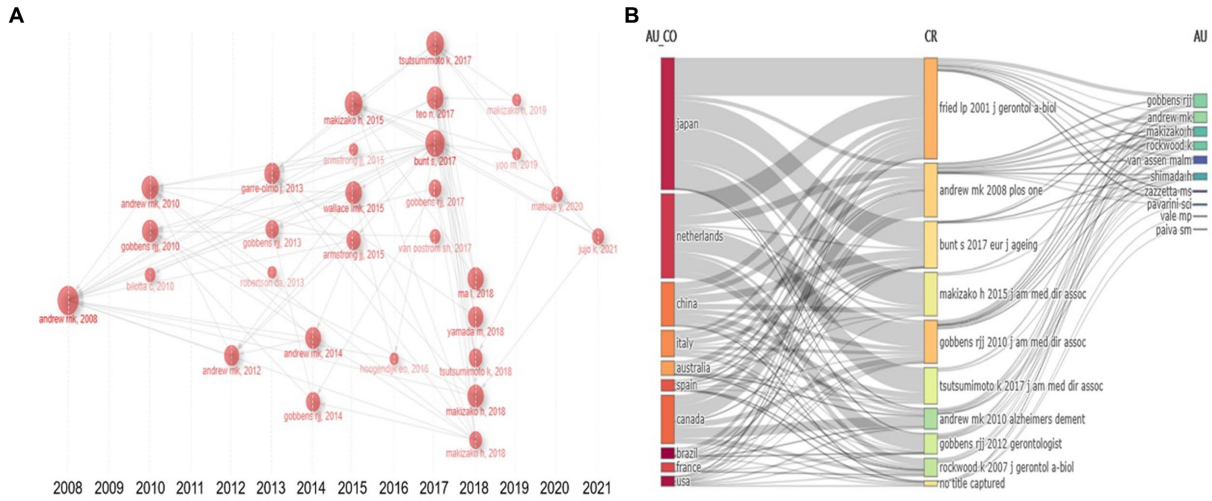

FIGURE 6
Analysis of co-cited literature. **(A)** The top 30 reference relationship networks by year are arranged in chronological order, with node size indicating the number of citations and arrows pointing to cited documents. **(B)** Three-field plot, the left field is the author country or institution, the middle field is the cited document, and the right field is the author.

research can be understood. Results indicate that ANDREW MK's 2008 article "Social vulnerability, frailty, and mortality in elderly people" was the most cited social frailty literature, with a total of 52 citations. Regarding years, 2017 (5 articles) was the most cited among literature on the same topics. This suggests that the research on social frailty has continued to increase in popularity and depth. Another noteworthy article is the second most cited article by Bunt S et al. in 2017. They first proposed the comprehensive concept of social frailty based on the concept of social needs in Social Production Function Theory and constructed a social frailty integration model that defined the concept of social frailty comprehensively from a social level, providing a complete concept of social frailty. Therefore, the citation frequency ranks high. In Figure 6B, the relationship between countries, authors, and citations in the field of social frailty is illustrated. The connections between the three regions represent the relationships between each other, and the line width indicates the frequency.

3.6 Keyword co-occurrence analysis

High-frequency keywords can reflect research hotspots in related fields, By tracking changes in keyword frequency over time, researchers can also observe how research interests and topics have evolved and adapted in response to relevant issues and developments in the field. The main metrics used in key co-occurrence analysis are frequency and centrality. Frequency measures how often a particular keyword appears in a dataset, indicating its relative importance in the field of study. Centrality, on the other hand, reflects the importance of nodes in a co-occurrence network. Nodes with high centrality have more connections with other nodes, indicating that they are important hubs in a network. They are often considered key drivers of research trends and hotspots in the field. The top five high-frequency keywords in Figure 7A are "social vulnerability" (101), "health" (96), "frailty" (79), "mortality" (74), and "older adult" (60). Keywords with high intermediation (centrality ≥0.1) are "health" (0.16), "risk" (0.14), "disability" (0.12), and "quality of life" (0.12), indicating that these are the main research focus areas in the field of social frailty. Figure 7B analyzes the distribution of high-frequency keywords over time. The closer the square color block color is to yellow, the higher the keyword popularity. In 2021–2022, the keyword color is mainly yellow, indicating that the popularity of social frailty research has continued to increase in the past 2 years. Figure 8A displays the keyword co-occurrence network plotted through VOSviewer. The timeline shows the average year, arranged in each column as a cluster, with the node size reflecting the importance of the keyword, while the darker the node color, the closer it is to 2020. This approach helps to better visualize the evolving research trends and hotspots in the field of social frailty.

The clustering process involves dividing the analyzed objects into groups based on the degree of correlation and grouping with a high degree of similarity. In the context of keyword analysis, the keyword cluster graph is extracted using the log-likelihood ratio (LLR) algorithm to extract keywords and plot. The cluster module value Q is set to 0.4582 ($Q > 0.3$), and the average contour value of the cluster S is set to 0.7559 ($S > 0.5$). This indicates that the clustering process is effective and reasonable. The larger the S value, the stronger the homogeneity (Shibata et al., 2008). In Figure 8B, the size of a cluster label corresponds to the number of keywords included in the cluster. The smaller the number of cluster labels, the larger the cluster size. The largest cluster is represented by 0# physical frailty, followed by 1# nutritional status and 2# anxiety, which are the top three clusters. This indicates that physical frailty, nutritional status, and anxiety are the most prominent research topics in the field of social frailty and have strongly overlapping keywords. The clustering analysis helps to identify groups of interrelated keywords and provides a comprehensive understanding of the research themes in the field of social frailty.

3.7 Keywords with citation bursts

Keyword with citation bursts can be performed using CiteSpace. To perform this analysis, the "Keyword" module should be selected, and the time partition should be set to "1" year. The "Top50" threshold should also be selected to identify keywords that are most relevant to the field of research. Additionally, the mutation analysis "burst terms" operation should be conducted to identify the research frontier in this field. By predicting the research trend and research frontier of a certain area, mutation term analysis can provide insights into the direction and focus of research in that field. It is important to note that the strength of the mutant word corresponds to the extent of the research trend of the keywords in the field. Figure 8C provides a list of the key words related to social frailty. The analysis shows that

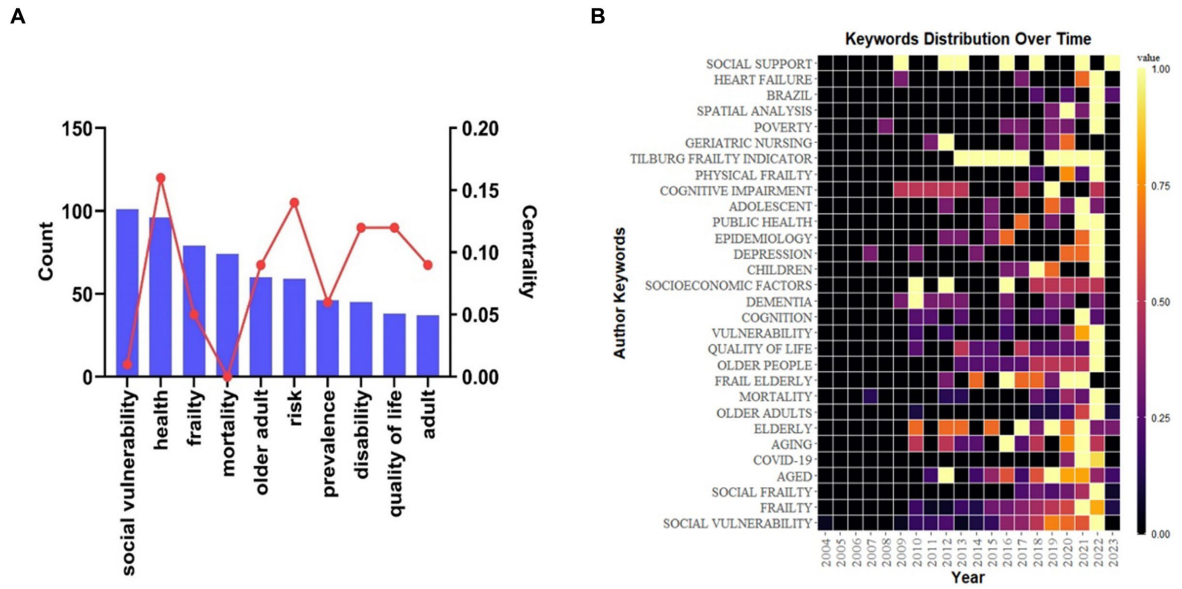

FIGURE 7
High-frequency keywords and heat maps. **(A)** High-frequency keywords, the top 10 keywords in the field of social weakness, the bar chart is the frequency of the keywords, and the line chart shows the centrality of the keywords. **(B)** Keywords distribution over time, the closer the square color block color is to yellow, the more popular the keywords.

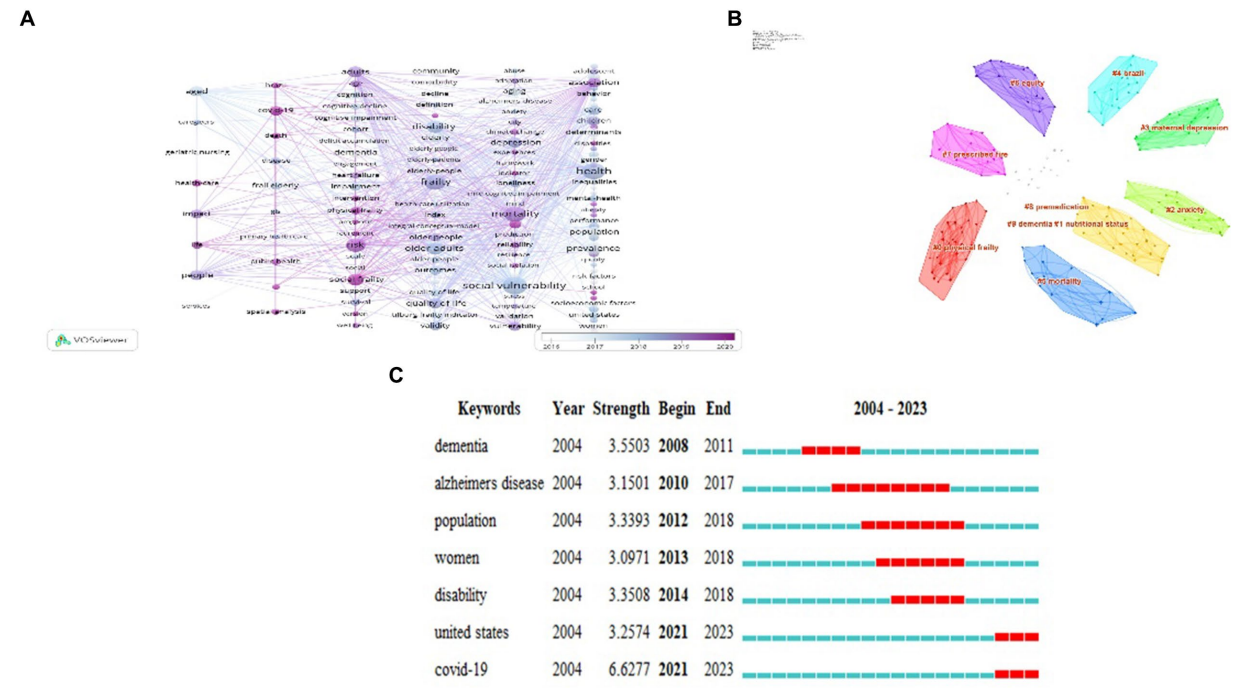

FIGURE 8
Keyword co-occurrence, clustering and strongest citation bursts analysis. **(A)** social frailty keywords co-appear in the network map, each column is a group, the keyword node size indicates the frequency, and the connection between keywords indicates the strength of the association. **(B)** Social frailty keyword clustering map, with a total of 179 nodes and 665 connections. Nodes with high homogeneity are clustered together, and different colors represent different clusters. **(C)** Top7 keywords with the strongest citation bursts, each blue line corresponds to a year, and the red line indicates that the keyword is frequently cited during that time period.

"dementia" was the earliest keyword that emerged in 2008 and continued to be relevant up until 2011. The keyword "Covid-19" (6.6277) had the greatest emergence and was the most timely, reflecting its recent and significant impact on social frailty research. In addition, "alzheimers disease" and "population" were identified as two keywords that have had the longest emergence within this field of study. Figure 8C analyzes keywords with the strongest citation bursts. The earliest keyword to appear in 2008 was "dementia." "Dementia" was the first keyword to appear in 2008. The cited outbreak of "Covid-19" (6.6277) is the strongest and time-sensitive, indicating that it has had a significant impact on social vulnerability research in the short term. "Alzheimer's disease" and "population" are the two keywords that have emerged in the field for the longest consecutive time.

4 Discussion

This study is based on data taken from 415 articles on social vulnerability authored by 1943 scholars in 254 journals listed in the Web of Science database from 2003 to 2022. After conducting an analysis of the data using CiteSpace, VOSviewer, and Biblioshiny, it was found that the number of articles related to social debilitation has increased exponentially over the last two decades. In 2022, there were 26 times as many articles as there were in 2004, reflecting a remarkable increase in attention in this area of research.

National publication volume indicates that Brazil has been the leading country in terms of publications and intermediary centrality in the field of social frailty related to older adults. The United States, with the largest number of independent publications, ranks second in total publications and has considerable influence. The differences between Brazil and the United States in terms of healthcare eligibility may influence perceptions of social frailty. Brazil's provision of universal healthcare through SUS may result in fewer barriers for the elderly in accessing basic healthcare services, thereby associating social frailty more closely with social support, living conditions, and economic security. Conversely, in the United States, the structure of healthcare insurance may lead to greater financial burdens for elderly people when accessing specific types of healthcare services, thus linking social frailty more closely to healthcare costs, insurance coverage, and individual financial status. Despite these differences, the concept of social frailty may encompass multiple dimensions, such as health status, social participation, and economic resources, in both countries, with the specific policies and social structures of each influencing the relative importance of these factors.

The author analysis results reveal that Andrew MK, from the School of Geriatrics at Dalhousie University in Canada, is the top author in terms of the number of publications and total citations. In 2008, Andrew MK published a paper titled "Social Vulnerability, Frailty and Mortality in Elderly People," which introduced the concept of social frailty using the deficit accumulation method. This study was the first to explore the relationship between social frailty, frailty, and mortality. The findings demonstrated a moderate correlation between social frailty and frailty, and a strong association of both with elderly mortality. This paper has been highly cited and is considered a seminal work in this field. Among the top 10 cited references, Andrew MK has

three articles, including "Social Vulnerability from a Social Ecology Perspective: A Cohort Study of Older Adults from the National Population Health Survey of Canada" and "Social Vulnerability Predicts Cognitive Decline in a Prospective Cohort of Older Canadians." These citation records illustrate the significant influence and noteworthy contributions of Andrew MK and her team in advancing the understanding of social debilitation.

Another highly cited article in this field is "Frailty and Cognitive Impairment – A Review of the Evidence and Causal Mechanisms" published by Robertson DA in 2013. This paper provides a comprehensive summary of the evidence and main pathological mechanisms related to frailty and cognitive impairment. It has received the highest number of overall and annual average citations and has made a significant impact on the field. Analysis of the cooperative network of cited authors demonstrates that there exist mature research teams in the area of social frailty, with close collaboration among them.

Among the top 10 journals with the highest number of publications on social frailty in the older adults, Brazil, the United States, and the United Kingdom each publish two journals. This corresponds with the national publication statistics, highlighting the notable contributions made by these countries in this field. In addition, the most cited journal in this area was J Am Med Dir Assoc (408) with a JCR subject category of Geriatrics & Gerontology and a JCR division of Q1. The journal's high impact factor of 7.802 for 2021 can be attributed to the publication of high-quality and highly-cited articles.

High-frequency keywords results demonstrate that "social vulnerability" has the highest frequency, which aligns with the research theme. "Health" follows as a high-frequency and highly mediating keyword, indicating that social frailty is closely linked to the health of older adults and is often associated with adverse health outcomes such as mortality (Ma et al., 2018), physical function, cognitive impairment (Tsutsumimoto et al., 2017), and depression. Additionally, the high-frequency keyword "frailty" and the largest cluster, 0# physical frailty, reveal a growing body of research demonstrating that social frailty is linked to physical frailty. Frail symptoms predict the development of social frailty (Nagai et al., 2020). "Risk," "disability," and "quality of life" are highly mediating keywords, revealing that the investigation of risk factors for social frailty is a current research focus. In a cohort study that explored frailty in older adults in Tanzania, the results suggest that social frailty is not only associated with frailty but also with mortality and disability (Cooper et al., 2022). Further linking social frailty and disability in older adults, Miriam Cappelli's systematic review illustrates that social frailty is often associated with functional decline in ADL/IADL in terms of basic social needs, social resources, social behaviors and activities, and general social resources (Cappelli et al., 2020). Social frailty increases the risk of disability in older adults (Makizako et al., 2015). Thus, timely and effective social interventions can prevent or delay functional decline and death.

Keywords clusters suggest that nutritional status and psychological aspects can impact the social frailty of the older adults. In a meta-analysis (Verlaan et al., 2017), researchers found that malnutrition and frailty were associated with community-dwelling older adults, with 68 percent of malnourished older adults experiencing frailty. Moreover, nutrition plays a crucial role in improving frailty in older adults (Hoogendijk et al., 2020). Current research confirms the longitudinal association between social frailty and nutrition and diet in older men (Huang et al., 2020). however, this association has not been confirmed in older women, presenting a potential area for future research. Understanding the psychological status of socially fragile older individuals is equally important. Previous studies have determined that psychological robustness is a decisive factor in social frailty (Sugie et al., 2022). Additionally, the prevalence of social debilitation is higher in older adults experiencing negative emotions such as loneliness (Hoogendijk et al., 2020), depression (Tsutsumimoto et al., 2018), or anxiety (Henry et al., 2023). Therefore, medical interventions seeking to alleviate the social weakness of older adults should include screening for depression and nutritional management in addition to providing social resources and increasing social activities.

Keywords strongest citation bursts analysis highlights that the link between social frailty and disease has received increased attention with a research emphasis on social frailty-related diseases such as "dementia" and "Alzheimer's disease." A five-year longitudinal study found that frailty significantly increases an individual's risk of transitioning from cognitive impairment to Alzheimer's disease (Trebbastoni et al., 2017). Moreover frail older adults are eight times more likely to develop cognitive impairment and dementia than healthy individuals (Kulmala et al., 2014). Additionally older adults who exhibit a high degree of frailty may have more pathological features of Alzheimer's disease and be diagnosed with dementia (Wallace et al., 2019). Japanese scholars Tsutsumimoto Kota (Tsutsumimoto et al., 2019) found that the social vulnerability of the elderly is closely related to Alzheimer's disease (AD) incidence. However the direct relationship between social frailty and Alzheimer's disease cannot be inferred. Consequently the question of whether preventative social vulnerability interventions can reduce the risk of Alzheimer's disease requires further confirmation from high-quality studies

Furthermore "Covid-19" is the keyword with the greatest outbreak intensity. The COVID-19 pandemic has significantly impacted the global community's health and wellbeing

especially the elderly population who are most at risk and vulnerable to the virus (Drane et al., 2021). Data suggests that one-quarter of COVID-19-related deaths occur among individuals aged 70–80 years and two-thirds of deaths occur among those over 80 years old (Calderón-Larrañaga et al., 2020). Since 2021 scholars worldwide have found that the social vulnerability of older populations has increased during the COVID-19 pandemic (Choi and Ko, 2022). Specifically

socially debilitated populations experience the health and economic consequences of COVID-19 leading to the continued accumulation of risks (Calderón-Larrañaga et al., 2020). Currently

global health responses have helped address the situation with risks associated with the frail elderly population gradually decreasing and the quality of life improving. The three words "population" "disability" and "united states" once again prove the analysis results of previous national cooperation papers and research hotspots. The keywords with the strongest citation bursts "population," "disability," and "United States "further validate the previous national cooperation papers' analysis results and research hotspots

5 Strengths and limitations

This study utilized the Web of Science core database and leveraged three visualization software tools to provide a comprehensive analysis of the literature on social debilitation from various perspectives. However, there are certain limitations to our approach. Firstly, research on social weakness is still in its early stages, and our study only represents the current state of research. Secondly, our search was

limited to a single database, which may have excluded potentially valuable information, and our results were restricted by search time and language (only English-language literature was included). In light of these constraints, future research should aim to conduct more inclusive systematic reviews of this area, incorporating a wider range of databases and addressing language limitations, to provide a more comprehensive exploration of the field of social debilitation.

6 Conclusion

This scientometric study explores social frailty in the field of older adults research, uncovering research hotspots and trends in the past 20 years. We identified the most influential countries, authors, and journals in the field, as well as the interrelationships between basic scientific knowledge and keyword research hotspots. Results demonstrate that the impact of social frailty on older adults' health, such as the relationship between social frailty and frailty, mortality, disability, and the psychological and nutritional status of the socially frail older adults, are research hotspots. Additionally, the link between social frailty and disease is the current research trend and future research direction. We hope that this study will provide researchers with a better understanding of general trends in the field and potential research directions and partners for future research pursuits.

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/s.

Author contributions

HW: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. XC: Data curation, Formal analysis, Funding acquisition, Software, Supervision, Visualization, Writing – original draft, Writing – review & editing. MZ: Data curation, Investigation, Methodology, Software, Visualization, Writing – review & editing. YW: Data curation, Investigation, Methodology, Software, Visualization, Writing – review & editing. LL: Conceptualization, Data curation, Funding acquisition, Methodology, Project administration, Resources, Supervision, 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

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The association of cognitive function and its changes with all-cause mortality among community-dwelling older adults

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Background: The association of cognitive function, its changes, and all-cause mortality has not reached a consensus, and the independence of the association between changes in cognitive function and mortality remains unclear. The purpose of this study was to evaluate the longitudinal association between baseline cognitive function and cognitive changes over 1 year with subsequent all-cause mortality among the older adults aged 60 and above.

Methods: A prospective cohort study utilizing the Community Older Adults Health Survey data. Initiated in 2018, the study annually assessed all individuals aged 60+ in Dalang Town, Dongguan City. Cognitive function was assessed using the Chinese version of the Mini-Mental State Examination (MMSE). A total of 6,042 older adults individuals were included, and multivariate Cox proportional hazard models were used to examine cognitive function's impact on mortality.

Results: Participants' median age was 70 years, with 39% men. Over a median 3.08-year follow-up, 525 died. Mortality risk increased by 6% per MMSE score decrease (adjusted *HR* = 1.06, 95%*CI*: 1.05–1.08). Compared to those with normal cognitive function at baseline, participants with mild cognitive impairment and moderate to severe cognitive impairment had significantly higher mortality risks (adjusted *HR* = 1.40, 95%*CI*: 1.07–1.82; *HR* = 2.49, 95%*CI*: 1.91–3.24, respectively). The risk of death was 5% higher for each one-point per year decrease in cognitive function change rate (*HR* = 1.05, 95%CI: 1.02–1.08). Compared with participants with stable cognitive function, those with rapid cognitive decline had a 79% increased risk of death (adjusted *HR* = 1.79, 95% *CI*: 1.11–2.87), with baseline cognitive function influencing this relationship significantly (*P* for interaction = 0.002).

Conclusion: Baseline cognitive impairment and rapid cognitive decline are associated with higher all-cause mortality risks in Chinese older adults. Baseline function influences the mortality impact of cognitive changes.

KEYWORDS

older adults, cognitive impairment, change, all-cause mortality, cohort study

1 Introduction

The World Health Organization estimates that the global population aged 60 and over will increase to 1.4 billion by 2030 (United Nations, 2023). As the global population undergoes aging, the associated issues are becoming more pronounced. This includes cognitive decline, which, in severe cases, can develop into cognitive impairment, and subsequently dementia. Cognitive impairment generally refers to varying degrees of cognitive function decline caused by several factors (including memory, computation, temporal and spatial orientation, structural ability, executive ability, language understanding, expression and application, etc.,) (Ni et al., 2022). It is now established that cognitive impairment is associated with various adverse outcomes such as falls, prolonged hospitalization and readmission (Buslovich and Kennedy, 2012; Callahan et al., 2015; Ma et al., 2021b). Dementia ranks as the seventh leading cause of death and it is one of the primary reasons for dependency and loss of autonomy among older adults worldwide (World Health Organization, 2023). However, the association between cognitive function and its changes with all-cause mortality lack adequate evidence from existing research.

Some studies have indicated that cognitive impairment in older adults is associated with an increased risk of all-cause mortality (Duan et al., 2020; Su et al., 2021; Diniz et al., 2022), but these studies only considered cognitive function at a single point in time. Research have shown that changes in cognitive function affect the risk of mortality in older adults. Recent cognitive decline or rapid cognitive decline has the higher risk of mortality while compared to stable (Bassuk et al., 2000; Hu et al., 2019). Furthermore, the joint progression of cognitive decline and physical frailty is associated with a higher mortality risk in older adults (Chen et al., 2023). Nonetheless, some studies report that, after adjusting for baseline cognitive function, a decline in cognitive ability does not add an extra mortality risk (Bruce et al., 1995). Research indicates that older adults have similar mortality rates when their cognitive decline reaches a higher degree, regardless of their baseline cognitive function, negating any life expectancy benefits of better baseline cognitive function (Tsui et al., 2022). Moreover, the dose-response relationships between baseline cognitive function, its changes, and mortality have not been accurately evaluated. In China, research on the association between cognitive function changes and mortality among community-dwelling older adults is lacking. Additionally, with significant changes in lifestyle, urbanization, and living environments in China over the past decade, the cognitive function of older adults and its changes may have also shifted, potentially affecting the association with mortality (Jia et al., 2020). This indicates the necessity for updated reports.

We are yet to reach a consensus on the association between cognitive function and mortality, and whether earlier measures of cognitive abilities confound this relationship. In this study, based on the Community Older Adults Health Survey follow-up cohort, we assessed the longitudinal associations of baseline cognitive function and cognitive changes over 1 year with subsequent all-cause mortality among Chinese older adults people aged 60 and above.

2 Materials and methods

2.1 Study design and participants

This study was based on the Community Older Adults Health Survey follow-up cohort, an ongoing prospective cohort targeting older adults residents in Chinese communities, specifically in Dalang Town, Dongguan City. Initiated in 2018, the cohort annually assesses individuals aged 60 years and above. Baseline data was gathered from surveys distributed in 2018, 2019, and 2020, with follow-up occurring the subsequent year, and ending at death or study closure (August 8th, 2023). Professional medical personnel conducted physical examinations, while face-to-face questionnaires were administered by trained students This study was approved by the Institutional Ethics Review Committee of the Affiliated Hospital of Guangdong Medical University (YJYS2022159), and written informed consent was obtained from all study participants.

A total of 6,848 participants aged 60 and above, without dementia at baseline were included. After excluding 733 individuals with incomplete information and 73 lost to follow-up, 6,042 participants were analyzed for the association between baseline cognitive function and all-cause mortality. A total of 3,293 individuals completed the second survey. After excluding 13 lost to follow-up, 3,280 participants were assessed for the association between cognitive function changes and all-cause mortality (**Figure 1**).

2.2 Outcomes

The survival status and date of death was queried from the Dongguan City death monitoring system using the resident identity card numbers after completion of baseline survey.

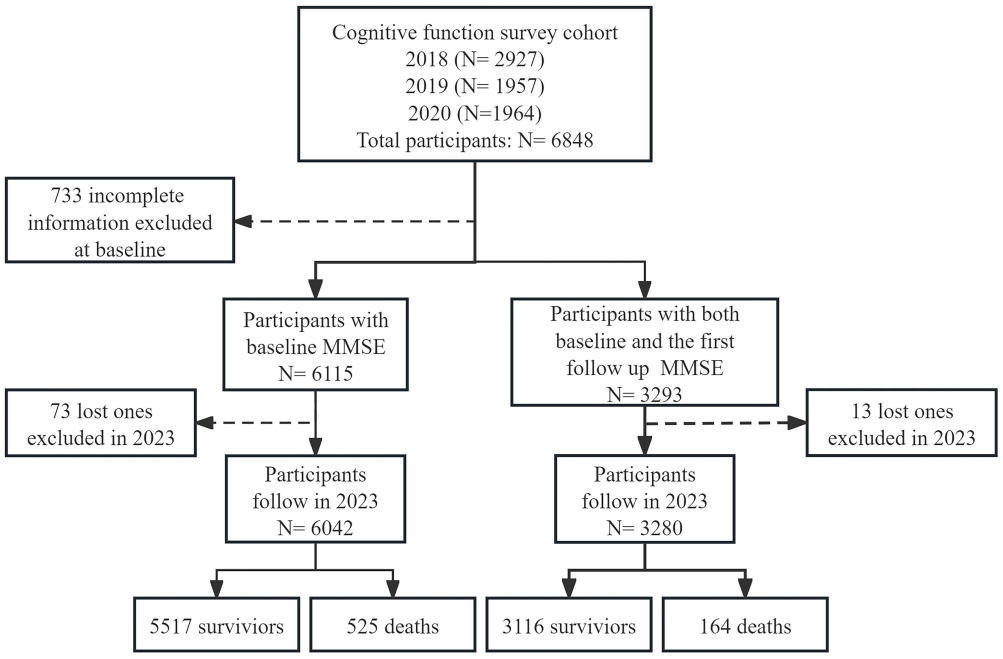

FIGURE 1
Flow chart of the study population.

2.3 Assessing baseline cognitive function and cognitive changes

Cognitive function was assessed using the Chinese version of the Mini-Mental State Examination (MMSE), which was adapted from the international MMSE (Folstein et al., 1975). This has been validated for reliability and validity within the Chinese population (Zhong et al., 2017; Gao et al., 2022). Assessments were conducted through face-to-face interviews without proxies. The MMSE score ranges from 0 to 30, with higher scores indicating better cognitive function: $\geq$ 26 was considered normal, 21–25 indicated mild cognitive impairment, and 0–20 denoted moderate to severe cognitive impairment (Perneczky et al., 2006).

Change in cognitive function was assessed using the rate of change in MMSE scores, calculated as [(baseline MMSE score - second survey MMSE score)/interval between the two surveys, years]. We categorized the rate of change of MMSE scores into four groups: cognitive improvement (rate less than zero), stable cognitive function (rate equal to zero), slow decline (rate greater than zero but less than or equal to the median decline), and rapid decline (rate greater than the median decline).

2.4 Covariates

We adjusted sociodemographic characteristics, health behaviors, and health status in the model. According to the literature (Lipnicki et al., 2019), these factors are considered potential confounders and were included as covariates. Covariates data was collected through questionaire surveys distributed at baseline. Sociodemographic characteristics included age (grouped), sex (man or woman), educational level (illiterate, primary school, junior high school and above), living situation (living alone, with spouse or partner, with children, with spouse and children, with other relatives or non-relatives), marital status (married, widowed, divorced, or never married), and satisfaction with housing. Health behaviors comprised smoking status (current smoker, former smoker, never smoked), alcohol intake (drinker, past, never), exercise frequency (daily, regularly, occasionally, never), and participation in community activities (mostly, sometimes, never). Health status was measured by body mass index (BMI) (underweight (<18.5), normal (18.5–23.9), overweight (24–27.9), obese ($\geq$ 28.0) (Jiao et al., 2020), common chronic diseases (self-reported hypertension, diabetes, heart disease, cerebrovascular disease), and mental state (including subjective difficulty concentrating, sadness, loneliness, memory issues, unwilling to go out, fatigue).

2.5 Statistical analysis

Cox proportional hazards models were established to determine the relationships between cognitive function and its changes with mortality. All study participants with missing data on the covariates were removed.

Cognitive function and its changes were modeled both as continuous variables (MMSE score; rate of change in MMSE score) and as categorical variables (normal cognitive function, mild impairment, or moderate to severe impairment; improvement, stable, slow decline, and rapid decline). Several models were performed: adjusting for (1) age and sex; (2) added educational level, living situation, marital status, satisfaction with housing, smoking, and health conditions; (3) for the association of changes in cognitive function and all-cause mortality, baseline MMSE score

was additionally adjusted. Data are reported as adjusted hazard ratios (HRs) and 95% confidence intervals (CIs).

Restricted cubic spline analysis was performed to examine the relationships between baseline MMSE scores and the rate of change in MMSE scores with mortality, using the median baseline MMSE score (25 points) and the rate of change in MMSE score (0.0%) as reference points, with knots at the 10th, 50th, and 90th percentiles. Survival curves were used to display the survival rate during the follow-up period for baseline cognitive function and changes in cognitive function.

Subgroup analyses were conducted to assess whether associations varied by age (60–69 years, 70–79 years, ≥80 years), and sex (men/women). Interaction terms between baseline cognitive function, cognitive function changes, and the above variables were added separately to the multivariate model. Further subgroup analysis was conducted to explore the associations of cognitive function changes and all-cause mortality at different levels of baseline cognitive function.

Sensitivity analyses addressed follow-up losses by including those lost to follow-up before the end of the study. Additionally, deaths occurring within 1 year of follow-up were excluded, to mitigate cognitive decline's potential bias.

A two-tailed *P*-value < 0.05 indicated statistical significance. Analyses were performed using R (version 4.2.2) for restricted cubic spline analyses and subgroup analyses; and SPSS 16.0 (IBM Corp., Inc., Chicago, IL, USA) for other analyses.

3 Results

3.1 Participant characteristics

The median age of the 6,042 participants at baseline was 70.0 years old. Approximately 39% were men, and 20% were illiterate, and 76% were married. At baseline, 56% (n = 3,383) of the participants had cognitive impairment, with 33% classified as mild and 23% as moderate to severe impairment. The overall median rate of change in MMSE scores (25th, 75th percentile) was 0.0 (−2.0, 2.0) points per year, with the normal cognitive function group showing a rate of 0.0 (−1.0, 3.0) points, the mild impairment group −1.0 (−4.0, 2.0) points, and the moderate to severe impairment group 0.0 (−4.0, 0.0) points. During a median follow-up period of 3.08 years, 525 deaths (8.69%) were observed (**Supplementary Table 1**).

3.2 Association between baseline cognitive function and mortality

Over 20,959 person-years of follow-up (normal cognitive function group: 8,867, mild impairment group: 7,135, moderate to severe impairment group: 4,957 person-years), the mortality rate was 2.50 per 100 person-years (with rates of 1.18, 1.93, and 5.69 per 100 person-years for the normal cognitive function, mild impairment, and moderate to severe impairment groups, respectively). Multivariate-adjusted models and restricted cubic splines demonstrated a linear monotonic negative association between baseline cognitive function (as a continuous variable) and all-cause mortality. The risk of death increased by 6% for each one-point decrease in MMSE score (adjusted *HR* = 1.06, 95% *CI*: 1.05–1.08) (**Figure 2A** and **Table 1**). Compared with the group with normal cognitive function at baseline, participants in both the mild impairment and moderate to severe impairment groups had an increased risk of all-cause mortality, with greater cognitive impairment associated with higher mortality risk (adjusted *HR* = 1.40, 95% *CI*: 1.07–1.82; *HR* = 2.49, 95% *CI*: 1.91–3.24, respectively) (**Figure 3A** and **Table 1**).

3.3 Association between changes in cognitive function and mortality

Mortality rates for cognitive improvement, stable, slow decline, and rapid decline groups were 1.31, 1.77, 1.61, and 2.35 per 100 person-years (with follow-up durations of 4,038, 2,321, 1,981, and 1,620 person-years, respectively). Multivariate-adjusted models and restricted cubic splines showed a linear monotonic negative association between the rate of cognitive function change and all-cause mortality. The risk of death was 5% higher for each one-point per year decrease in cognitive function change rate (adjusted *HR* = 1.05, 95% *CI*: 1.02–1.08) (**Figure 2B** and **Table 2**). Compared with participants with stable cognitive function, those with rapid decline had a 79% increased risk of death (adjusted *HR* = 1.79, 95% *CI*: 1.11–2.87). No significant difference in mortality risk between participants with cognitive improvement or slow decline and those with stable cognitive function (**Figure 3B** and **Table 2**).

3.4 Subgroup analysis

The subgroup analysis showed increased all-cause mortality risk for those with moderate to severe cognitive impairment and rapid cognitive decline. Individuals with moderate to severe impairment, across all age groups, faced a significantly higher mortality risk compared to those with normal cognitive function. Men with mild impairment, and both genders with severe impairment, showed increased mortality risks, more pronounced in men. No significant difference in mortality risk was observed across age and sex subgroups. (*P* for interaction ≥ 0.05) (**Figure 4A**).

Participants aged 70–79 and women experiencing rapid decline had a higher mortality risk than those with stable function. While rapid decline's impact on mortality wasn't significant for normal and severely impaired groups, those with severe impairment and slow decline faced higher mortality compared to those stable. Significant differences in mortality risk due to cognitive function changes were noted across baseline levels (*P* for interaction = 0.002), not by age or sex (*P* for interaction ≥ 0.05) (**Figure 4B**).

3.5 Sensitivity analysis

The results of the sensitivity analysis were similar to those of the main analysis, indicating robust findings when participants lost to follow-up before the end of the study were considered as censored or when participants who died within 1 year of follow-up were excluded (**Supplementary Table 2**).

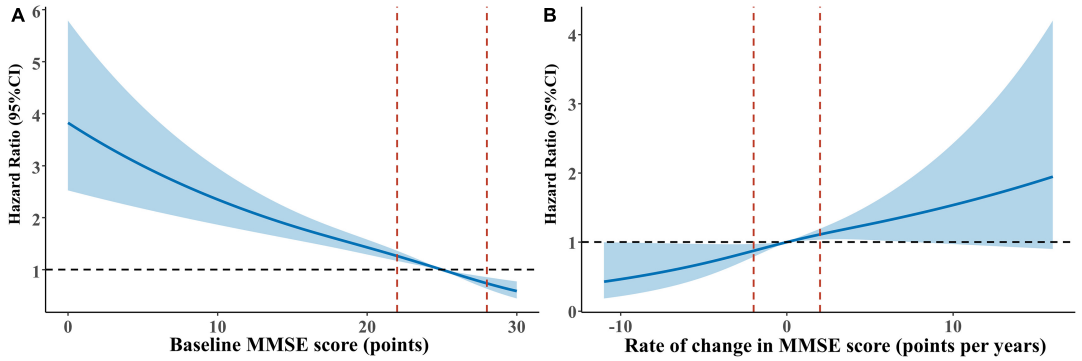

FIGURE 2
Restricted cubic splines for the association of baseline cognitive function and cognitive function change with all-cause mortality. **(A)** Baseline cognitive function and all-cause mortality: reference point is the median value of baseline MMSE score (25 points). **(B)** Cognitive function change and all-cause mortality: reference point is the median value of cognitive change (0.0%). (Age, sex, education, marital status, living arrangement, housing satisfaction, smoking status, drinking status, physical exercise, community activities, body mass index, hypertension, diabetes, heart disease, cerebrovascular disease, psychological status were adjusted for both panels **(A,B)**. Baseline MMSE score was additionally adjusted for panel **(B)** hazard ratios are indicated by solid lines and 95% confidence intervals by dashed lines, with knots placed at 10th, 50th, and 90th percentiles.

TABLE 1 The association between baseline cognitive function and all-cause mortality.

Categorical	Participants	Events	Model 1[a]		Model 2[b]	
			HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
MMSE score	6,042	525	1.08 (1.06, 1.09)	<0.001	1.06(1.05, 1.08)	<0.001
Normal	2,659	105	Reference	–	Reference	–
MCI	2,012	138	1.53 (1.18, 1.98)	0.001	1.40 (1.07, 1.82)	0.013
MSCI	1,371	282	3.08 (2.39, 3.96)	<0.001	2.49 (1.91, 3.24)	<0.001

HR, hazard ratio; CI, confidence interval; MMSE, Mini-Mental State Examination; MCI, mild cognitive impairment; MSCI, moderate to severe cognitive impairment.
Normal: MMSE score ≥ 26 points; MCI: MMSE score 21–25 points; MSCI: MMSE score ≤ 21points.
a: Adjusted for age and sex.
b: Additionally adjusted for education, marital status, living arrangement, housing satisfaction, smoking status, drinking status, physical exercise, community activities, body mass index, hypertension, diabetes, heart disease, cerebrovascular disease, psychological status.

4 Discussion

In this community-based prospective cohort study, we discovered a significant association between baseline cognitive function and all-cause mortality among individuals aged 60 years and above. First, we observed that the risk of death was significantly higher in older adults with mild and moderate to severe cognitive impairment at baseline, compared with those with normal baseline cognitive function. Moreover, when compared with stable cognitive function, we observed that rapid cognitive decline was associated with a higher all-cause mortality risk. Subgroup analysis confirmed the universality of these relationships among older adults of different age groups, sexes, and baseline cognitive states. We also observed significant differences in the association between cognitive function changes and all-cause mortality across different baseline levels of cognitive function. Compared to participants with normal cognitive function at baseline, individuals who had mild cognitive impairment at baseline and showed a rapid decline in cognitive function, as well as those with moderate to severe cognitive impairment at baseline but experienced a slower decline in cognitive function, both face a higher risk of all-cause mortality.

Our study results are consistent with some existing research. Lower baseline cognitive function is associated with an increased risk of all-cause mortality among older adults individuals. For instance, research conducted on Chinese community-dwelling older adults indicated that a one-point increase in MMSE score correlates with a 4% reduction in mortality risk (Su et al., 2021). Another study highlighted that individuals aged 65 and above with cognitive impairment had more than double the risk of death compared to those with normal cognitive function (Wang et al., 2020). Similar trends were observed in the Bambui Aging Cohort and Korean cohorts, where cognitive impairment was linked with a significantly higher mortality risk (Lee et al., 2018; Diniz et al., 2022). European studies further confirmed that poor cognitive ability is independently associated with increased mortality (Hayat et al., 2018). The mechanisms linking cognitive impairment with all-cause mortality are not entirely clear, but one possible explanation is that individuals with cognitive deficits may have difficulty recognizing and reporting their symptoms and signs, leading to delayed and insufficient diagnosis of health conditions. Additionally, impaired individuals may face challenges in treatment adherence, such as failing to follow medical instructions for medication and inappropriate dietary intake, and often lack physical activity, thereby increasing their future risk of death (Mossakowska et al., 2014).

Regarding changes in cognitive function, current studies suggest that rapid cognitive decline is associated with a higher risk of death (Rajan et al., 2014; Yaffe et al., 2016; Lv et al., 2019).

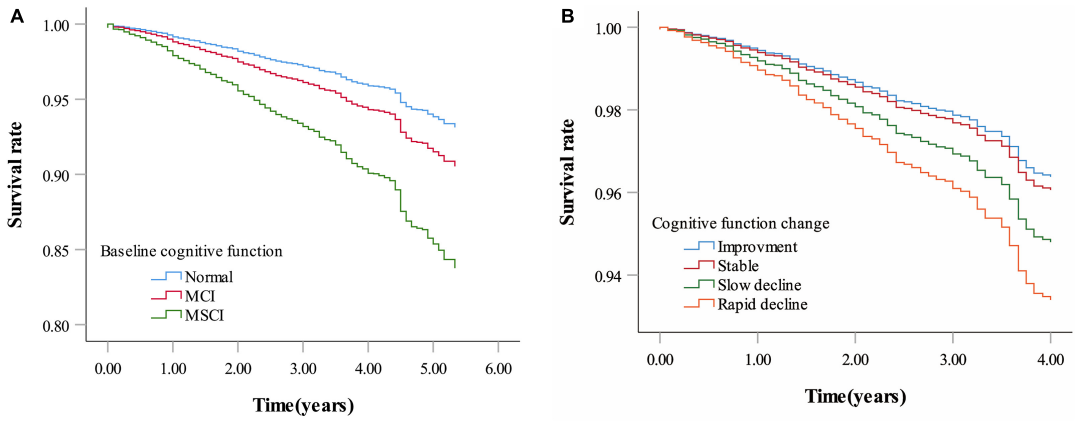

FIGURE 3
Survival rate by baseline cognitive function and cognitive function change. **(A)** Survival rate by baseline cognitive function. **(B)** Survival rate by cognitive function change. Age, sex, education, marital status, living arrangement, housing satisfaction, smoking status, drinking status, physical exercise, community activities, body mass index, hypertension, diabetes, heart disease, cerebrovascular disease, psychological status were adjusted for both panels **(A,B)**. Baseline MMSE score was additionally adjusted for panel **(B)** (MCI: Mild cognitive impairment; MSCI: Moderate to severe cognitive impairment. Normal: MMSE score ≥ 26 points; MCI: MMSE score 21–25 points; MSCI: MMSE score ≤ 21points. Improvement—rate of change in MMSE score less than zero; stable—rate of change in MMSE score equal to zero; slow decline—rate of change in MMSE score greater than zero but equal to or less than the median of the rate of change showing decline; rapid decline—rate of change in MMSE score greater than the median of the rate of change showing decline).

TABLE 2 The association between change in cognitive function and all-cause mortality.

Categorical	Partici-pants	Events	Model 1[a]		Model 2[b]		Model 3[c]	
			HR (95%CI)	*P*-value	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
Rate of change in MMSE score	3,280	164	1.02 (0.99, 1.06)	0.155	1.02 (0.99, 1.06)	0.180	1.05 (1.02, 1.09)	0.003
Improvement	1,247	53	0.82 (0.54, 1.23)	0.326	0.87 (0.57, 1.31)	0.492	0.93 (0.62, 1.42)	0.748
Stable	725	41	Reference	–	Reference	–	Reference	–
Slow decline	715	32	1.02 (0.54, 1.62)	0.935	1.00 (0.62, 1.62)	0.990	1.46 (0.90, 2.37)	0.129
Rapid decline	593	38	1.15 (0.74, 1.80)	0.531	1.18 (0.74, 1.87)	0.504	1.79 (1.11, 2.87)	0.016

HR, hazard ratio; CI, confidence interval; MMSE, Mini-Mental State Examination. Improvement, rate of change in MMSE score less than zero; stable, rate of change in MMSE score equal to zero; slow decline, rate of change in MMSE score greater than zero but equal to or less than the median of the rate of change in those showing decline; rapid decline, rate of change in MMSE score greater than the median of the rate of change in those showing decline.
a: Adjusted for age and sex.
b: Additionally adjusted for education, marital status, living arrangement, housing satisfaction, smoking status, drinking status, physical exercise, community activities, body mass index, hypertension, diabetes, heart disease, cerebrovascular disease, psychological status.
c: Additionally adjusted for baseline MMSE score.

The Chinese Longitudinal Healthy Longevity Survey (CLHLS) indicated that rapid cognitive decline was associated with a 75% higher mortality rate (Lv et al., 2019). Another longitudinal cohort study found that each unit decline in cognitive ability increased the risk of death by 90% (Rajan et al., 2014). Additionally, a cohort study of community-dwelling older women indicated that participants with the fastest rate of cognitive decline (the worst fifth, declining more than 0.14 percentage points per year) had a 28% increased risk of death (Yaffe et al., 2016). This suggests that rapid cognitive decline may be a marker of impending end of life. The relationship between cognitive decline and increased all-cause mortality risk can be explained through various biological and psychosocial mechanisms. Firstly, cognitive decline may be an early marker of neurodegenerative diseases such as Alzheimer's disease, which are themselves associated with higher mortality rates (Rajan et al., 2014). Research also suggests that psychosocial factors such as loneliness and lack of social support may be linked with accelerated cognitive decline and subsequent increased risk of death. These social factors can exacerbate cognitive decline by increasing stress responses and psychological stress (Ma et al., 2022). Additionally, vascular risk factors, vascular diseases, and mental health status have been reported to be associated with cognitive decline (Lipnicki et al., 2019; Ma et al., 2021a; Lu et al., 2022), but our study found no significant change after adjusting for these variables. Studies also suggest that inflammatory central nervous system diseases, cerebrovascular diseases, toxic-metabolic encephalopathies, and central nervous system tumors can cause rapid cognitive decline (Hermann and Zerr, 2022), suggesting that these factors might concurrently lead to cognitive decline and death, or that cognitive decline, once initiated, may accelerate the dying process. These suggestions warrant further investigation.

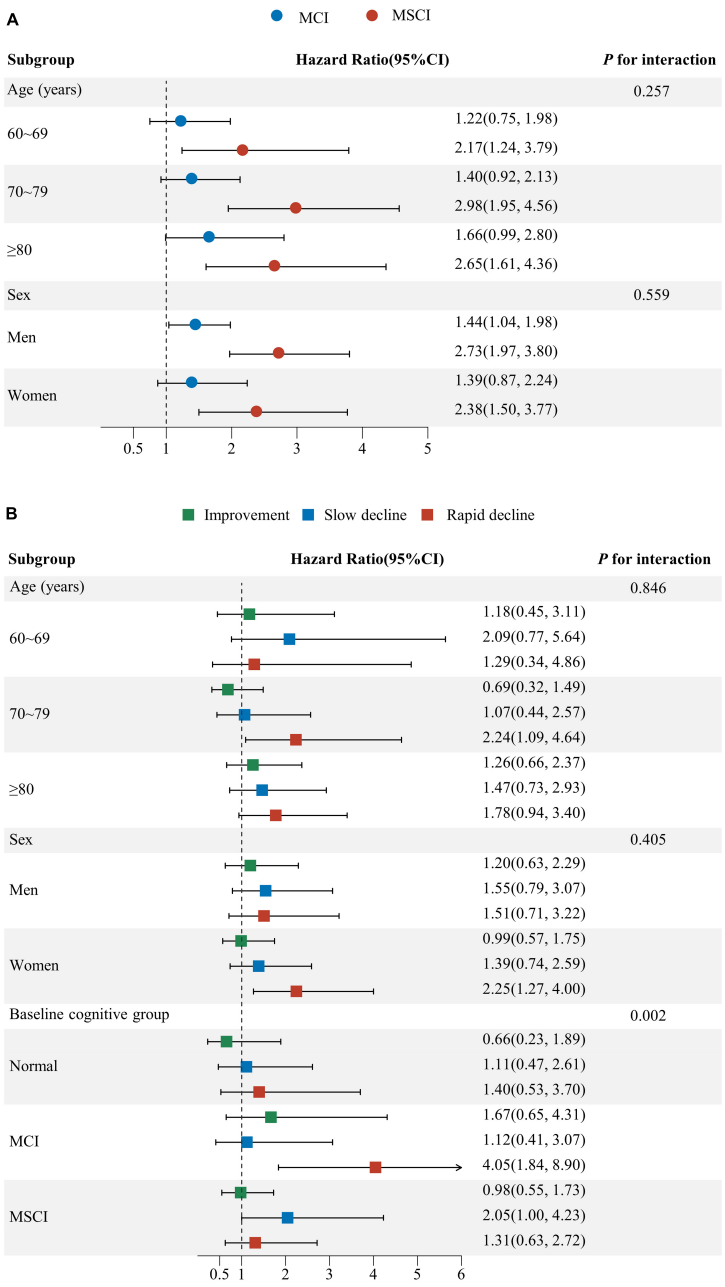

FIGURE 4
Subgroup analysis for the association of baseline cognitive function and cognitive function change with all-cause mortality. **(A)** Subgroup analysis by age, sex for baseline cognitive function; **(B)** Subgroup analysis by age, sex and baseline cognitive function for cognitive function change. Age, sex, education, marital status, living arrangement, housing satisfaction, smoking status, drinking status, physical exercise, community activities, body mass index, hypertension, diabetes, heart disease, cerebrovascular disease, psychological status were adjusted for Subgroup analysis **(A,B)**. Baseline MMSE score was additionally adjusted for subgroup analysis **(B)** (CI: confidence interval; MCI: mild cognitive impairment; MSCI: moderate to severe cognitive impairment. Normal: MMSE score ≥ 26 points; MCI: MMSE score 21–25 points; MSCI: MMSE score ≤ 21points. Improvement—rate of change in MMSE score less than zero; stable—rate of change in MMSE score equal to zero; slow decline—rate of change in MMSE score greater than zero but equal to or less than the median of the rate of change showing decline; rapid decline—rate of change in MMSE score greater than the median of the rate of change showing decline).

In subgroup analysis, we observed the impact of age on the association between cognitive function and all-cause mortality. Adults aged 70–79 years with rapid cognitive decline had a higher risk of all-cause mortality, consistent with previous research (Schupf et al., 2005; Wu et al., 2014). Cognitive decline in relatively young older adults may reflect processes directly related to an increased risk of death, such as the rate of biological aging rather than chronological aging (Bassuk et al., 2000). The association between cognitive function and all-cause mortality was not significant in individuals aged 80 and above, possibly indicating survival bias. We also found that participants with mild cognitive impairment at baseline who experienced rapid cognitive decline, as well as those with moderate to severe cognitive impairment at baseline but experienced a slower

decline in cognitive function, both face a higher risk of all-cause mortality. This finding highlights the urgency of early identification and intervention in cognitive impairments, as well as the importance of monitoring cognitive function changes to reduce the risk of mortality. Future work should focus on seeking effective interventions and how to tailor these interventions for different populations (such as subgroups divided by age, gender, and baseline health status). Additionally, exploring the potential biomarkers and mechanisms between cognitive decline and frailty and mortality risk will provide us with a deeper understanding.

This study had several strengths, including the community-based prospective cohort of older adults and it was the first to assess the association between cognitive function and its changes with all-cause mortality from both continuous and categorical perspectives. The findings highlighted the close association of cognitive function and its changes with all-cause mortality among older adults. Given the dynamic nature of older adults' cognitive function, early screening and identification of cognitive decline to formulate appropriate prevention strategies to halt or delay cognitive decline are crucial (Clare et al., 2017), and this provides a basis for further research.

The study's insights are limited by its geographical focus on Dongguan City, China, potentially affecting the generalizability to wider populations. The observational spans—4 years for mortality and 3 for cognitive changes—may not fully reveal long-term outcomes. Diagnosing dementia through cognitive assessments may overlook undiagnosed cases, risking misclassification bias. Participant exclusions and unmeasured confounders like diet and inflammation could bias results, necessitating caution. Thus, broader, long-term studies are needed to validate our findings.

5 Conclusion

Among Chinese community-dwelling older adults individuals aged 60 years and above, mild and moderate to severe cognitive impairment, as well as rapid cognitive decline, were associated with a higher risk of all-cause mortality. Furthermore, the baseline cognitive function status affected the association between changes in cognitive function and all-cause mortality. Future efforts should focus on regular cognitive assessments of older adults, monitoring disease progression and mortality, and developing preventive strategies to halt or delay the process of cognitive decline and reduce the associated mortality risk.

Data availability statement

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

Author contributions

SJL: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review and editing. XH: Investigation, Writing – review and editing. LW: Investigation, Writing – review and editing. XT: Investigation, Writing – review and editing. YO: Investigation, Writing – review and editing. WJ: Investigation, Writing – review and editing. YY: Investigation, Writing – review and editing. JY: Investigation, Writing – review and editing. KC: Investigation, Writing – review and editing. XiZ: Investigation, Writing – review and editing. XuZ: Investigation, Writing – review and editing. JX: Investigation, Writing – review and editing. SBL: Investigation, Writing – review and editing. MY: Conceptualization, Supervision, Writing – review and editing. JN: Conceptualization, Supervision, Writing – review and editing. CP: Writing – review and editing, Validation. XC: Writing – review and editing, Validation.

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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.2024.1419235/full#supplementary-material

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Enhancing predictive validity of motoric cognitive risk syndrome for incident dementia and all-cause mortality with handgrip strength: insights from a prospective cohort study

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Background: This study aimed to assess whether integrating handgrip strength (HGS) into the concept of motoric cognitive risk (MCR) would enhance its predictive validity for incident dementia and all-cause mortality.

Methods: A cohort of 5, 899 adults from the Health and Retirement Study underwent assessments of gait speed, subjective cognitive complaints, and HGS were involved. Over a 10-year follow-up, biennial cognitive tests and mortality data were collected. Cox proportional hazard analyses assessed the predictive power of MCR alone and MCR plus HGS for incident dementia and all-cause mortality.

Results: Patients with MCR and impaired HGS (MCR-HGS) showed the highest adjusted hazard ratios (AHR) for dementia (2.33; 95% CI, 1.49–3.65) and mortality (1.52; 95% CI, 1.07–2.17). Even patients with MCR and normal HGS (MCR-non-HGS) experienced a 1.77-fold increased risk of incident dementia; however, this association was not significant when adjusted for socioeconomic status, lifestyle factors, and medical conditions. Nevertheless, all MCR groups demonstrated increased risks of all-cause mortality. The inclusion of HGS in the MCR models significantly improved predictive discrimination for both incident dementia and all-cause mortality, as indicated by improvements in the C-statistic, integrated discrimination improvement (IDI) and net reclassification indices (NRI).

Conclusion: Our study underscores the incremental predictive value of adding HGS to the MCR concept for estimating risks of adverse health outcomes among

older adults. A modified MCR, incorporating HGS, could serve as an effective screening tool during national health examinations for identifying individuals at risk of dementia and mortality.

KEYWORDS

motoric cognitive risk syndrome, all-cause mortality, handgrip strength, Cox regression, net reclassification indices, integrated discrimination improvement

Introduction

The global increase in both the elderly population and life expectancy has led to a significant rise in dementia cases, presenting a substantial public health challenge. Approximately 55 million people worldwide are affected by dementia, with the economic impact estimated at 1.1% of the global gross domestic product, a figure that is expected to double by 2030 (WHO, 2023). Projections indicate that the number of people living with dementia will rise from 55 million in 2019 to 139 million by 2050, with associated costs likely to surpass $2.8 trillion annually by 2030 (Alzheimer's Disease International, 2023). In light of these projections, enhancing our understanding of dementia risk factors is essential, particularly through prospective, population-based studies. Although modifiable risk factors such as body mass index, alcohol consumption, smoking, poor diet, and physical activity have been linked to dementia (Livingston et al., 2020), data on markers of cognitive and physical capability, including subjective cognitive decline (Slot et al., 2019), gait speed (Dumurgier et al., 2017), muscular strength (Carson, 2018), or their combination (Chen et al., 2012; Montero-Odasso et al., 2020), are still limited.

Motoric cognitive risk syndrome (MCR) is a predementia condition characterized by both slow gait and subjective cognitive decline in elderly individuals without dementia (Verghese et al., 2013). Studies have shown that MCR prevalence varies from 2 to 18% in different countries (Congcong and Linping, 2021), with a pooled prevalence of 9.7% among individuals aged 60 and older across 17 countries (Verghese et al., 2014). MCR is linked to an increased risk of multiple falls (RR 1.77, 95% CI 1.25, 2.51) (Callisaya et al., 2016), incident dementia (Verghese et al., 2014; Beauchet et al., 2020), disability (Chhetri et al., 2017) and all-cause mortality (Bortone et al., 2022; Pajuelo-Vasquez et al., 2023). These findings highlight that MCR involves both cognitive and mobility impairments, posing challenges for families and healthcare systems. While slow gait in older adults has multiple causes (Camicioli et al., 1998; Verghese et al., 2007), including cognitive complaints in the MCR criteria improves its predictive validity (Verghese et al., 2014). Although informant reports can help in identifying dementia, their reduced sensitivity might overlook solitary older adults, thus narrowing the group of older adults considered at risk. The variability in the criteria for MCR is balanced by mutual enhancements, making MCR a more effective predictor of cognitive decline than either slow gait or cognitive complaints alone.

Physical capability, also known as physical functioning, describes an individual's ability to perform daily physical tasks. Objective measures such as handgrip strength (HGS), walking speed, chair rising, and standing balance are not only indicators of physical capability but also markers for current and future health outcomes (Cooper et al., 2011), including all-cause mortality (Cooper et al., 2010). However, research into physical capability and dementia faces challenges including small sample sizes, short follow-up periods, and inadequate adjustment for confounding factors. Additionally, previous studies have shown the incremental predictive power of including chair rising or standing balance tests in established MCR frameworks (Sekhon et al., 2019b; Chung and Byun, 2023), but their prognostic value for all-cause mortality has not been fully explored. Muscle strength, especially HGS, is a valuable marker of wellbeing, associated with the ability to perform activities of daily living (ADLs). In the context of MCR, which involves subjective cognitive concerns and a slowing of gait speed while maintaining independence in basic ADLs, a decline in HGS might be overlooked without careful attention to MCR patients. HGS, assessed using a hand-held dynamometer, is favored for its simplicity, reliability, and cost-effectiveness, making it a preferred method in epidemiological studies. Several studies have demonstrated that HGS is an effective screening tool for predicting adverse outcomes and mortality in middle-aged and elderly populations (Bohannon, 2008; Cooper et al., 2010), as well as in very old community-dwelling populations (Ling et al., 2010). Furthermore, recent studies suggest that HGS may indicate brain health and cognitive decline (Alfaro-Acha et al., 2006; McGrath et al., 2019), although these associations could be prone to reverse causation bias. Further research into the links between HGS, MCR, and adverse health outcomes in large-scale population studies is needed to clarify its potential prognostic value.

The relationship between HGS, MCR, cognitive function, and gait in older adults has increasingly attracted scholarly interest. Jia et al. (2023) identified a strong link between HGS and MCR, suggesting that early identification of HGS asymmetry and decline might facilitate the prevention and treatment of MCR. Similarly, Zhang et al. (2020) found a negative correlation between HGS and the prevalence of MCR in older men, noting that more significant reductions in HGS were associated with an increased risk of MCR. Although various subtypes of MCR have been identified based on quantitative gait parameters (Allali et al., 2016) or cognitive subdomains (Bortone et al., 2022), the potential of HGS to predict future all-cause dementia and mortality has not yet been investigated. Moreover, to the best of our knowledge, no studies have concurrently assessed whether MCR or MCR-HGS estimates dementia and all-cause mortality in a large, nationwide, community-based population, or whether MCR patients with normal HGS have improved predictive accuracy over using MCR alone.

Addressing these research gaps, we proposed a modified MCR framework that incorporates both MCR and HGS, based on well-established criteria, and utilized data from a prospective cohort of community-dwelling older adults without dementia. We investigated the concurrent validity of MCR and MCR-HGS in predicting incident dementia and all-cause mortality. Our analysis also examined whether this modified MCR framework, including HGS, offers additional predictive value for incident dementia and all-cause mortality compared to using MCR alone in this nationwide cohort study.

Materials and methods

Sample

This study utilized data from Waves 10–15 of the Health and Retirement Study (HRS), a comprehensive longitudinal study exploring the aging process in Americans aged 51 and older. The HRS employs a multi-stage probability sampling method to achieve a nationally representative sample of this demographic (Heeringa and Connor, 1995). It gathers self-reported information on demographics, chronic health conditions, daily activities, disability status, and other health determinants initially and biennially thereafter. Starting in 2006, the HRS introduced an enhanced face-to-face interview including physical performance tests, biomarker collections, and a leave-behind questionnaire on psychosocial issues. In 2006, half of the households were randomly selected for the enhanced interview, with the remaining households included in 2008, a method maintained in later waves. Additional details on the HRS's recruitment tactics and structure are provided in earlier publications (Heeringa and Connor, 1995).

The baseline analysis merged data from the 2008–2009 (Wave 9) and 2010–2011 (Wave 10) cycles, the first time participants were queried about Alzheimer's disease (AD) or dementia, replacing previous questions about "memory-related disease." Mortality information has been available since 2011. A total of 22,034 participants completed Wave 10 and were tracked biennially until 2020–2021 (Wave 15). The University of Michigan Institutional Review Board approved the HRS study. The final sample included 5,089 individuals who were 65 years or older, had comprehensive baseline data on MCR measures, reported no difficulties with ADLs or instrumental activities of daily living (IADLs) at baseline, were not diagnosed with AD or dementia initially, and were alive in 2010/2011. Figure 1 illustrates the flow of participants through each stage of selection based on these criteria.

Measures

Motoric cognitive risk syndrome

MCR syndrome was defined by the presence of subjective cognitive complaints and slow gait in older adults who did not have a mobility disability or dementia (Verghese et al., 2012, 2013, 2014). In the HRS, gait speed, measured in meters per second, was determined by the time it took to walk a 2.5-meter course at a normal pace within participants' homes. Slow gait was defined as performance at least one standard deviation (SD) below the age and sex-adjusted mean, a criterion previously used in the HRS to define MCR (Ayers and Verghese, 2016). Details of the cut-off points for slow gait were provided in Supplementary Table 1.

Subjective cognitive complaints were assessed using two questions: 1. "How would you rate your memory at the present time? Would you say it is excellent, very good, good, fair, or poor?" and 2. "Compared with the previous interview, would you say your memory is now better, about the same, or worse than it was?" Responses of "fair" or "poor" to the first question, or "worse" to the second, were used to identify cognitive complaints.

Handgrip strength

Muscle strength was evaluated using the average of two handgrip strength (HGS) measurements with a dynamometer on the dominant hand. The Smedley spring-type handgrip dynamometer (Scandidact; Odder, Denmark) was utilized for this purpose. Prior to testing, trained interviewers explained the HGS protocols and adjusted the dynamometer to fit the hand size of each participant. A practice trial was conducted with the participant's arm positioned at the side and the elbow flexed at 90 degrees. Following the identification of the dominant hand, participants were instructed to squeeze the dynamometer with maximal effort, starting with the non-dominant hand. HGS was measured twice on each hand, alternating between hands. Participants who were unable to stand or position their arm while grasping the dynamometer were allowed to be seated and rest their upper arm on a supporting object during the HGS testing. Further details on the HGS measurement protocol in the HRS are available elsewhere (Crimmins et al., 2016). Weakness was identified when grip strength fell below thresholds adjusted for Body Mass Index (BMI) and gender, as established in the Cardiovascular Health Study (CHS) (Fried et al., 2001). Details of the criteria for weakness definition were also provided in Supplementary Table 1. Participants were noted as having missing data for physical measures if they were unable to perform the assessments due to lack of appropriate facilities or equipment, or due to recent surgery.

Dementia

Biennial cognitive function tests were administered by trained HRS interviewers either in-person or via telephone using the Modified Telephone Interview for Cognitive Status (TICS-m), which is a global cognition test based on the Mini-Mental State Examination. The TICS-m includes immediate and delayed 10-noun free recall tests (score range: 0–10 for each), a serial seven subtraction test (score range: 0–5), and a counting backward from 20 test (score range: 0–2). Higher scores indicate better cognitive performance. During each assessment, HRS participants were classified as having normal cognition, mild cognitive impairment (MCI), or dementia based on established thresholds and comprehensive evaluations, including expert clinician adjudication from the Aging, Demographics, and Memory Study (ADAMS), a dementia sub-study within the HRS framework. The diagnosis of dementia was based on physician-diagnosed dementia and TICS scores between 0 and 6 (Langa et al., 2005; Crimmins et al., 2011).

All-cause mortality

Mortality data were collected, including the year and month of death, sourced from an exit interview or the core interview of a spouse or partner.

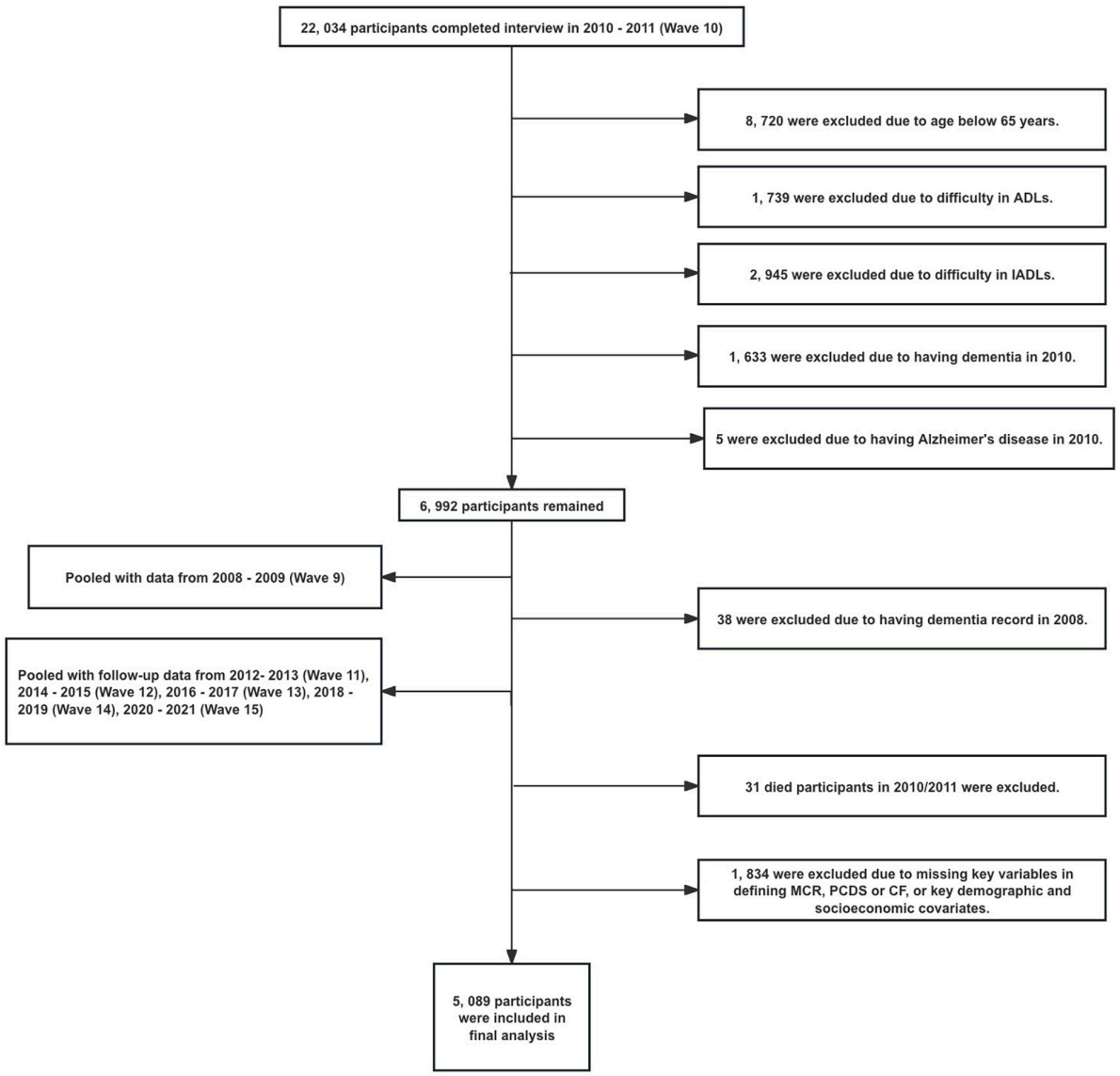

FIGURE 1
Study flowchart of participant selection.

Statistical analysis

We assessed differences between the non-MCR groups, MCR patients with normal handgrip strength (MCR-non-HGS), and MCR patients with impaired handgrip strength (MCR-HGS) using a two-sided, independent *t*-test and the χ^2 test. To evaluate the impact of MCR and MCR-HGS on all-cause dementia and mortality, Cox proportional hazards regression analysis was employed. The observation period ranged from the index date to the earliest of the following events: onset of dementia, death, or the end of the observation period on 31 December 2018. Adjusted hazard ratios (AHRs) were calculated for health controls, MCR-non-HGS, and MCR-HGS to predict the onset of dementia and all-cause mortality, initially in an unadjusted model. Adjustments for covariates were made in two stages: Model 1 adjusted for age and gender, while Model 2 further incorporated socioeconomic factors (education level, marital status), lifestyle factors (excessive drinking), and medical conditions (hypertension and diabetes). The predictive accuracy of all models was assessed using discrimination, which is defined by the model's ability to differentiate between individuals who develop dementia and those who do not, quantified using Harrell's C-statistic with survival taken into account. To determine the extent of the incremental predictive value added by including HGS (as a continuous variable) to the MCR base model, net reclassification indices (NRI) and integrated discrimination improvement (IDI) were calculated and compared.

Several sensitivity analyses were conducted to verify the stability of our findings. First, to focus on new cases and reduce reverse causation bias, individuals diagnosed with dementia or who died within two years of follow-up were excluded (Sensitivity analysis I). Second, to address missing data, ten imputed data sets were generated using the multiple imputation by chained equations (MICE) method (Wulff and Jeppesen, 2017) for covariates with missing values, and the main analyses were reperformed to

check robustness (Sensitivity analysis II). Statistical analyses were conducted using two-tailed tests with a significance level set at $P < 0.05$ and 95% confidence intervals, employing Stata (version 17) for all statistical procedures.

Results

Baseline characteristics

The initial characteristics of the study participants are detailed in Table 1. The cohort initially included 5,089 individuals, with prevalence rates of 2.3% for MCR-non-HGS patients and 1.1% for MCR-HGS patients. Among these, MCR-HGS patients were the oldest, with an average age of 77.44 ± 7.37 years and the highest percentage of males at 57.89% in this group. Over the follow-up period, 1,542 patients (30.3%) died. The incidence rates of all-cause dementia were 35.3% for MCR-non-HGS patients and 56.1% for MCR-HGS patients.

Relationships of MCR, MCR-non-HGS patients, and MCR-HGS patients with incident dementia and all-cause mortality

Table 2 shows significant relationships between MCR and MCR-HGS and increased risks of incident dementia, and all models reveal increased risks of all-cause mortality (all p-values < 0.001). MCR-HGS had the highest AHRs for both outcomes, with 2.33 (95% CI, 1.49–3.65) for dementia and 1.52 (95% CI, 1.07–2.17) for mortality. MCR-non-HGS patients had a 1.77-fold increased risk of incident dementia (95% CI, 1.21–2.59) when adjusted for age and gender; however, this relationship was not significant when further adjusted for socioeconomic status, lifestyle factors, and medical conditions. Still, a persistent increased risk of all-cause mortality was noted, with a 1.40-fold increase (95% CI, 1.03–1.91) after comprehensive adjustments. For MCR-HGS patients, AHRs for dementia and mortality consistently decreased across models, while for all MCR patients, AHRs initially increased from the unadjusted model to adjusted Model 1, then decreased with further adjustments. Sensitivity analyses I (Supplementary Table 2) and II (Supplementary Table 3) consistently indicated an elevated risk of dementia for MCR and MCR-HGS patients, as well as increased mortality across all groups.

Added value of HGS to MCR syndrome in predicting incident dementia and all-cause mortality

Compared with MCR alone, the discrimination (C-statistic) for predicting incident dementia and all-cause mortality is higher when HGS is included (MCR+HGS), as shown in Table 3. The C-statistic significantly increased from 0.7142 for MCR alone to 0.7194 for MCR+HGS in predicting incident dementia (p-value = 0.023), and from 0.7114 for MCR alone to 0.718 for MCR+HGS in predicting all-cause mortality (p-value < 0.001). Additionally, incorporating HGS into the multivariate model improves discrimination (IDI = 0.0022 for incident dementia and 0.01 for all-cause mortality, p-value < 0.01). The NRI also underscores this improved discrimination when continuous HGS is added to MCR prediction models (NRI = 0.0751 for incident dementia, p-value = 0.0445; NRI = 0.1735 for all-cause mortality, p-value < 0.0001).

The Kaplan–Meier curve, depicted in Figure 2, illustrates the duration to incident dementia or all-cause mortality, stratified by MCR-non-HGS, MCR-HGS, and healthy controls, with adjustments made for all covariates. Both curves show a decline over the follow-up period, with a notably pronounced decrease observed among patients (all p-values for log-rank tests < 0.0001).

Discussion

To our knowledge, this is the first study to assess the benefit of integrating HGS with MCR in predicting incident dementia and all-cause mortality among a large, representative cohort of older adults across a follow-up period exceeding 10 years. Our results corroborate previous studies on the accuracy of MCR in estimating dementia risk, despite variations in study populations, follow-up lengths, and definitions of MCR and dementia diagnosis. We demonstrate the discriminative and predictive power of the MCR-HGS combination in forecasting future adverse health outcomes, thereby enabling the early identification of older adults in need of further clinical evaluation and those at increased risk of developing dementia. Additionally, we found that MCR patients with normal handgrip strength do not show a heightened risk of incident dementia following comprehensive adjustment, highlighting the improved clinical utility and applicability of the MCR-HGS approach, especially in environments where handgrip strength assessment is practical.

The AHR for all-cause dementia among MCR-HGS patients (2.33; 1.49–3.65) was comparable to that reported for MCR in a multicohort study (AHR = 1.93) (Verghese et al., 2014), and exceeded the rates found for other modified MCR concepts such as MCR-TUG (timed-up-and-go test, AHR = 2.03) and MCR-OLS (one-leg-standing test, AHR = 2.05) from previous studies (Chung and Byun, 2023). However, we found no significant associations between MCR-non-HGS and incident dementia after adjusting for all confounders, which suggests that diminished muscle strength might act as an early marker of impaired neural processing (Alfaro-Acha et al., 2006), offering greater sensitivity and precision in measuring cognitive function than subjective cognitive decline. In contrast, an MCR subtype characterized using the 5-times-sit-to-stand, which includes a balance component, was less predictive of cognitive decline than MCR defined by slow gait in earlier studies (Sekhon et al., 2019b). The complex nature of maximum grip strength, which requires intricate coordination of numerous motor units and brain networks, was highlighted (Jia et al., 2023). Previous research has also connected MCR with reduced gray matter volume, particularly in regions such as the premotor cortex and prefrontal areas, alongside lacunar lesions in the frontal lobe, indicating a better capability to predict neurodegenerative cortical dementia over subcortical types (Beauchet et al., 2016;

TABLE 1 Characteristics of included patients at baseline according to MCR status and handgrip strength.

Variable	Non-MCR (n = 4913)	MCR patients with normal handgrip strength (n = 119)	MCR patients with impaired handgrip strength (n = 57)	p-value
Age	74.74 ± 6.13	72.62 ± 4.97	77.44 ± 7.37	< 0.001
Male	2, 085 (42.44%)	46 (38.66%)	33 (57.89%)	0.044
Educational background				
Illiterate	764 (15.55%)	35 (29.41%)	21 (36.84%)	< 0.001
Primary or above	2, 911 (59.25%)	73 (61.34%)	29 (50.88%)	
Secondary or above	1, 238 (25.20%)	11 (9.24%)	7 (12.28%)	
Married	3, 053 (62.14%)	61 (51.26%)	34 (59.65%)	0.051
Medical history				
Hypertension	1, 669 (33.97%)	30 (25.21%)	56 (75.68%)	0.067
Diabetes	1, 081 (22.00%)	38 (31.93%)	11 (19.30%)	0.032
Excessive drink	3, 488 (71.00%)	100 (84. 03%)	43 (75.44%)	0.006
Incident all-cause dementia	814 (16.59%)	28 (23.53%)	20 (35.71%)	< 0.001
Mortality	1, 468 (29.88%)	42 (35.29%)	32 (56.14%)	< 0.001

TABLE 2 Multivariable analysis for the prediction of dementia and all-cause mortality including baseline characteristics.

	Unadjusted HR[a] (95% CI)	Model 1[b]: adjusted HR (95% CI)	Model 2[c]: adjusted HR (95% CI)
All-cause dementia			
No	Ref.	Ref.	Ref.
MCR patients with normal handgrip strength	1.37 (0.94–2.00)	1.77 (1.21–2.59)	1.33 (0.91–1.95)
MCR patients with impaired handgrip strength	3.21 (2.06–5.01)	2.78 (1.78–4.34)	2.33 (1.49–3.65)
MCR	1.80 (1.34–2.41)	2.09 (1.56–2.80)	1.63 (1.21–2.18)
All-cause mortality			
No	Ref.	Ref.	Ref.
MCR patients with normal handgrip strength	1.13 (0.84–1.54)	1.58 (1.16–2.15)	1.40 (1.03–1.91)
MCR patients with impaired handgrip strength	2.32 (1.64–3.30)	1.68 (1.18–2.38)	1.52 (1.07–2.17)
MCR	1.46 (1.15–1.84)	1.62 (1.28–2.05)	1.33 (1.05–1.68)

[a]HR, hazard ratio. [b]Model 1 adjusted for age and gender. [c]Model 2 further adjusted for educational background, marital status, excessive drinking, hypertension and diabetes.

TABLE 3 Modification of the predictive value after adding the handgrip strength to the MCR syndrome.

	Adjusted HR[a] (95% CI)[b]	C-statistic	Δ C-statistic	p-value	IDI[c]	p-value	NRI[d]	p-value
All-cause dementia								
MCR	1.63 (1.21–2.19)	0.7142						
MCR+handgrip strength	1.53 (1.14–2.06)	0.7194	0.0052	0.023	0.0022	0.0036	0.0751	0.0445
All-cause mortality								
MCR	1.45 (1.15–1.84)	0.7114						
MCR+handgrip strength	1.33 (1.05–1.68)	0.718	0.0066	< 0.001	0.01	< 0.0001	0.1735	< 0.0001

[a]HR, hazard ratio. [b]95% CI, 95% confidence interval. [c]IDI, integrated discrimination improvement. [d]NRI, net reclassification indices.

Sekhon et al., 2019a). Moreover, neural networks associated with MCR displayed atrophy in gray matter areas involved in gait control, particularly in planning and modulation, rather than in motor execution. Yet, detailed studies on the structural relationships between HGS and MCR within the central nervous system are still scarce. Considering the ease of measuring HGS,

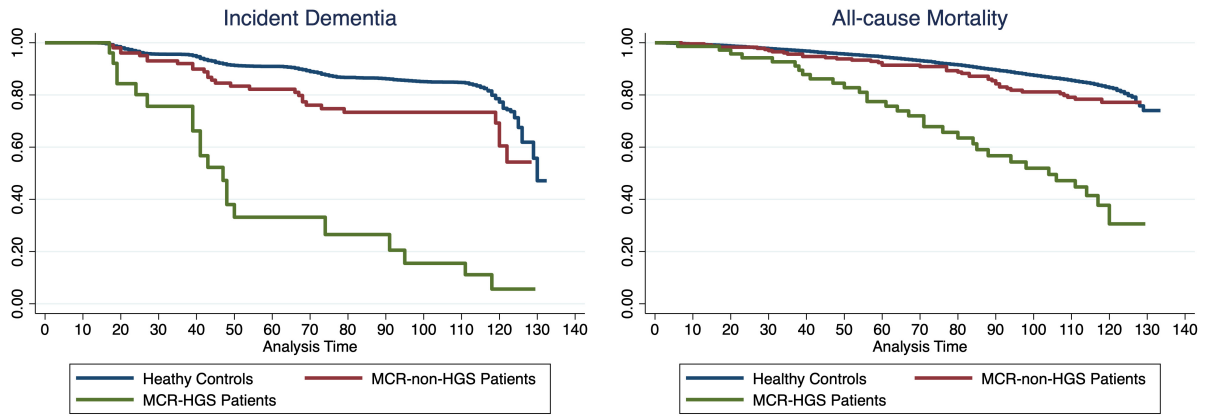

FIGURE 2
Kaplan-Meier Survival Curve showing the proportion of dementia-free or survival participants during follow-up between MCR-non-HGS, MCR-HGS patients and healthy controls.

MCR-HGS could be advocated as a valuable diagnostic tool for predicting adverse outcomes in older adults. More research is necessary to determine the pathological importance of HGS and to clarify the prognostic significance of MCR-HGS in forecasting future all-cause dementia and mortality (Blumen et al., 2019).

In our study, the AHR for all-cause mortality among MCR-HGS patients was 1.52 (95% CI 1.07–2.17), a magnitude similar to those reported for MCR syndrome (Ayers and Verghese, 2016), moderate-to-severe cognitive impairment (Kelman et al., 1994; Sachs et al., 2011; Perna et al., 2014), and other predementia syndromes (Gussekloo et al., 1997; Park et al., 2014). In contrast to incident dementia, a consistent and significant association was observed between MCR-non-HGS and all-cause mortality across all models. Specifically, the mortality risks were 1.58 (95% CI 1.16–2.15) and 1.40 (95% CI 1.03–1.91) in adjusted Models 1 and 2, respectively. Predementia syndromes may elevate mortality risk by exacerbating geriatric syndromes that are associated with higher mortality in the aging population. For instance, cognitive impairment can increase the risk of life-threatening events such as delirium (Inouye, 2006), depression (Pellegrino et al., 2013), medication mismanagement (Hayes et al., 2009), and falls (Doi et al., 2015). Previous studies have shown that MCR is associated with a higher risk of developing Alzheimer's disease dementia and vascular dementia subtypes (Verghese et al., 2013, 2014). Moreover, pathologies related to dementia, including cerebrovascular disease and regional brain atrophy particularly in the frontal lobes, have been linked to increased mortality risks (Nägga et al., 2014).

MCR-HGS shows incremental predictive validity for all-cause mortality beyond that of MCR alone in our study. While both low HGS and slow gait speed are associated with a higher risk of mortality (Cooper et al., 2010), previous studies have not investigated the combined effects of HGS, gait speed, and subjective cognitive complaints on mortality. Several possible reasons can explain this observation. First, muscle weakness associated with aging may indicate chronic disease (Guadalupe-Grau et al., 2015) and a decline in physical function (Bohannon, 2008; Bouchard et al., 2009), both of which are connected to a higher risk of mortality (Yerrakalva et al., 2015; Pavasini et al., 2016). Second, changes in HGS can more quickly reflect nutritional deficiencies or recovery compared to alterations in muscle mass (Norman et al., 2011). Malnutrition can heighten mortality risk, with changes in related biomarkers potentially making elderly patients more susceptible to infections and associated mortality (Yoshikawa and High, 2001; Norman et al., 2011). Third, simultaneous declines in cognitive and physical capabilities correlate with reduced hemoglobin levels (Atkinson et al., 2005), which may directly reduce oxygen delivery to the brain, peripheral nerves, and muscles. Moreover, poor physical performance is linked to significant endocrine dysfunction, inflammation, and oxidative stress, all factors that increase mortality risk (Cooper et al., 2010).

This study supports the validity of modified MCR concepts (MCR-HGS) as estimators of dementia and mortality in a nationally representative, homogeneous population, following adjustments for age-related confounding factors. Although neurophysiologic tests are generally expensive and require specialized professionals for administration, MCR-HGS provides a simple and efficient alternative for identifying high-risk individuals. Using continuous measurements minimizes information loss, and dichotomized variables for HGS can be derived from population-based cut-points (Bahat et al., 2020) or previous guidelines (Blanquet et al., 2022). Furthermore, the MCR-HGS assessment is not influenced by the participant's educational level or by learning effects from repeated testing, which enhances its credibility and validity. Nevertheless, the approach has several limitations. Additional HGS testing, while potentially increasing the ability to discriminate negative health outcomes, also adds to the physicians' workload and limits the feasibility of remote assessments due to the need for dynamometers. The lack of objective neuropsychological testing may lead to the oversight or misdiagnosis of some conditions. However, a sensitivity analysis that excluded participants diagnosed with dementia within two years of the index date strengthened the robustness of our findings. Moreover, due to differences in individual HGS profiles across various countries, our conclusions may not be generalizable to other populations. Future research involving multi-country cohorts is warranted to validate our findings across diverse populations. Finally, it was not possible to control for other confounding variables that may influence dementia development, such as APOE genotype or imaging biomarkers (Baumgart et al., 2015), in this study.

Conclusion

Our extensive nationwide cohort study demonstrates the added value of handgrip strength in the modified MCR (MCR-HGS) for predicting incident dementia and all-cause mortality, beyond the original MCR concepts. These results indicate that modified MCR can act as an effective and practical screening method to estimate the risks of dementia and mortality during national health assessments in older populations. Future research should explore the cost-effectiveness of incorporating HGS measurements in clinical or community settings versus reliance on self-reported questionnaires to identify potential patients. Additionally, further studies on the physical and neurobiological characteristics of MCR-HGS as a risk factor for dementia and mortality are needed, along with analyses of how MCR combined with other physical capabilities might better identify at-risk individuals.

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://hrsdata.isr.umich.edu/data-products/public-survey-data.

Ethics statement

The studies involving humans were approved by the University of Michigan Institutional Review Board approved the HRS study. 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

WB: Conceptualization, Data curation, Methodology, Supervision, Validation, Visualization, Writing – original draft. RM: Formal analysis, Methodology, Software, Validation, Visualization, Writing – review & editing. YY: Formal analysis, Methodology, Supervision, Validation, Visualization, Writing – review & editing. JX: Data curation, Funding acquisition, Project administration, Supervision, Visualization, Writing – review & editing. LQ: Conceptualization, Data curation, Methodology, 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.

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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.2024.1421656/full#supplementary-material

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Profiles of physical frailty, social frailty, and cognitive impairment among older adults in rural areas of China: a latent profile analysis

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Background: As China rapidly ages, it has now become a deeply aging society with the largest number of older individuals in the world. The issue is particularly severe in rural areas. With the aging population growing and the older population expanding, health problems are becoming more prevalent among older individuals, particularly frailty and cognitive impairments. This study aimed to identify the profiles of physical frailty, social frailty, and cognitive impairment among older adults and explore the influencing factors.

Methods: In this cross-sectional study, participants were recruited from six villages in four cities in Shandong Province, China from July to October 2023 through cluster random sampling. Latent profile analysis was used to determine the profiles of physical frailty, social frailty, and cognitive impairment. Chi-square tests and Mann–Whitney U tests were used for univariate analysis, while binary logistic regression was used to analyze the related factors.

Results: Seven hundred and sixty-nine older adult care in rural areas showed two profiles: the "high cognitive function and low frailty" group (73.7%, $n = 567$) and the "low cognitive function and high frailty" group (26.3%, $n = 202$). A binary logistic regression found that older people were more likely to be aged 80 or older (OR = 2.253, $p = 0.029$), have a low income level (OR = 1.051, $p = 0.007$), have one or two (OR = 2.287, $p = 0.004$), or more than three chronic diseases (OR = 3.092, $p = 0.002$), and report moderate (OR = 3.406, $p = 0.024$) or poor health status (OR = 9.085, $p < 0.001$) in the "low cognitive function and high frailty" group. Meanwhile, older adults who have completed high school (OR = 0.428, $p = 0.005$) or junior college and above (OR = 0.208, $p = 0.009$), and engage in adequate physical activity (OR = 0.319, $p < 0.001$) were more likely to be in the "high cognitive function and low frailty" group.

Conclusion: In the future, medical professors should increasingly prioritize promptly identifying and intervening in cognitive decline and frailty status in older individuals without delay.

KEYWORDS

older adults, physical frailty, social frailty, cognitive impairment, latent profiles analysis

1 Introduction

Population aging is a worldwide trend. Today, every country in the world is witnessing a swift growth in both the size and proportion of the population who are 60 years and older. Low- and middle-income countries are currently the most important observers and attestors experiencing the great change, such as China (1). The aging population in China is characterized by a shift in urban and rural areas, with rural areas aging at a higher level and at a faster rate than cities (2). The health problems of rural older adults are more serious than those of older individuals living in urban areas. Human aging is a complicated, individualized, and irreversible phenomenon that usually has an impact on physical, cognitive, and social abilities (3). With advancing age, older people are increasingly at risk of frailty and cognitive impairment (4).

Frailty is a multi-dimensional concept, including physiological, psychological, social and other areas (5, 6). It is an age-related condition, which drastically affects the quality of life and independence of older adults, as well as posing a tremendous burden on their families and society (7). Physical frailty is a vulnerability status characterized by a decline in physical reserve, reduced stress resistance, increased susceptibility of the body, and proneness to diseases (8). It is a severe consequence of the deterioration of multiple bodily functions (9), leading to fatigue, falls, extended sickness and even death (10). According to Fried frailty criteria, it is composed of five elements, including weight loss, exhaustion, low muscle strength, slow walking, low physical activity (11). Just like physical frailty, as individuals age, both their physical and psychological resilience diminishes, leaving them more susceptible to stress and illness, resulting in psychological distress and ultimately psychological frailty. Psychological frailty comprises four sets of components: mood problems, cognitive issues, other mental health concerns, and fatigue-related problems (12). Psychological frailty can be defined as a state of mental susceptibility and limited psychological resilience, combining cognitive, emotional, and fatigue-related factors (13). Even more importantly, social frailty is described as a state of deficiency in critical general and social resources, social behaviors, as well as self-management abilities essential for satisfying one's social needs (14). In simpler terms, if people are unable to reach the crucial resources needed to meet their basic social needs, it indicates that the person is struggling with social frailty (15). Moreover, it has a detrimental effect on general well-being throughout all life stages, particularly during old age.

A prospective cohort study revealed that physical frailty affects the development of social frailty (16). In this study, the findings of 342 socially robust older adults living in the community at the two-year follow-up indicated that both gait speed and muscle strength were identified as crucial independent risk factors for future social decline. At the same time, research has shown that social frailty is a predictor of physical frailty (17). The results of a longitudinal study suggest that older adults who developed social frailty at baseline are at a higher risk of developing physical frailty. As a result, physical and social frailty may influence each other.

Cognitive impairment is another significant indicator of aging in the older population (18). Individuals' cognitive function is the fundamental capacity to achieve and maintain a high-quality life (19). Frailty has a significant and negative influence on cognitive performance. Frailty has accelerated the deterioration of cognitive function in older individuals (20). Similarly, a prior study has demonstrated that older adults with subjective cognitive decline are more likely to be frail (21). At the present, an increasing number of studies have presented that frailty and cognitive function are interconnected, having a bidirectional relationship (22, 23).

Despite examining the characteristics of frailty or cognitive function from an individual perspective using latent class analysis in previous studies (24, 25), researchers have often considered one variable as the influencing factor and explored its relationship with another. Scholars seldom view these two potential conditions, which could coexist in older individuals, as a whole in order to examine their characteristics and relationships. As such, it is unclear what the current state of frailty and cognitive function is in older adults when viewed from an individual perspective.

In the current study, we chose physical frailty, social frailty, and cognitive impairment as the variables of interest and explored the heterogeneity of these variables among individuals based on all measurements through latent profile analysis. Additionally, certain variables with significant differences between profiles were incorporated into the multivariate analysis to determine the factors impacting the latent profiles.

2 Methods

2.1 Design and participants

The study employed a cross-sectional design, and participants were recruited from six villages in four cities in Shandong Province, China from July to October 2023 through cluster random sampling. Participants were eligible if they were (1) aged 60 years or older, (2) living in rural areas, and (3) able to understand and cooperate with the study. They were excluded if they (1) had hearing or visual impairments, (2) had multiple physical or psychological illnesses, or (3) refused to answer or provide incomplete responses to the questionnaire.

2.2 Sample size

It is generally suggested that the sample size for multivariate statistics should be more than 10 events per variable (26). In our study, the regression analysis included 16 observational variables, so the sample size should be a minimum of 160 people. The final sample included 769 older adults living in communities.

2.3 Measurements

Socio demographic characteristics included age, sex, BMI, education level, income level, marital status, number of children, frequency of visits by family and friends, smoking, drinking, number of chronic diseases, self-reported health status, and the use of walking aids.

2.3.1 International physical activities questionnaire

The International Physical Activity Questionnaire (IPAQ) is a reliable tool used to measure physical activity in many countries. It has shown good reliability and validity (27). The Chinese version of the International Physical Activity Questionnaire short form (IPAQ-C)

consists of seven questions, covering four activities: vigorous intensity activities, moderate intensity activities, walking, and sitting (28). They were assigned 8.0, 4.0, 3.3, and 1.1 metabolic equivalent (MET), respectively. Total physical activity is shown as metabolic equivalent (MET) minutes per day. The total metabolic equivalent/min (MET-min) was calculated using the formula: (8.0 × vigorous-intensity activity minutes × days) + (4.0 × moderate-intensity activity minutes × days) + (3.3 × walking minutes ×days) + (1.1 × sitting minutes × days). The physical activity levels were divided into three categories: low (<600 MET-min/week), medium (600–2,999 MET-min/week), and high (≥3,000 MET-min/week).

2.3.2 Mini nutritional assessment short form

The Mini Nutritional Assessment (MNA) is an efficient tool to assess the nutritional status of older adults, and it can be completed in about 10 min (29). MNA-SF comprises six questions chosen from MNA, covering weight loss, BMI, eating problems, mobility limitations, acute illnesses, and neuropsychological issues (30). The MNA-SF total score is 14, with scores of <8 indicating malnutrition, scores of 8–11 indicating a risk of malnutrition, and scores of >11 indicating no malnutrition. The Cronbach's α was 0.80.

2.3.3 Mini-mental state examination

MMSE is a universal questionnaire used to assess cognitive impairment, comprising 5 cognitive domains: orientation in time and place, memory, attention and calculation, recall, and language. It includes 30 questions with a maximum score of 30, where higher scores suggest superior cognitive abilities (31). MMSE-C is a specific cognitive evaluation tool that has been developed based on China's realities to evaluate the cognitive condition of the Chinese older population (32). The Cronbach's α was 0.83, and the reliability and validity were good.

2.3.4 Fried frailty phenotype

Frailty was measured with the Fried's frailty phenotype (33). It consists of five criteria: unintentional weight loss 10 kg during last year, lack of energy and fatigue, low handgrip strength, low gait speed, low physical activity. If an individual meets any one of the five criteria, then the score will be 1; otherwise, the score will be 0. The total scores range from 0 to 5, and higher scores indicate more severe frailty. Participants scored 0 were defined as non-frail, scored 1 or 2 as prefrail, and scored ≥ 3 as frail. The Chinese Fried frailty phenotype showed good reliability and validity, with a Cronbach's α of 0.93 (34).

2.3.5 Social frailty scale

Social frailty was assessed using an 8-item Social Frailty Scale (SFS-8) (35), which includes 8 items in three dimensions: social resources (three items), social activities and financial resources (three items), and social need fulfillment (two items). The total score of the scale ranged from 0 to 8, with larger scores indicating higher levels of social frailty. Participants with a score of 0–1 was considered non-SF; 2–3 was considered pre-SF; and a score of ≥4 indicated SF.

2.4 Data collection

Before data collection, our research team members all received uniform training to maintain consistency and standardization in this task. We gather data by distributing questionnaires face-to-face and then collecting them. While collecting data, team members explained the study to eligible participants and assisted those who had difficulty in completing the questionnaire.

2.5 Data analysis

In this study, SPSS 26.0 was conducted to statistical description and analysis, while Mplus 8.3 was used for latent profile analysis (LPA). Firstly, categorical variables were presented as frequencies and percentages, while non-normal continuous variables were shown as the median (M) and interquartile range (IQR). Secondly, the correlations of study variables in Spearman's product moment were examined. Thirdly, we determined the optimal model by progressively increasing the number of profiles in the model and comparing the fitness. In order to determine the appropriate number of profiles, we evaluated several metrics, including the Akaike Information Criterion (AIC), the Bayesian Information Criterion (BIC), the Sample-Size-Adjusted BIC (aBIC), the Entropy, the Lo–Mendell–Rubin Likelihood Ratio Test (LMR), and the Bootstrap Likelihood Ratio Test (BLRT). A smaller value of the first three classes indicated a better fit. Entropy was used to assess classification accuracy, with a greater value indicating better accuracy. When the value surpasses 0.8, the accuracy will exceed 90% (36). The LMR and BLRT were used to compare the current model with the previous one, and if the probability value is significant ($p < 0.05$), it indicates that a k-profile model is better than a k-1 profile model (37). Thirdly, we performed a χ^2 test or Fisher exact test and a Mann–Whitney U test to compare the characteristics of subgroups within the population and make inter-group comparisons. The variables with statistical significance in univariate analysis were included in a multivariate analysis to identify the factors that influenced the latent profiles. A p-value of <0.05 indicated statistical significance.

3 Results

3.1 Participants' characteristics

Table 1 presents the characteristics of the participants. The participants ranged in age from 60 to 93 years old (72.17 ± 5.77), with the majority falling between 70 and 79 years old. The majority of older people were married (82.8%, $n = 637$). Over half of them had 3 to 5 children (54.6%, $n = 420$). Despite the fact that over three-fifths of the participants do not smoke (63.5%, $n = 488$) or drink (69.7%, $n = 536$), most still consider their physical health to be moderate (73.2%, $n = 563$).

3.2 Correlations, median, and interquartile range for the study variables

The correlations, medians, and interquartile ranges for the study variables are presented in Table 2, indicating significant associations among all of the variables.

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TABLE 1 Characteristics of participants ($N = 769$).

Characteristics	*N* (*M*)	% (IQR)
Age		
60–69	279	36.3
70–79	409	53.2
≥80	81	10.5
Sex		
Male	391	50.8
Female	378	49.2
BMI		
<18.5	39	5.1
18.5 ~ 23.9	346	45.0
24.0 ~ 27.9	256	33.3
≥28.0	128	16.6
Education level		
Primary school and below	334	44.7
Junior school	242	31.5
High school	136	17.7
Junior college or above	47	6.1
Income level		
Good	273	35.5
Moderate	440	57.2
Bad	56	7.3
Marital status		
Married	637	82.8
Unmarried/Divorced/ Widowed	132	17.2
Co-residence		
With spouse	600	78
With children	76	9.9
Alone	93	12.1
Number of children		
≤2	319	41.5
3–5	420	54.6
>5	30	3.9
Frequency of visits by family and friends		
Usually	133	17.3
Occasionally	600	78.0
Hardly ever	36	4.7
Smoking		
No	488	63.5
Yes	281	36.5
Drinking		
No	536	69.7
Yes	233	30.3
Number of chronic diseases		
0	200	26.0
1–2	464	60.3
≥3	105	13.7
Self-reported health status		
Good	108	14.0
Moderate	563	73.2
Bad	98	12.7
Use of walking aids		
No	717	93.2
Yes	52	6.8
Physical activity		
Low	44	5.7
Medium	205	26.7
High	520	67.6
Nutritional status		
Malnutrition	4	0.5
A risk of malnutrition	288	37.5
No malnutrition	477	62.0

TABLE 2 Spearman's product moment correlation coefficients of study variables.

Variables	Cognitive function	Physical frailty	Social frailty	*M*	IQR
Cognitive function	–			22	7
Physical frailty	−0.308**	–		1	2
Social frailty	−0.114**	0.189**	–	1	2

**$p < 0.01$.

3.3 Results of latent profile analysis

In Table 3, as the number of profiles increases from one to four, there is a gradual decrease in AIC, BIC and aBIC, with a consistent *p*-value of BLRT <0.05, as well as an increase in entropy. However, some proportions in the three-profile model account for too few people, and the *p*-value of LMRT is >0.05 in both the three- and four-profile models. Considering the model performance, practical significance, and interpretability, the final optimal model determined was the two-profile model. As shown in Table 4, the average attribution probability of community older adults belonging to the profile ranged from 83.3 to 93.8%, indicating the reliability of the LPA results in this study.

3.4 Naming of latent profile

As we can see, the latent profiles had different characteristics regarding the study variables in Figure 1. Five hundred and

TABLE 3 Latent profile analysis for model fit statistics.

Profile	k	Likelihood	AIC	BIC	aBIC	LMRT (*P*)	BLRT (*P*)	Entropy	Proportion
1	6	−3271.990	6555.980	6583.851	6564.798				
2	10	−3189.639	6399.273	6445.724	6413.969	0.0000	0.0000	0.707	0.737/0.263
3	14	−3164.632	6357.263	6422.295	6377.838	0.1534	0.0000	0.798	0.672/0.309/0.018
4	18	−2613.336	5262.673	5346.285	5289.126	0.2143	0.0000	1.000	0.397/0.256/0.124/0.224

k, free parameters; AIC, Akaike information criterion; BIC, Bayesian information criterion; aBIC, adjusted BIC; LMRT, Lo–Mendell-Rub test; BLRT, Bootstrap Likelihood ratio test.

TABLE 4 Average attribution probabilities for each latent profile.

Class	Profile 1	Profile 2
Profile 1	0.938	0.062
Profile 2	0.167	0.833

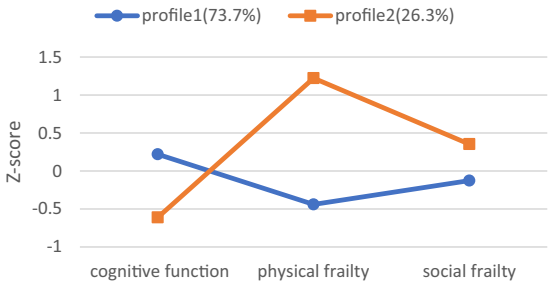

FIGURE 1
Two-profile model and probability on study variables in z-score format.

sixty-seven community-dwelling older adults (73.7%) had higher scores for cognitive function, lower scores for physical frailty, and social frailty in profile 1, which was labeled as the "high cognitive function and low frailty" group. Two hundred and two community-dwelling older adults (26.3%) had lower scores for cognitive function, higher scores for physical frailty, and social frailty in profile 2, which was classified as the "low cognitive function and high frailty" group.

3.5 Inter-profile characteristic differences

The differences in demographic characteristics, cognitive function, physical frailty, and social frailty between two subgroups were compared using the chi-square test, Fisher exact test, and Mann–Whitney U test, as shown in Table 5. The results indicated significant differences in age, education level, income level, marital status, co-residence, number of children, drinking, number of chronic diseases, self-reported health status, use of walking aids, physical activity, nutritional status, cognitive function, physical frailty, and social frailty ($p < 0.05$). In both subgroups, the majority of community-dwelling older adults were aged 70–79 years old, had a primary school education or lower, held a middle-income status, and were married and living with a spouse. It is interesting to observe that the "high cognitive function and low frailty" group has a greater number of older adults with high physical activity and good nutritional status.

3.6 Influences of factors on the latent profiles

A binary logistic regression was conducted to explore the factors influencing the two subgroups based on the LPA results. Table 6 indicates that age, education level, income level, number of chronic diseases, self-reported health status, and physical activity have statistically significant influences on the latent profiles. When comparing the "high cognitive function and low frailty" group with the "low cognitive function and high frailty" group, it was found that older individuals in the latter group were more likely to be aged 80 or older (OR = 2.253, $p = 0.029$), have a low income level (OR = 1.051, $p = 0.007$), have one or two (OR = 2.287, $p = 0.004$), or even more than three chronic diseases (OR = 3.092, $p = 0.002$), and report moderate (OR = 3.406, $p = 0.024$) or poor health status (OR = 9.085, $p < 0.001$). Meanwhile, older adults in the former group were found to have completed high school (OR = 0.428, $p = 0.005$) or junior college and above (OR = 0.208, $p = 0.009$), and engage in adequate physical activity (OR = 0.319, $p < 0.001$).

4 Discussion

The main purpose of this study was to classify subgroups of cognitive function, physical frailty, and social frailty in community-dwelling older individuals. The results of LPA determined two subgroups - the "high cognitive function and low frailty" group and the "low cognitive function and high frailty" group.

Specifically, the older individuals belonging to the "high cognitive function and low frailty" group, accounting for 73.7% of the total, were identified by their better cognitive function and fewer frailties. The older community members in the "low cognitive function and high frailty" group, comprising 26.3% of the total, were identified by their poorer cognitive function and more severe frailties. Levels of physical frailty and social frailty were found to be similar, as they were either high or low simultaneously in two latent profiles. Moreover, both were found to have a negative association with cognitive function. This result supported our classification of subgroups for cognitive function, physical frailty, and social frailty in older individuals living in the community. The findings of this research were consistent with a prior systematic review, which indicated that cognitive decline and physical frailty frequently co-occur among older individuals (38). In addition, two studies conducted in Japan have also shown that social frailty is associated with both cognitive impairment and physical frailty in older individuals living in the community, with these symptoms often overlapping (39, 40). A possible explanation for this phenomenon was that as older adults experience the debilitating

TABLE 5 Inter-profile characteristic differences.

Characteristics	High cognitive function and low frailty *n* = 567 (73.7%) *n* (%) or M (IQR)	Low cognitive function and high frailty *n* = 202 (26.3%) *n* (%) or M (IQR)	X^2/Z	*p*
Age			41.698	<0.001
60–69	233 (41.1)	46 (22.8)		
70–79	295 (52.0)	114 (56.4)		
≥80	39 (6.9)	42 (20.8)		
Sex			0.013	0.908
Male	289 (51.0)	102 (50.5)		
Female	278 (49.0)	100 (49.5)		
BMI			0.230	0.973
<18.5	30 (5.3)	9 (4.5)		
18.5 ~ 23.9	254 (44.8)	92 (45.5)		
24.0 ~ 27.9	189 (33.3)	67 (33.2)		
≥28.0	94 (16.6)	34 (16.8)		
Education level			22.805	<0.001
Primary school and below	228 (40.2)	116 (57.4)		
Junior school	185 (32.6)	57 (28.2)		
High school	111 (19.6)	25 (12.4)		
Junior college or above	43 (7.6)	4 (2.0)		
Income level			29.415	<0.001
Good	224 (39.5)	49 (24.3)		
Moderate	316 (55.7)	124 (61.4)		
Bad	27 (4.8)	29 (14.4)		
Marital status			12.587	<0.001
Married	486 (85.7)	151 (74.8)		
Unmarried/Divorced/Widowed	81 (14.3)	51 (25.2)		
Co-residence			16.701	<0.001
With spouse	463 (81.7)	137 (67.8)		
With children	46 (8.1)	30 (14.9)		
Alone	58 (10.2)	35 (17.3)		
Number of children			8.516	0.014
≤2	249 (43.9)	70 (34.7)		
3–5	301 (53.1)	119 (58.9)		
>5	17 (3.0)	13 (6.4)		
Frequency of visits by family and friends			1.845	0.397
Usually	92 (16.2)	41 (20.3)		
Occasionally	449 (79.2)	151 (74.8)		
Hardly ever	26 (4.6)	10 (5.0)		
Smoking			3.385	0.066
No	349 (61.6)	139 (68.8)		
Yes	218 (38.4)	63 (31.2)		
Drinking			5.543	0.019
No	382 (67.4)	154 (76.2)		
Yes	185 (32.6)	48 (23.8)		

(Continued)

TABLE 5 (Continued)

Characteristics	High cognitive function and low frailty *n* = 567 (73.7%) *n* (%) or M (IQR)	Low cognitive function and high frailty *n* = 202 (26.3%) *n* (%) or M (IQR)	X^2/Z	*p*
Number of chronic diseases			37.185	<0.001
0	178 (31.4)	22 (10.9)		
1–2	326 (57.5)	138 (68.3)		
≥3	63 (11.1)	42 (20.8)		
Self-reported health status			83.764	<0.001
Good	45 (7.9)	63 (31.2)		
Moderate	428 (75.5)	135 (66.8)		
Bad	94 (16.6)	4 (2.0)		
Use of walking aids			44.061	<0.001
No	549 (96.8)	168 (83.2)		
Yes	18 (3.2)	34 (16.8)		
Physical activity			115.101	<0.001
Low	8 (1.4)	36 (17.8)		
Medium	124 (21.9)	81 (40.1)		
High	435 (76.7)	85 (42.1)		
Nutritional status			22.305	<0.001[a]
Malnutrition	0 (0.0)	4 (2.0)		
A risk of malnutrition	192 (33.9)	96 (47.5)		
No malnutrition	375 (66.1)	102 (50.5)		
MMSE	23 (6)	19 (5)	−11.750	<0.001
FFP	1 (1)	2 (1)	−20.725	<0.001
SFS	1 (2)	2 (2)	−6.213	<0.001

syndrome, they may have low physical activity, slow movement, fatigue, and weakness. Consequently, they may avoid social activities, participate less in social activities, shrink their social circle, and ultimately develop social frailty. Conversely, social frailty can lead to a decrease in social activities for older adults, smaller social circles, reduced motor function, declining cognitive abilities, and ultimately physical and cognitive deterioration.

Our research also aimed to explore the factors that influence the classification of cognitive function and frailty in older members of the community. Through our study, we have identified age, education level, income level, number of chronic diseases, self-reported health status, and physical activity as significant influencers of cognitive performance, physical frailty, and social frailty in older adults living in the community.

Age was identified as a risk factor for cognitive function and frailty status in community-dwelling older adults in this study. Frailty, a prevalent age-related geriatric syndrome, frequently accompanies cognitive decline in older individuals (41). The coexistence of physical frailty and cognitive decline in older people is defined as cognitive frailty (42). As individuals age, their physiological functions tend to deteriorate, causing a reduction in their visual, auditory, and perceptual capacities, a decline in their physical performance, and low levels of physical activity, ultimately leading to physical frailty (9). Moreover, a previous study conducted on older adults in Shanghai also found that advanced age (81–85 years old) is associated with an increased risk of suffering from both physical frailty and cognitive impairment concurrently (43). Conversely, with a decline in physical and cognitive abilities, older individuals tend to self-isolate, which reduces their social engagement, interaction, and perceived social support, ultimately leading to social frailty.

Educational level and financial status as influencing factors of cognitive function and frailty status of older individuals in the community has been confirmed in this study. In rural areas, older adults often have access to fewer educational opportunities and resources, resulting in a lower level of education than their urban peers (44). An analysis using data from the Birjand Longitudinal Aging Study (BLAS) found that the level of education has an impact on physical, cognitive, psychological, and social frailty, as well as the relationships between them, among community-dwelling older adults (45). A lower income level is also a significant risk factor. Older individuals in rural areas predominantly depend on income from agricultural labor and odd jobs, lacking a stable source of income, which ultimately results in lower overall income levels compared to urban older adults (46). A systematic review of longitudinal studies has revealed that a lower income level has been identified as a risk factor associated with the development or progression of frailty in older adults living in the community (47). Social frailty among older individuals is also influenced by their educational level (48). It is our speculation that having sufficient financial resources guarantees a

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TABLE 6 Binary logistic regression for the latent profiles.

Characteristics	*B*	SE	Wald χ^2	Exp(B)	95%	*p*
Age						
60–69			5.678			0.058
70–79	0.448	0.234	3.672	1.565	0.990, 2.473	0.055
≥80	0.812	0.372	4.775	2.253	1.087, 4.669	0.029
Education level						
Primary school and below			13.624			0.003
Junior school	−0.450	0.234	3.706	0.637	0.403, 1.008	0.054
High school	−0.849	0.306	7.714	0.428	0.235, 0.779	0.005
Junior college or above	−1.571	0.599	6.887	0.208	0.064, 0.672	0.009
Income level						
Good			7.619			0.022
Moderate	0.357	0.228	2.453	1.429	0.914, 2.233	0.117
Bad	1.051	0.387	7.364	2.861	1.339, 6.112	0.007
Marital status						
Unmarried/Divorced/Widowed	−0.786	−0.587	1.794	0.456	0.144, 1.439	0.180
Co-residence						
With spouse			3.249			0.197
With children	0.508	0.438	1.345	1.663	0.704, 3.925	0.246
Alone	1.161	0.645	3.243	3.193	0.903, 11.299	0.072
Number of children						
≤2			2.344			0.310
3–5	0.138	0.215	0.410	1.148	0.753, 1.750	0.522
>5	−0.552	0.480	1.320	0.576	0.225, 1.476	0.251
Drinking						
Yes	−0.263	0.235	1.248	0.769	0.485, 1.219	0.264
Number of chronic diseases						
0			11.029			0.004
1–2	0.827	0.284	8.486	2.287	1.311, 3.991	0.004
≥3	1.129	0.359	9.889	3.092	1.530, 6.248	0.002
Self-reported health status						
Good			20.308			<0.001
Moderate	1.226	0.542	5.105	3.406	1.176, 9.863	0.024
Bad	2.207	0.587	14.143	9.085	2.877, 28.694	<0.001
Use of walking aids						
Yes	0.701	0.410	3.008	2.035	0.912, 4.540	0.083
Physical activity	−1.143	0.172	43.896	0.319	0.227, 0.447	<0.001
Nutritional status	−0.333	0.196	2.890	0.717	0.488, 1.052	0.089

good quality of life for older adults in their later years, delaying the onset of frailty. Meanwhile, having enough wealth reserves can also help maintain the crucial social connections of older adults, increase their involvement in social activities, and slow the progression of social decline. If the physical and social functions of older adults remain normal, their cognitive function is also usually not impacted.

Number of chronic diseases and self-reported health status were significant in this study. With advancing age, individuals become more prone to weakness and illness, making them more susceptible to chronic diseases and frailty. The onset of chronic diseases can deteriorate physical function, diminish resistance to external stimuli, and ultimately increase the risk of frailty (49). Chronic illnesses and frailty are closely related conditions that often worsen each other and have a significant negative impact on the health and quality of life of older individuals (50). Moreover, a study revealed that community-dwelling older individuals with multiple chronic diseases have a

higher level of frailty (51). More and more concrete evidence indicates that chronic diseases, particularly the presence of multiple chronic diseases, are significant predictors of poor self-rated health (52, 53). An individual's self-reported health status is a subjective perception of their overall physical and mental well-being. Because chronic diseases are long-lasting and cannot be cured, older individuals often experience poor self-health status, negative emotions, and low life satisfaction (54). As a result, we speculated that they may refuse to participate in social activities, be more prone to depressive symptoms, and experience social frailty. A prior study found that older adults living alone with poor self-rated health are more likely to be depressed (55), which supports our findings in this study.

Older individuals with low levels of physical activity are at a higher risk of developing frailty compared to those with high levels of physical activity. Regular exercise was shown in a previous study to have a significant negative correlation with prefrailty and frailty (56). Physical exercise can enhance muscle strength in older individuals (57), diminish age-related inflammatory responses (58), enhance bodily functions, and thus delay and lessen frailty (59). As more research emerges, it is becoming increasingly clear that exercise has the potential to improve cognitive function in older adults by activating individual physiological mechanism (60) and providing psychological benefits (61). Additionally, engaging in physical activity can reduce social frailty, alleviating feelings of loneliness through interaction with others and building new social connections through participation in community activities (62).

5 Limitations

This study has some limitations. Firstly, since this study is cross-sectional, the results should not be interpreted as causal. In order to confirm the causal relationship, a longitudinal study should be conducted in the future. Secondly, certain sociodemographic variables and social frailty are self-reported, which may cause subjective bias. In future studies, further scientific measurements should be used. Thirdly, due to study constraints, variables such as sleep quality, healthy habits, and other factors that may affect cognitive function and frailty status in older individuals were not accounted for or included in the regression analysis. In future studies, we can gather more related variables in order to conduct a more comprehensive and thorough analysis of the influencing factors.

6 Conclusion

Our study divided cognitive function and frailty status in older adults into two subgroups: the "high cognitive function and low frailty" group, and the "low cognitive function and high frailty" group, each with distinct group characteristics. It indicates that frailty and cognitive impairment often coexist in older individuals, and they reciprocally impact each other. Older adults with cognitive impairments are more susceptible to physical and social decline, and vice versa. Age, education level, income level, number of chronic diseases, self-reported health status, and physical activity were found to be influencing factors for cognitive function and frailty status in older people. This finding improves our understanding of cognitive function and frailty status in older adults and implies that we should identify and intervene in cognitive decline and frailty status in older individuals in a multidimensional and comprehensive approach as soon as possible.

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 Ethics Committee of Qingdao University (QDU310 HEC-2022278). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent was provided by the participants themselves or their legal guardians/next of kin.

Author contributions

QD: Conceptualization, Data curation, Writing – original draft. XB: Data curation, Writing – original draft. TW: Investigation, Software, Writing – original draft. ML: Investigation, Software, Writing – review & editing. FZ: Writing – review & editing, Project administration, Supervision. CL: Writing – review & editing, Funding acquisition, 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.

Publisher's note

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Cognitive function in dyslipidemia patients: exploring the impact of statins

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Background: Evidence regarding the relationship between the use of statins and cognitive outcomes presents varying findings. This study aims to analyze the relationship between sustained statin use and cognitive performance in dyslipidemia patients.

Methods: This study presents findings from the Beijing Ageing Brain Rejuvenation Initiative (BABRI) study, in which a cohort of community-dwelling dyslipidemia patients (Entire sample, $N = 1{,}062$, aged 50–86) was recruited. Participants were divided into two groups based on their sustained use statins (Statins group, $N = 677$) or not use any lipid-lowering agents (Untreated group, $N = 385$). Furthermore, the entire sample was stratified by age into the middle-aged sample ($N = 451$) and the older people sample ($N = 611$), following a similar categorization based on statin application. ANCOVA was used to evaluate the relationship between sustained statin use and cognitive function.

Results: Overall, in the total sample, the statins group demonstrated better cognition in overall cognition, memory, visuospatial ability, attention, executive function, and language domains compared to the untreated group. Moreover, the statins group only showed better performance in attention among the middle-aged sample. In the older people sample, statins group exhibited superior cognitive performance across various cognitive domains compared to untreated group.

Conclusion: Among dyslipidemia patients in Beijing community, sustained statin users exhibited superior cognitive function across all domains compared to untreated individuals, with particularly noticeable improvements among those aged 65 and above. These findings underscore the protective effect of statins on cognitive function in dyslipidemia patients, highlighting significant benefits for the older people population.

KEYWORDS

cognitive function, statins, dyslipidemia, aging cohorts, middle-aged, elderly

1 Introduction

Statins, commonly prescribed for cardiovascular conditions such as dyslipidemia and etc., primarily act by inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, thereby reducing cholesterol synthesis (1). Given the established link between elevated cholesterol and cardiovascular diseases, statins play a pivotal role in lowering

peripheral blood cholesterol, particularly in reducing low-density lipoprotein cholesterol (LDL-C), thereby aiding in the reduction of atherosclerotic cardiovascular disease and other cardiovascular risks (2, 3). Beyond their established role in managing lipid metabolism and serving as primary prevention or secondary prevention for coronary heart disease and cerebrovascular diseases, research suggests that statins may offer potential benefits in reduce the risk of cognitive impairment-associated conditions such as Alzheimer's disease (AD) and dementia (4, 5). The observed effect could be attributed to the ability of statins to penetrate the blood–brain barrier (BBB) (6, 7), along with their anti-inflammatory, antioxidant, and synaptic plasticity-regulating properties (8, 9). Moreover, they regulate cerebral cholesterol metabolism, thereby promoting neuroprotection (10, 11). At the same time, other studies have found that statins can regulate hippocampal neurogenesis by upregulating Wnt signaling through dependent inhibition of the Mevalonate (MVA) Pathway (12). Additionally, there is evidence that statins are effective inducers of axon and dendrite growth (13). In summary, the regulation of cognitive function by statins may involve two key mechanisms: first, by modulating cholesterol metabolism and other pathways in the central nervous system, and second, by lowering peripheral blood cholesterol to reduce cardiovascular and cerebrovascular risks (14). These multifaceted effects provide potential biological explanations for the effects of statins on cognitive function. Despite these benefits, controversy remains surrounding the relationship between statin use and cognition in the general population. On February 28, 2012, the U.S. Food and Drug Administration (FDA) mandated the inclusion of a warning label on statins, due to insights provided from post-marketing surveillance, observational studies (15–19), and randomized controlled trials (RCTs) (20, 21) hinting at potential adverse effects on cognitive function. Critiques of RCTs and observational data suggest a potential link between this adverse effect and the use of high-dose statins (22). A review summarizing a series of randomized controlled trials found that statins did not exhibit clear adverse effects on patients' cognitive function in short-term studies. However, long-term follow-up research indicated a significant reduction in the incidence of dementia among patients treated with statins (23). However, there is still no conclusive evidence that statins cause clinically significant cognitive impairment (22, 24, 25) or that statins reduce the risk of dementia or cognitive impairment (26).

Based on the above background, we decided to use data from the Beijing Aged Brain Rejuvenation Initiative (BABRI) cohort, which is a community-based cohort study that mainly focuses on population aging, especially cognitive aging and its determinants. A screening of 1,062 dyslipidemia patients was conducted using the baseline database of the BABRI cohort. The primary objective was to assess sustained use of statin drugs affect various cognitive functions in dyslipidemia patients compared to those not using any lipid-lowering medication. The aim was to precisely pinpoint the impact of statins on various cognitive functions in individuals dealing with dyslipidemia. Subsequently, dyslipidemia patients were categorized into two sample—older people and middle-aged—in order to investigate more comprehensively the effects of statins on cognitive function in hyperlipidemic patients across different age groups.

2 Materials and methods

2.1 Study cohort and measures

Participants in the cross-sectional study were sourced from the Beijing community, a prospective, community-based cohort (27, 28). This study selected a group of dyslipidemia patients from the BABRI baseline database as follows. Among the 7,625 participants included in the BABRI database and meeting the specified inclusion and exclusion criteria, a group consisting of 1,477 individuals with dyslipidemia was identified. The inclusion criteria as follows: (1) individuals aged 50 or above; (2) attainment of 6 or more years of formal education; (3) all diagnoses of dyslipidemia were made by physicians in Beijing area's tertiary hospitals, according to the 2018 AHA Guideline on the Management of Blood Cholesterol (29), validated by medical records from community healthcare centers; (4) willingness to engage in face-to-face interviews. Exclusion criteria are as follows: (1) individuals diagnosed with dementia, Parkinson's disease, other degenerative neurological disorders, psychiatric conditions, or brain tumors; (2) incapacity to undergo cognitive assessments due to physical or mental disabilities.

Furthermore, the medication status of dyslipidemia patients was determined through their medical records or self-reports, with exclusive attention given to the utilization of any medication falling within the class of HMG-CoA reductase inhibitors (Including any hydrophilic or lipophilic statins, with no dose restrictions, such as simvastatin, atorvastatin, rosuvastatin, etc.), with a minimum duration of continuous usage exceeding 6 months. Following the exclusion of patients with unclear or irregular medication records and those taking alternative lipidlowering agents, a final sample of 1,062 dyslipidemia patients with well-documented medication records were categorized into a statins-user group ($n = 677$) and an untreated group ($n = 385$).

Other covariates encompassed age, gender, education, diabetes, hypertension, smoking and obesity. Face-to-face interviews were used to assess age, education, gender and smoking and obesity. Smoking status was determined by self-reported smoking habits. Participants were classified as obese if their body mass index (BMI) exceeded ≥ 30, based on criteria from the World Health Organization Global Health Observatory data. Additionally, in accordance with guidelines from the ADA and AHA, diagnoses of type 2 diabetes and hypertension were performed by physicians at tertiary hospitals in the Beijing area, with patient medical records reviewed at community health care centers.

2.2 Neuropsychological tests

The current study employed a comprehensive neuropsychological test battery to evaluate general cognition and five cognitive domains, consistent with previous research (27). The Mini-Mental State Examination (MMSE) (30) and Montreal Cognitive Assessment (MoCA) (31) acted as comprehensive tools to measure general cognitive function. Memory assessment involved the Auditory Verbal Learning Test (AVLT) (32) and recall in the Rey-Osterrieth Complex Figure Test (CFT) (33). Evaluating visuospatial ability involved administering the CFT copy and the Clock-Drawing Test (CDT) (34). Language proficiency was gauged using the Category Verbal Fluency Test (CVFT) (35) and the Boston Naming Test (BNT) (36). Attention was scrutinized via the Trail-Making Test (TMT) (37) part A and the Symbol Digit

Modalities Tests (SDMT) (38), while executive function was measured by the TMT part B and the Stroop Color-Word Test (SCWT) (39).

2.3 Statistical analysis

Demographic characteristics, cognitive performance, and disease status were reported separately for the total sample ($n = 1,062$), the middle-aged sample ($n = 451$), and the older people sample ($n = 611$). One-way ANOVA or the χ^2 test was used to test for significant differences between the groups. Given the known impact of age on cognitive function, participants were further categorized into middle-aged and older people sub sample. In these sub sample, the effects of regular statins use on each cognitive test was assessed using one-way ANCOVA, with age, gender, education, hypertension, and diabetes as concomitant variables. All analyses were performed in SPSS 27.0 (IBM Corp, Armonk, NY).

3 Results

Among the 7,625 participants screened in the BABRI database, participants from non-Beijing communities ($n = 2,549$) were first excluded, as well as those with incomplete basic medical records ($n = 3,420$) and incomplete cognitive assessments ($n = 209$). Based on this criterion, a total of 1,477 patients with dyslipidemia were identified. Of these, 385 patients were excluded due to unclear or non-standardized treatment records. Among the remaining 1,062 patients, 677 regularly used statins for more than 6 months (Statins group), while 385 patients did not receive any intervention (Untreated group). To investigate the potential benefits of statin usage across various age groups, the 1,062 patients were further divided into a middle-aged sample ($n = 611$) and an older people sample ($n = 451$). Within these two samples, the middle-aged statin group comprised 266 individuals, with the middle-aged untreated group consisting of 185 individuals. The older people statin group encompassed 411 individuals, whereas the older people untreated group comprised 200 individuals (see Figure 1).

Among the total sample of 1,062 participants with dyslipidemia, the average age was 65.91 ± 7.37 years. The statins group, with an average age of 66.46 ± 7.33 years, was older than the untreated group (64.95 ± 7.38 years, $F = 10.4$, $p = 0.001$). Education ($F = 2.05$, $p = 0.15$) and gender ($\chi^2 = 0.02$, $p = 0.889$) showed no significant differences between the two groups (Table 1). In the middle-aged sample, the statins group (59.21 ± 3.52 years) and untreated group (58.81 ± 3.73 years) exhibited no significant differences in age ($F = 1.34$, $p = 0.25$), education ($F = 1.17$, $p = 0.28$), and gender ($\chi^2 = 1$, $p = 0.49$) (Table 2). Within the older people sample (average age 76.4 ± 6.7 years), the statins group (71.16 ± 4.95 years) and untreated group (70.63 ± 4.97 years) showed no significant differences in age ($F = 1.53$, $p = 0.21$), education ($F = 1.22$, $p = 0.27$), or gender ($\chi^2 = 0.52$, $p = 0.29$) (Table 3). Simultaneously, both in the total sample and within the middle-aged and older people sub sample, the prevalence of hypertension and diabetes was significantly higher in the statins group in comparison to the untreated group.

In the comprehensive sample of 1,062 patients, significant differences were observed between the statin group and the untreated group across multiple cognitive domains, including general cognitive function (MoCA, $F = 9.96$, $p = 0.002$), memory (CFT delay, $F = 4.6$, $p = 0.032$), visual–spatial function (CFT copy, $F = 8.64$, $p = 0.003$), attention (DST, $F = 14.71$, $p < 0.001$), executive function (TMTB, $F = 7.588$, $p = 0.006$), and language (BNT, $F = 11.23$, $p = 0.001$) (see Table 1). In the older people sample, the statin group exhibited differences compared to the untreated group across general cognitive function (MoCA, $F = 8.76$, p = 0.003), memory (CFT delay, $F = 6.61$, $p = 0.014$), visual–spatial function (CFT copy, $F = 5.72$, $p = 0.017$), attention (DST, $F = 9.33$, $p = 0.002$), executive function (SCWT, $F = 4.5$, $p = 0.034$; TMTB, $F = 5.75$, p = 0.017), and language (BNT, $F = 9.445$, p = 0.002) (see Table 2). Finally, in the middle-aged sample,

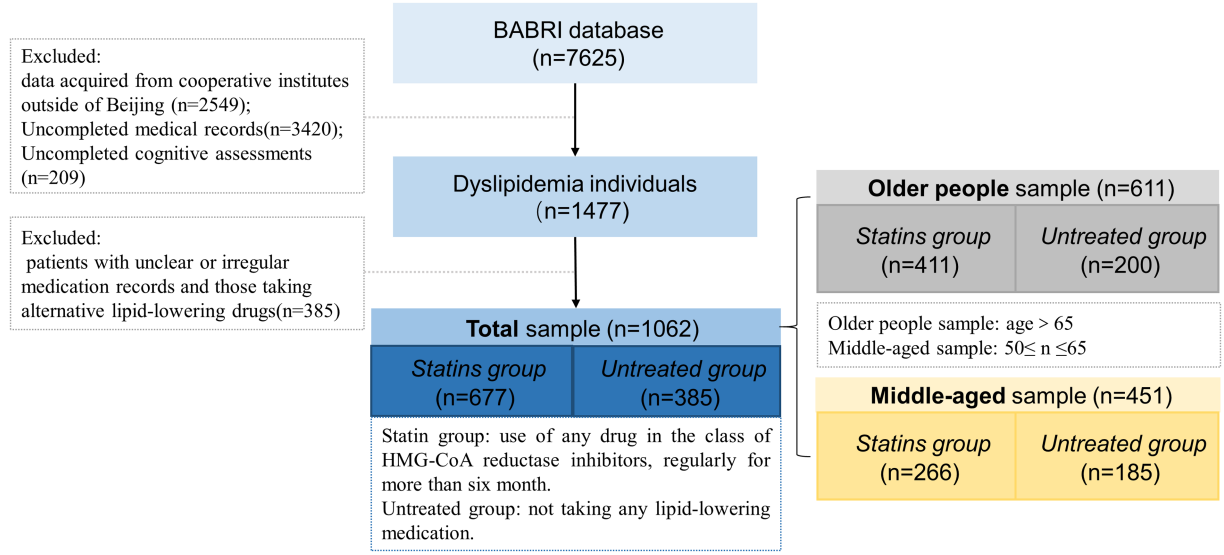

FIGURE 1
Flow chart of the Dyslipidemia patients inclusion process. The total data volume from the BABRI database ($n = 7,625$) presented in this flowchart is accurate up to January 2018. Since that time, the database has continually expanded, and BABRI has now enrolled over 10,000 participants.

TABLE 1 Significant intergroup differences in demographic data and multidomain cognitive performance of the two groups in total patients.

Variables (M ± SD)	Untreated (n = 385)	Statins (n = 677)	F/χ^2	P
Demographic information				
Age	64.95 ± 7.38	66.46 ± 7.33	10.4	0.001**
Education	11.18 ± 2.68	11.43 ± 2.76	2.05	0.15
Gender	116/269	201/476	0.02	0.889
Physical health				
Type 2 Diabetes	107/278	283/394	20.73	<0.001***
Hypertension	224/161	476/201	16.07	<0.001***
Smoking	46/339	62/615	2.25	0.134
Obesity	35/350	49/628	1.16	0.218
General cognition				
MMSE	27.45 ± 2.18	27.56 ± 2.11	2.46	0.117
MOCA	22.34 ± 2.51	22.83 ± 3.23	9.96	0.002**
Memory				
AVLT-N5	4.93 ± 2.48	4.89 ± 2.40	0.19	0.660
AVLT-N1N5	27.23 ± 8.43	27.23 ± 8.41	0.53	0.466
CFT delay	12.33 ± 7.30	13.04 ± 6.63	4.6	0.032*
Visuospatial ability				
CFT copy	32.97 ± 5.39	33.71 ± 3.92	8.64	0.003**
CDT	23.18 ± 5.45	23.46 ± 5.49	0.53	0.468
Attention				
SDMT	33.05 ± 10.39	33.10 ± 10.07	2.47	0.117
TMTA	58.96 ± 22.13	60.04 ± 22.39	0.07	0.796
DST	12.01 ± 2.11	12.41 ± 2.14	14.71	<0.001***
Executive function				
SCWT	78.47 ± 22.22	78.48 ± 21.93	1.82	0.178
TMTB	170.58 ± 68.92	165.97 ± 65.87	7.59	0.006**
Language				
VFT	45.55 ± 8.71	45.42 ± 8.72	0.47	0.492
BNT	23.48 ± 3.48	24.09 ± 3.27	11.23	0.001**

Values are mean ± SD or Nos. of participants. The comparisons of age, education, and various cognitive function between the two groups were performed with ANOVA. The p-values for gender, diabetes, hypertension, obesity, and smoking ratio were obtained using a Chi-square test. Significance: *p < 0.05, **p < 0.01, ***p < 0.001. Edu, Education; MMSE, Mini-mental state examination; MoCA, Montreal cognitive assessment; AVLT-N5, Auditory verbal learning test number 5; AVLT-N1N5, Auditory verbal learning test number1-number5; CFT-delay, Recall in the Rey-Osterrieth complex figure test; CFT copy, Copy in the Rey-Osterrieth complex; CDT, Clock-drawing test; SDMT, Symbol digit modalities tests; TMTA, Trail-making test part A; DST, Digital symbol test; SCWT, Stroop color-word test; TMTB, Trail-making test part B; CVFT, Category verbal fluency test; BNT, Boston naming test.

TABLE 2 Significant intergroup differences in demographic data and multi domain cognitive performance of the two groups in older people sample.

Variables (M ± SD)	Untreated (n = 200)	Statins (n = 411)	F/χ^2	P
Demographic information				
Age	70.63 ± 4.97	71.16 ± 4.95	1.53	0.219
Education	11.09 ± 3.08	11.37 ± 3.02	1.22	0.269
Gender	71/129	135/276	0.52	0.287
Physical health				
Type 2 Diabetes	52/148	180/231	18.09	<0.001***
Hypertension	125/75	302/109	7.71	0.006**
Smoking	20/180	30/381	1.48	0.225
Obesity	16/184	20/391	1.96	0.161
General cognition				
MMSE	27.21 ± 2.33	27.39 ± 2.16	1.25	0.265
MOCA	22.27 ± 3.75	22.81 ± 3.16	8.76	0.003**
Memory				
N5	4.61 ± 2.52	4.59 ± 2.47	0.04	0.842
N1N5	27.95 ± 8.29	26.14 ± 8.57	0.27	0.605
CFT delay	11.58 ± 7.04	12.76 ± 6.62	6.61	0.014*
Visuospatial ability				
CFT copy	32.59 ± 6.07	33.50 ± 4.31	5.72	0.017*
CDT	23.79 ± 5.37	23.99 ± 5.55	0.89	0.345
Attention				
SDMT	30.61 ± 9.72	30.88 ± 9.8	1.23	0.268
TMTA	63.12 ± 22.83	63.66 ± 23.46	3.82	0.051
DST	11.82 ± 2.19	12.24 ± 2.23	9.33	0.002**
Executive function				
SCWT	85.22 ± 24.32	82.19 ± 22.18	4.53	0.034*
TMTB	189.34 ± 75.66	180.33 ± 73.18	5.75	0.017*
Language				
VFT	43.75 ± 8.54	44.11 ± 8.86	0.52	0.473
BNT	23.36 ± 3.59	24.08 ± 3.48	9.45	0.002**

Values are mean ± SD or Nos. of participants. The comparisons of age, education, and various cognitive function between the two groups were performed with ANOVA. The p-values for gender, diabetes, hypertension, obesity, and smoking ratio were obtained using a Chi-square test. Significance: *p < 0.05, **p < 0.01, ***p < 0.001 MMSE, Mini-mental state examination; MoCA, Montreal cognitive assessment; AVLT-N5, Auditory verbal learning test number 5; AVLT-N1N5, Auditory verbal learning test number1-number5; CFT-delay, Recall in the Rey-Osterrieth complex figure test; CFT copy, Copy in the Rey-Osterrieth complex; CDT, Clock-drawing test; SDMT, Symbol digit modalities tests; TMTA, Trail-making test part A; DST, Digital symbol test; SCWT, Stroop color-word test; TMTB, Trail-making test part B; CVFT, Category verbal fluency test; BNT, Boston naming test.

the statin group exhibited differences only in the attention domain (DST, F = 5.488, p = 0.02) (see Table 3).

4 Discussion

Our population-based study unveiled a significant correlation between sustained statin use and enhanced cognitive performance among dyslipidemia patients in Beijing communities. Even after adjusting for demographic variables and potential confounders, such as other cardiovascular risks, dyslipidemia patients who regularly took statins demonstrated notably improved cognitive performance, particularly in executive function, memory, and language. Furthermore, this trend persisted across both middle-aged and older people samples, albeit with a slight decrease observed in the middle-aged group and a more pronounced effect in individuals aged 65 and above.

TABLE 3 Significant intergroup differences in demographic data and multidomain cognitive performance of the two groups in middle age patients.

Variables (M ± SD)	Untreated (*n* = 185)	Statins (*n* = 266)	F/χ^2	*P*
Demographic information				
Age	58.81 ± 3.73	59.21 ± 3.52	1.34	0.247
Education	11.29 ± 2.16	11.52 ± 2.3	1.17	0.280
Gender	45/140	66/200	1	0.499
Physical health				
Type 2 Diabetes	55/130	103/153	3.88	0.049*
Hypertension	99/86	174/92	6.47	0.011*
Smoking	26/159	32/234	0.45	0.505
Obesity	19/166	27/239	0.02	0.898
General cognition				
MMSE	27.71 ± 1.99	27.82 ± 1.87	0.73	0.392
MOCA	22.41 ± 3.256	22.86 ± 2.887	1.91	0.168
Memory				
N5	5.25 ± 2.394	5.35 ± 2.224	0.02	0.889
N1N5	28.57 ± 8.38	28.92 ± 7.886	0.03	0.874
CFT delay	13.11 ± 7.511	13.46 ± 6.64	0.07	0.789
Visuospatial ability				
CFT copy	33.36 ± 4.547	34.03 ± 3.18	3.04	0.082
CDT	22.52 ± 5.48	22.63 ± 5.356	0.01	0.935
Attention				
SDMT	35.57 ± 10.479	36.48 ± 9.529	1.05	0.306
TMTA	54.59 ± 20.543	54.45 ± 19.815	0.01	0.942
DST	12.22 ± 1.996	12.66 ± 1.96	5.49	0.020*
Executive function				
SCWT	71.42 ± 17.133	72.94 ± 20.376	0.37	0.545
TMTB	150.98 ± 54.80	143.96 ± 44.639	1.71	0.191
Language				
VFT	47.43 ± 8.51	47.47 ± 8.08	0.01	0.970
BNT	23.60 ± 3.372	24.11 ± 3.051	1.81	0.179

Values are mean ± SD or Nos. of participants. The comparisons of age, education, and various cognitive function between the two groups were performed with ANOVA. The *p*-values for gender, diabetes, hypertension, obesity, and smoking ratio were obtained using a Chi-square test. Significance: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. Edu, Education; MMSE, Mini-mental state examination; MoCA, Montreal cognitive assessment; AVLT-N5, Auditory verbal learning test number 5; AVLT-N1N5, Auditory verbal learning test number1-number5; CFT-delay, Recall in the Rey-Osterrieth complex figure test; CFT copy, Copy in the Rey-Osterrieth complex; CDT, Clock-drawing test; SDMT, Symbol digit modalities tests; TMTA, Trail-making test part A; DST, Digital symbol test; SCWT, Stroop color-word test; TMTB, Trail-making test part B; CVFT, Category verbal fluency test; BNT, Boston naming test.

The lipid peroxidation theory of dementia suggests that damage to the BBB in dementia patients leads to the entry of external lipids into the brain, resulting in the accumulation of "adipose inclusion" and abnormalities in brain lipid metabolism, brain cholesterol alters the degradation of amyloid precursor protein, triggering the onset of dementia and accelerating the progression of dementia (40, 41). Consequently, dyslipidemia is thought to be an important risk factor for cognitive dysfunction and dementia (42, 43). Cognitive impairment is frequently observed to be accompanied by elevated serum cholesterol and low-density lipoprotein (LDL) levels (44). Even after adjusting for factors such as age and the APOEε4 allele, an increase in serum cholesterol remains associated with a threefold increase in dementia risk (45). It is commonly believed that lipid-lowering therapy is thought to be beneficial in reducing the incidence of AD and delaying cognitive decline (46). Our study emphasizes that regular use of statin medications has a positive impact on the cognitive function of patients with dyslipidemia. In addition, the beneficial effect is more pronounced in individuals aged 65 and above, especially among those who are already susceptible to cognitive impairment. These results are in line with previous observational cohort studies (16, 47), whether employed for cholesterol regulation in dyslipidemia patients or as a preventive measure against various cardiovascular and cerebrovascular conditions (48), statins have demonstrated a favorable influence on cognitive function. The explanation for differences across older people and middle-aged samples can be attributed to the fact that older people dyslipidemia participants, who are more likely to use statin medications over an extended period and often have a higher prevalence of chronic conditions such as hypertension and diabetes, may benefit from the potential accumulation of long-term protective effects and the mitigation of cognitive decline by controlling underlying risk factors, as well as from potential neuroprotective effects due to their aging nervous system. The differences across different age groups have also been confirmed in previous studies, indicating that statin use can reduce the incidence of dementia in healthy older people populations (49). Certainly, dietary therapy is also an important treatment method for patients with dyslipidemia (50). In this study, all patients received dietary therapy guidance and advice from hospitals, community health service centers, and our team. However, since the majority of the dyslipidemia patients included in this study are from northern China, where dietary habits tend to be rich in oil, salt, sugar, and fat, it is challenging for them to adhere to a healthy dietary regimen. Therefore, for most patients, taking medication regularly is easier than maintaining a healthy diet.

Additionally, it is worth noting that this study primarily examines the benefits of sustained statin use in community-dwelling patients with dyslipidemia, with a focus on a population that is not comprised of cognitive impairment or dementia patients. Therefore, it does not address potential time-dependent confounding factors related to worsened medication adherence due to cognitive impairment (51). Of course, there are conflicting views in epidemiological studies regarding the impact of statin drugs on dementia (51, 52), particularly in randomized controlled trials (RCTs) where the use of statin drugs has been shown not to reduce the risk of dementia (53, 54). Currently, there is no consensus on the potential efficacy of statins in preventing dementia or AD (22, 51). Padala et al. (55, 56) found in their studies on populations with dementia and cognitive impairment that statin use can lead to cognitive decline, while discontinuing statins may result in the reversal of cognitive impairment. In contrast, the Rotterdam Study found that statin use, whether lipophilic or hydrophilic, was associated with a reduced risk of Alzheimer's disease in the general population (57). An absence of

a consensus may stem from differences in experimental design across studies, such as the selection of study populations. Patients who already have cognitive impairments may respond differently to medication compared to those with normal cognition. This is particularly relevant for lipophilic statins, which may regulate cholesterol production in the brain, affecting neuronal structure and function and leading to transient cognitive decline (69). Additionally, factors such as study duration, medication dosage and concurrent drug use, the cognitive assessment tools used, and potential biases introduced by different study populations may also contribute to the variability in results. However, patients who accept and continue statin therapy are significantly associated with their education level, socioeconomic status, and cholesterol levels, all of which are closely related to the risk of dementia. Since the participants in this study were all older individuals from urban areas, this group tends to have better health awareness and medication adherence compared to older individuals from rural areas, this "healthy user effect" is also one of the issues that this study needs to address (58).

Our study has several strengths. Firstly, it explores the relationship between statin medication use and cognitive function in a relatively large community population, reflecting real-world conditions. Additionally, the study provides a comprehensive assessment of multidimensional cognitive function in all dyslipidemia patients. The findings indicate that the statins group outperformed the untreated group in various cognitive domains. Previous research has often been limited by focusing solely on employing one or two cognitive tests (47, 53), while our study comprehensively assessed the impact of statins on cognitive function in various domains among dyslipidemia patients. Furthermore, this study also investigated the relationship between statin medications and cognitive function in patients with dyslipidemia across different age groups. The findings revealed that the benefits of regular statin use are more significant in the older people sample, while in the middle-aged group, cognitive function gains from regular statin use are only evident as a trend.

While this study provides valuable insights, it is not without limitations. First, as a cross-sectional study, it cannot determine the long-term effects of statins on individuals with dyslipidemia. Longitudinal follow-up studies or well-designed randomized controlled trials are needed to optimize experimental design and analysis methods. These studies should precisely account for various confounding variables, including lipid fluctuations (59), different genetic variations (such as APOE, LDLR, CETP, etc.) (60, 61), guidelines for treatment of dyslipidemia, statin dosage (62, 63), and sex differences (64), to minimize bias and accurately quantify the specific cognitive benefits of statins for individuals with dyslipidemia. Additionally, this study solely explores the impact of statin therapy on the cognitive function of dyslipidemia patients and does not include individuals at cardiovascular risk who use statins for preventive purposes. Due to constraints in acquiring biological specimens, this study was not able to account for the APOE ε4 carriage status among subjects. Recent research suggests that the advantageous cognitive effects of statin therapy might be more pronounced among carriers of the APOE ε4 allele (65). Additionally, it is important to note that due to limitations in the available data, our study did not differentiate between the hydrophilic and lipophilic properties of statin medications among participants. While prior research has explored this issue, consensus on whether different types of statins exhibit divergent effects on cognition remains inconclusive (23, 66). Despite lipophilic statins being more likely to enter the central nervous system compared to hydrophilic statins, hydrophilic statins can also cross the blood–brain barrier with the assistance of certain active transport proteins, such as the OATP family transporters (67, 68). The impact of these confounding factors may constrain inferences drawn from observational studies, leading to conclusions that could vary to some extent based on the specific cohorts examined and the potential confounding variables controlled for in multivariate analyses.

5 Conclusion

Our population-based study has unveiled a notable correlation between consistent statin usage and improved cognitive performance among dyslipidemia patients residing in Beijing communities. Even after adjusting for demographic variables and potential confounders, such as other cardiovascular risks, dyslipidemia patients who maintained regular statin intake exhibited enhanced cognitive performance, notably in executive function, memory, and language. Moreover, this effect remained consistent across both middle-aged and older people samples, although a slight decrease was observed in the middle-aged group compared to a more pronounced impact in individuals aged 65 and above. Looking ahead, there is a pressing need for long-term follow-up studies or meticulously designed randomized controlled trials to comprehensively understand and quantify the specific cognitive benefits conferred by statin medications in dyslipidemia patients.

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 Institutional Review Board of the Imaging Center for Brain Research at Beijing Normal 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

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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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Association of frailty and serum neurofilament light chain levels: the mediating role of estimated glomerular filtration rate

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Background: Both frailty and elevated serum neurofilament light chain (sNfL) levels are linked to cognitive impairment. However, evidence of their relationship is lacking, and whether it was mediated by renal function was unknown. This study aimed to investigate the association between frailty and sNfL levels in a representative U.S. population, and to explore the potential mediating role of estimated glomerular filtration rate (eGFR) in this relationship.

Methods: Data from 1,782 participants aged 20–75 years in the 2013–2014 National Health and Nutrition Examination Survey (NHANES) were analyzed. Frailty was assessed using a 49-item frailty index, and participants were categorized as non-frail, pre-frail, or frail. sNfL levels were measured using acoustic emission technology. Multivariable linear regression models and restricted cubic spline analyses were employed to examine the associations between frailty, eGFR, and sNfL levels. Mediation analysis was conducted to evaluate the role of eGFR in the frailty-sNfL relationship.

Results: The prevalence of pre-frailty and frailty was 45.39 and 11.60%, respectively. A significant positive association was observed between frailty score and sNfL levels (adjusted β: 39.97, SE: 11.07, $p = 0.003$), with a linear relationship confirmed by restricted cubic spline analysis. Frail individuals had significantly higher sNfL levels compared to non-frail participants (adjusted β: 11.86, SE: 5.42, $p = 0.04$). eGFR was negatively associated with sNfL levels (adjusted β: -0.23, SE: 0.05, $p < 0.001$). Mediation analysis revealed that eGFR accounted for 12.52% of the total effect of frailty on sNfL levels ($p < 0.0001$).

Conclusion: This study demonstrates a significant association between frailty and elevated sNfL levels in a representative U.S. population, with eGFR partially mediating this relationship. These findings suggest that sNfL may serve as a potential biomarker for frailty-related neuronal damage and highlight the importance of kidney function in this association. Further research is warranted to explore the clinical implications of these findings in frailty assessment and management strategies.

KEYWORDS

frailty, serum neurofilament light chain, eGFR, mediation analysis, NHANES

1 Introduction

Neurofilament light chain (NfL) is a critical structural component of the neuronal cytoskeleton, essential for maintaining axonal integrity and function (Bridel et al., 2019; Koini et al., 2021). Under normal conditions, blood NfL levels remain low due to tight homeostatic regulation (Hviid et al., 2022). However, axonal damage or degeneration leads to the release of NfL proteins into the cerebrospinal fluid and subsequently into the bloodstream (Dietmann et al., 2023; Kölliker Frers et al., 2022). Elevated serum NfL (sNfL) levels have emerged as a valuable biomarker for various neurodegenerative diseases, including multiple sclerosis (Bittner et al., 2021), Alzheimer's Disease (Novobilský et al., 2023), and acute hepatic porphyrias (Sgobbi et al., 2024). These elevated levels reflect the extent of axonal damage and disease progression, correlating with disease severity (Disanto et al., 2017; Preische et al., 2019). Recent studies have highlighted the impact of elevated NfL levels on cognitive function, emphasizing its significance as a biomarker for cognitive impairment (He et al., 2021; Liu et al., 2024; Wheelock et al., 2023). Additionally, NfL levels have been found to mediate the connection between depressive symptoms and cognitive function in older adults (Xu et al., 2024).

Frailty, a geriatric syndrome characterized by decreased physiological reserve and increased vulnerability to stressors, has become a significant health concern in aging populations (Collard et al., 2012). This multidimensional condition is associated with adverse health outcomes, including falls, hospitalization, disability, and mortality (Ji et al., 2024; Ning et al., 2024). Frailty is intricately linked to cognitive impairment and depression in older adults. Studies have shown that frail individuals are at a higher risk of experiencing neuropsychiatric symptoms, especially in the context of Alzheimer's disease and mild cognitive impairment (Chi et al., 2024). Cognitive decline, depressive symptoms, and functional disability are significantly correlated with frailty, indicating a strong association between these factors (Chi et al., 2024; Monteiro and Borges, 2023). Cognitive frailty, a combination of physical frailty and cognitive impairment, is considered a risk factor for late-life depression, emphasizing the bidirectional relationship between frailty and depression (Panza et al., 2023). Older adults with cognitive frailty are more susceptible to depression, with somatic symptoms being prevalent, highlighting the importance of recognizing and addressing mental health issues in this population (Panza et al., 2023).

The relationship between frailty and serum neurofilament light chain levels may also be influenced by renal function, as measured by glomerular filtration rate (GFR). Impaired renal function can lead to altered levels of circulating biomarkers, including sNfL (Akamine et al., 2020; Polymeris et al., 2022), potentially complicating the interpretation of cognitive and physical health assessments. As kidney function declines, the clearance of various neurotoxic substances may be affected (Lim et al., 2021; Pieniazek et al., 2021), which could exacerbate both neurodegenerative processes and frailty. Thus, understanding the role of GFR in the association between frailty and sNfL levels is essential for elucidating the shared biological mechanisms underlying these conditions.

Identifying the relationship between frailty, sNfL, and renal function may facilitate a better understanding of their complex interplay. However, the precise nature of these associations and the factors influencing them remain to be fully elucidated. Despite the potential significance of these interrelationships, there is a paucity of research directly examining the association between frailty, sNfL levels, and renal function. Addressing these knowledge gaps is crucial for advancing our understanding of frailty pathophysiology and improving risk stratification and management strategies.

To address this research gap, we conducted an analysis utilizing data from the National Health and Nutrition Examination Survey (NHANES) between 2013 and 2014. Our study aims to explore the association between frailty and sNfL levels in a population representative of the United States, while also investigating the mediating role of estimated glomerular filtration rate (eGFR) in this relationship. This approach may uncover new insights into the complex relationship between frailty, neurodegeneration, and cognitive health in aging populations.

2 Materials and methods

2.1 Study participants

The National Health and Nutrition Examination Survey (NHANES) is a comprehensive, ongoing cross-sectional survey conducted in the United States by the National Center for Health Statistics. It aims to include a representative sample of the general, non-institutionalized population across all age groups. The survey employs a stratified, multistage, clustered probability sampling design, with oversampling of non-Hispanic Black and Hispanic individuals, low-income populations, and older adults. NHANES comprises a structured home interview followed by a standardized health examination, including physical assessments and laboratory tests. For detailed information about NHANES, please refer to the NHANES website.[1] The original survey received approval from the Centers for Disease Control and Prevention Research Ethics Review Board, with written informed consent obtained from all adult participants. Our present analysis was deemed exempt by our institutional review board due to the use of a completely de-identified dataset.

This study utilized data from the NHANES 2013–2014 cycle, as illustrated in Figure 1. The initial sample included 10,175 participants. Participants with missing serum neurofilament light chain (sNfL) data were excluded ($n = 8,104$). Participants with age < 20, missing data on frailty assessment, and other incomplete data of covariates, including sex, ethnicity, marital status, family income, smoking status, drinking status, and body mass index (BMI), were also excluded ($n = 289$). Finally, a total of 1,782 participants were included in the analysis.

2.2 Assessment of frailty

We assessed frailty using the frailty index (FI) approach proposed by Hakeem et al. This index comprises 49 variables spanning multiple systems, including cognition, dependency, depressive symptoms, comorbidities, general health status, hospital utilization, physical performance, body measurements, and laboratory test values (Searle et al., 2008; Shi, 2023). Participants were required to complete at least

1 https://wwwn.cdc.gov/nchs/nhanes/

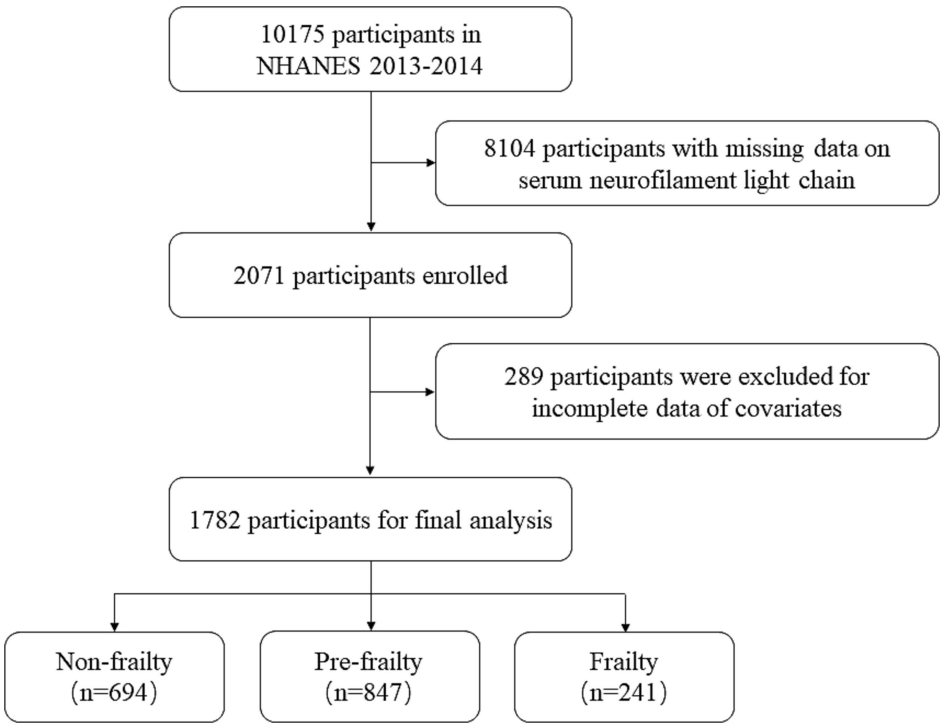

FIGURE 1
Flowchart of the study population.

80% (approximately 40 items) of the 49 frailty items to be included in the analysis. Frailty was quantified using a deficit accumulation approach, with the frailty score calculated by summing specific deficit items and dividing by the total number of considered items. This resulted in a score ranging from 0 to 1, where 0 represents no deficit and 1 indicates a complete deficit (see Supplementary Table S1).

For analytical purposes, we transformed this continuous score into a categorical variable based on cutoffs established in previous literature (Blodgett et al., 2015; Chen et al., 2019; Miller et al., 2017). Participants were categorized into three groups: non-frailty (FI $\leq$ 0.10), pre-frailty (0.10 < FI $\leq$ 0.21), and frailty (FI > 0.21). A comprehensive overview of the variables included in the frailty index and their corresponding scores is provided in Supplementary Table S1.

2.3 Measurement of serum NfL levels

Blood samples were collected from half of the participants aged 20–75 years who provided consent. The samples were analyzed using acoustic emission technology on the Attelica immunoassay system, which employs acridol chemiluminescence and paramagnetic particles to enhance sensitivity and speed during the sNfL immunoassay process. The assay procedure involves initial incubation of the sample with acridinium-ester (AE)-labeled antibodies that bind to the NfL antigen, followed by the introduction of paramagnetic particles (PMPs) coated with capture antibodies to form antigen–antibody-PMP complexes. Unbound AE-labeled antibodies are then removed, and acid and base are added to initiate chemiluminescence, with subsequent light emission measurements. Rigorous quality assurance procedures were maintained throughout the analysis and measurement processes (Fitzgerald et al., 2022). The assay's lower limit of quantification was 3.9 pg./mL (defined as the concentration at which the coefficient of variation was $\leq$20%), and the upper limit was 500 pg./mL. AE immunoassays offer several advantages over other established assays, including high quantum yields, rapid kinetics, hydrophilicity, hydrolytic stability, and small size. Detailed methodology can be found at: https://wwwn.cdc.gov/Nchs/Nhanes/2013-2014/SSSNFL_H.htm.

2.4 Assessment of covariates

To minimize confounding effects, we identified essential factors including age (<39 years, 40–59 years, $\geq$60 years), sex (male and female), ethnicity (Non-Hispanic White, Mexican American, Non-Hispanic Black, Other Hispanic, and Other Race), marital status (Divorced, Living with partner, Married, Never married, Separated, Widowed), education level (Less than 9th grade, 9-11th grade, High school graduate or equivalent, Some college or AA degree, College graduate or above), family income, body mass index (BMI) (under & healthy weight < 25 kg/m^2, overweight 25–30 kg/m^2, and obesity $\geq$30 kg/m^2), smoking status (never, former, current smoker), drinking status (never, former, current drinker), and chronic diseases (including stroke, hypertension, diabetes mellitus (DM), hyperlipidemia, and depression) as major potential confounders. Family income was classified into three categories based on the poverty income ratio (PIR) as defined by a US government report: low (PIR $\leq$1.3), medium (PIR >1.3 to 3.5), and high (PIR $\geq$3.5). Chronic diseases were defined based on participants' self-reported diagnoses by a doctor or other healthcare professional. The estimated glomerular filtration rate

(eGFR) was calculated using the creatinine equation of the Chronic Kidney Disease Epidemiology Collaboration (Levey et al., 2009).

2.5 Statistical analysis

All analyses were conducted according to the recommended NHANES analysis guidelines, using appropriate weighting as suggested by the National Center for Health Statistics to obtain estimates generalizable to the US population. Continuous variables are presented as weighted means (SE), while categorical variables are reported as numbers and weighted proportions.

We used generalized linear models to assess the associations between frailty status, eGFR, and sNfL levels. β coefficients, standard errors (SE), and corresponding 95% confidence intervals (CIs) were employed to quantify these relationships. Three regression models were constructed to control for confounding factors: Model 1 (unadjusted), Model 2 (adjusted for age, sex, and ethnicity), and Model 3 (further adjusted for education level, marital status, family income, smoking status, drinking status, and BMI). Additionally, we performed multivariate-adjusted (Model 3) restricted cubic spline (RCS) analyses to characterize non-linear relationships between frailty status, eGFR, and sNfL levels, with knots at the 10th, 50th, and 90th percentiles. Non-linearity was assessed using likelihood tests.

Stratified analyses were conducted to elucidate the association between frailty status and sNfL levels within distinct subgroups defined by age, sex, BMI, ethnicity, education level, smoking status, drinking status, and family income. *P*-interaction between dietary inflammation and each stratified variable was tested. The interactive effects of frailty status and eGFR on sNfL levels were examined using interaction terms in weighted multivariate linear regression analyses. Mediation analysis was performed to evaluate whether the effect of frailty status on sNfL levels could be explained by eGFR, quantifying the total effect, direct effect, and indirect effect. The proportion of the effect attributable to the mediator was calculated by dividing the indirect effect by the total effect. All statistical analyses were conducted using R software (version 4.3.3), with a two-sided $p < 0.05$ considered statistically significant.

3 Results

3.1 Characteristics of study participants grouped by frailty status

Table 1 presents the demographic characteristics of the participants stratified by frailty status. A total of 1782 participants were included in the study, of whom 694 were non-frail, 847 were pre-frail, and 241 were frail. Their mean age (SE) was 45.25 ± 0.52 years, of which 858 (49.33%) were male and 924 (50.67%) were female. The average frailty score was 0.13 ± 0.00, with pre-frailty and frailty prevalence of 45.39 and 11.60%, respectively. Compared to non-frail individuals, frail participants were significantly older (mean age 54.92 vs. 41.19 years), more likely to be female (68.03% vs. 39.07%), had lower family income (39.93% vs. 21.02%), higher prevalence of hypertension (75.88% vs. 17.99%) and diabetes mellitus (62.29% vs. 15.41%), higher rates of obesity (54.22% vs. 27.65%), lower estimated glomerular filtration rate (eGFR) (mean 84.34 vs. 98.56 mL/min/1.73m^2), and higher serum neurofilament light chain (sNfL) levels (mean 30.47 vs. 13.60 pg./mL) (all $p < 0.01$).

3.2 Associations between frailty and sNfL levels

Table 2 illustrates the relationship between frailty and sNfL levels. A significant association was observed between the continuous frailty score and sNfL levels in Model 1 (Adjusted β (SE): 56.63 (12.28), $p < 0.001$). This association remained significant after adjusting for potential confounders in Model 2 (Adjusted β (SE): 45.29 (11.9), $p = 0.01$) and Model 3 (Adjusted β (SE): 39.97 (11.07), $p = 0.003$). Participants in the frailty group showed a significantly positive association with sNfL levels compared to the non-frailty group, which persisted after controlling for potential confounding factors in Model 2 (Adjusted β (SE): 13.71 (5.35), $p = 0.04$) and Model 3 (Adjusted β (SE): 11.86 (5.42), $p = 0.04$). In the pre-frailty group, a positive but non-significant association was observed in Model 2 (Adjusted β (SE): 1.95 (1.16), $p = 0.14$) and Model 3 (Adjusted β (SE): 1.34 (1.04), $p = 0.22$).

The nonlinear relationship between frailty and sNfL was explored using restricted cubic spline (RCS) regression. Figure 2 presents the results of multivariate linear regression with RCS, revealing a linear and positive correlation between frailty score and sNfL levels (P for non-linearity = 0.0519).

3.3 Subgroup analysis for the association of frailty and sNfL levels

Subgroup analyses were conducted to investigate whether the relationship between frailty status and sNfL levels was influenced by factors such as age, sex, BMI, ethnicity, education level, smoking status, drinking status, and family income (Table 3). After adjusting for potential confounders, significant associations were observed between frailty status and sNfL levels in males, participants aged 40–59 years and ≥ 60 years, overweight individuals, those with college graduate or higher education, never smokers, current drinkers, and those with low family income. Detailed results of trend and interaction analyses are presented in Table 3.

3.4 Associations between eGFR and sNfL levels

Table 4 demonstrates the relationship between eGFR and sNfL levels. A significantly negative association was observed between eGFR (as a continuous variable) and sNfL levels, persisting after adjusting for potential confounders in Model 2 (Adjusted β (SE): −0.23 (0.06), $p = 0.004$) and Model 3 (Adjusted β (SE): −0.23 (0.05), $p < 0.001$). Participants with eGFR <60 mL/min/1.73m^2 showed a positive but statistically non-significant association with sNfL levels compared to those with eGFR ≥60 mL/min/1.73m^2 after adjusting for potential confounders in Model 2 (Adjusted β (SE): 14.79 (6.46), $p = 0.05$) and Model 3 (Adjusted β (SE): 11.88 (6.39), $p = 0.08$). RCS regression analysis revealed a non-linear correlation between eGFR and sNfL levels (P for non-linearity = 0.001).

10.3389/fnagi.2024.1475505

TABLE 1 Baseline characteristics of participants from NHANES 2013–2014 by categories of frailty status.

Characteristics	Total	Non-frailty	Pre-frailty	Frailty	*p*-value
No. of participants	1,782	694	847	241	
Age (years)	45.25 (0.52)	41.19 (0.69)	46.62 (0.79)	54.92 (0.73)	< 0.0001
Age group, %					< 0.0001
<39	596 (37.40)	322 (48.78)	251 (33.17)	23 (11.75)	
40–59	673 (38.29)	236 (34.06)	338 (40.55)	99 (45.10)	
≥60	513 (24.31)	136 (17.15)	258 (26.28)	119 (43.14)	
Sex, %					< 0.0001
Female	924 (50.67)	286 (39.07)	474 (57.24)	164 (68.03)	
Male	858 (49.33)	408 (60.93)	373 (42.76)	77 (31.97)	
Ethnicity, %					< 0.001
Non-Hispanic White	822 (67.18)	332 (68.96)	368 (64.45)	122 (71.27)	
Mexican American	242 (8.93)	97 (9.96)	118 (8.84)	27 (5.50)	
Non-Hispanic Black	318 (11.46)	78 (6.90)	190 (15.04)	50 (14.32)	
Other Hispanic	158 (5.38)	65 (6.32)	73 (5.03)	20 (3.26)	
Other Race	242 (7.06)	122 (7.87)	98 (6.65)	22 (5.64)	
Marital status, %					< 0.001
Divorced	208 (10.55)	56 (7.07)	92 (10.80)	60 (22.48)	
Living with partner	134 (7.09)	46 (5.65)	75 (8.56)	13 (6.70)	
Married	961 (57.48)	394 (60.24)	457 (56.55)	110 (50.86)	
Never married	345 (19.45)	169 (23.97)	151 (17.66)	25 (9.68)	
Separated	52 (1.97)	10 (1.09)	28 (2.17)	14 (4.50)	
Widowed	82 (3.45)	19 (1.98)	44 (4.25)	19 (5.79)	
Education level, %					< 0.001
Less than 9th grade	109 (3.54)	36 (3.05)	45 (3.32)	28 (6.24)	
9-11th grade	248 (10.93)	85 (9.36)	122 (11.04)	41 (16.44)	
High school graduate or equivalent	375 (20.32)	141 (19.57)	180 (20.17)	54 (23.82)	
Some college or AA degree	570 (33.71)	201 (29.80)	281 (35.64)	88 (40.90)	
College graduate or above	478 (31.43)	231 (38.22)	218 (29.83)	29 (12.60)	
Family income, %					< 0.0001
Low	613 (25.00)	198 (21.02)	288 (24.96)	127 (39.93)	
Medium	598 (33.06)	220 (29.74)	307 (36.38)	71 (32.33)	
High	571 (41.94)	276 (49.24)	252 (38.66)	43 (27.74)	
BMI (kg/m^2)	29.44 (0.27)	27.34 (0.19)	30.38 (0.45)	33.59 (0.83)	< 0.0001
BMI group, %					< 0.0001
≤25	529 (28.92)	287 (38.94)	209 (23.33)	33 (14.53)	
25.1–29.9	575 (33.03)	217 (33.42)	288 (33.45)	70 (31.25)	
≥30	667 (37.59)	188 (27.65)	347 (43.22)	132 (54.22)	
Smoking status, %					< 0.001
Never	990 (56.49)	435 (63.70)	455 (54.19)	100 (38.81)	
Former	407 (22.90)	135 (20.05)	203 (24.60)	69 (26.84)	
Current smoker	384 (20.59)	123 (16.25)	189 (21.20)	72 (34.35)	
Drinking status, %					< 0.0001
Never	224 (10.95)	80 (9.60)	103 (11.60)	41 (13.45)	
Former	281 (12.81)	69 (7.09)	144 (14.26)	68 (28.34)	
Current drinker	1,277 (76.24)	545 (83.31)	600 (74.14)	132 (58.21)	

(Continued)

TABLE 1 (Continued)

Characteristics	Total	Non-frailty	Pre-frailty	Frailty	*p*-value
Stroke, %					< 0.0001
No	1735 (97.49)	694 (100.00)	828 (97.88)	213 (86.69)	
Yes	47 (2.51)	0 (0.00)	19 (2.12)	28 (13.31)	
Hypertension, %					< 0.0001
No	1,063 (63.02)	560 (82.01)	454 (54.96)	49 (24.12)	
Yes	719 (36.98)	134 (17.99)	393 (45.04)	192 (75.88)	
DM, %					< 0.0001
No	1,176 (70.33)	559 (84.59)	527 (66.58)	90 (37.71)	
Yes	590 (28.68)	133 (15.41)	307 (33.42)	150 (62.29)	
Hyperlipidemia, %					< 0.0001
No	562 (32.28)	280 (40.71)	250 (29.32)	32 (12.55)	
Yes	1,220 (67.72)	414 (59.29)	597 (70.68)	209 (87.45)	
Depression, %					< 0.0001
No	1,611 (91.55)	694 (100.00)	789 (92.70)	128 (56.79)	
Yes	167 (8.28)	0 (0.00)	57 (7.30)	110 (43.21)	
sNfl (pg/ml)	16.83 (1.18)	13.60 (0.67)	16.42 (1.25)	30.47 (5.95)	0.01
sNfl group, %					< 0.001
Q1	446 (26.01)	212 (30.35)	208 (25.87)	26 (10.45)	
Q2	452 (25.75)	201 (28.79)	208 (24.11)	43 (20.89)	
Q3	440 (24.08)	164 (22.64)	212 (25.17)	64 (25.17)	
Q4	444 (24.16)	117 (18.23)	219 (24.85)	108 (43.49)	
eGFR (mL/min/1.73m^2)	95.94 (0.69)	98.56 (1.21)	96.42 (1.09)	84.34 (1.76)	< 0.0001
eGFR group, %					< 0.0001
≥60 mL/min/1.73m^2	1,687 (95.37)	681 (98.37)	806 (94.98)	200 (85.80)	
<60 mL/min/1.73m^2	95 (4.63)	13 (1.63)	41 (5.02)	41 (14.20)	

BMI, Body mass index; DM, diabetes mellitus; sNfl, serum neurofilament light chain; eGFR, estimated glomerular filtration rate.

TABLE 2 The association between frailty and sNfl levels, with results weighted for sampling strategy.

Unweighted no./population size		Neurofilament light chain (pg/mL)					
		Model 1, Adjusted β (SE)	*p*-Value	Model 2, Adjusted β (SE)	*p*-Value	Model 3, Adjusted β (SE)	*p*-Value
Frailty score	1782/189254495	56.63 (12.28)	<0.001	45.29 (11.9)	0.01	39.97 (11.07)	0.003
Frailty group							
Non-frailty	694/81414609	Ref		Ref		Ref	
Pre-frailty	847/85895577	2.82 (1.10)	0.02	1.95 (1.16)	0.14	1.34 (1.04)	0.22
Frailty	241/21944309	16.87 (5.54)	0.01	13.71 (5.35)	0.04	11.86 (5.42)	0.04
p for trend		0.003		0.021		0.024	

SE, standard error; sNfl, serum neurofilament light chain. Model 1: unadjusted. Model 2: adjusted for age, sex, ethnicity. Model 3: adjusted for all the factors in Model 2 and education level, marital status, family income, smoking status, drinking status, and BMI.

3.5 The mediation effects of eGFR on the association of frailty and sNfL levels

Figure 3 presents the results of mediation analysis, adjusted for potential confounders. The total effect of frailty on sNfL was 3.68 (95% CI: 1.73, 5.81; $p < 0.0001$), while the indirect effect mediated through eGFR was 0.46 (95% CI: 0.07, 1.05; $p < 0.0001$). The proportion of the association mediated by eGFR was 12.52% ($p < 0.0001$).

4 Discussion

This study aimed to investigate the association between frailty and sNfL levels in a representative U.S. population and to explore the mediating role of eGFR in this relationship. Our findings reveal several important insights into the complex interplay between frailty, neuronal damage, and kidney function. First, we observed a significant positive association between frailty and sNfL levels in our study

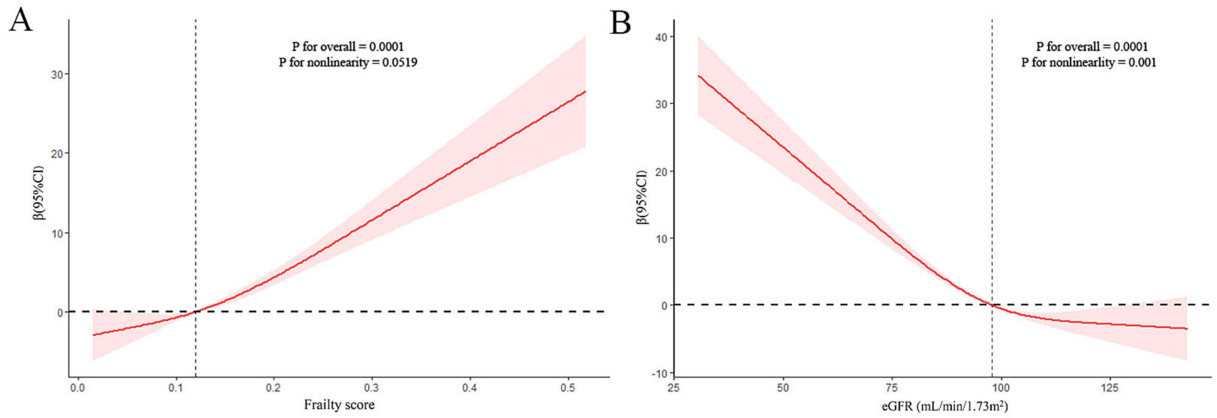

FIGURE 2
Restricted cubic spline (RCS) analysis with multivariate-adjusted associations (Model 3) between frailty **(A)** or estimated glomerular filtration rate (eGFR) **(B)** and serum neurofilament light chain (sNfL) levels.

population. The prevalence of pre-frailty and frailty was considerable, at 45.39 and 11.60%, respectively. Importantly, although the restricted cubic spline (RCS) model allows for the assessment of non-linear relationships, our analysis revealed an approximately linear association between frailty scores and sNfL levels across the observed range, as indicated by the RCS analysis (P for non-linearity = 0.0519). Frail individuals exhibited significantly higher sNfL levels compared to non-frail participants, even after adjusting for potential confounders. We also observed a negative association between eGFR and sNfL levels. Notably, eGFR was found to mediate the relationship between frailty and sNfL levels, accounting for 12.52% of the total effect.

The concept of frailty as an accelerated aging process is well-supported by numerous studies demonstrating its association with various markers of biological aging (Kuiper et al., 2023; Mitchell et al., 2023; Sepúlveda et al., 2022). A study conducted by Bountziouka et al. (2022) found that frailty was significantly associated with shorter telomere length, supporting the link between frailty and accelerated cellular aging. Phyo et al. (2024) found that frailty was associated with multiple epigenetic age acceleration indicators, including the DunedinPACE and GrimAge, further confirming the close relationship between frailty and biological aging. Neurodegeneration, characterized by the progressive loss of structure or function of neurons, is increasingly recognized as a critical element in the development and progression of frailty (Gómez-Gómez and Zapico, 2019; Ward et al., 2022). Evidence suggests that frail individuals exhibit higher rates of cognitive decline and are at an increased risk of developing neurodegenerative conditions (Cao et al., 2023; Li C. et al., 2023; Robertson et al., 2013). Kulmala et al. (2014) demonstrated frailty is strongly associated with cognitive impairment and clinically diagnosed dementia among persons aged 76 and older. Li R. et al. (2023) demonstrated in a longitudinal study that severe frailty was significantly associated with the subsequent decline in cognitive function. In the five identified frailty trajectories, participants with mild frailty and frailty were all significantly associated with the subsequent cognition decline in the elderly (Li R. et al., 2023). Neuroimaging studies have provided further evidence of the neurobiological underpinnings of this relationship. Du et al. demonstrated that white matter hyperintensities (WMHs) mediate the association between frailty and cognitive impairment in moyamoya disease (MMD) (Du et al., 2024). These findings revealed a complex interplay between frailty and neurodegeneration. Neurofilament light chain has emerged as a robust biomarker for neurodegeneration due to its sensitivity to neuronal damage and its ability to reflect disease severity and progression (Gaetani et al., 2019; Lu et al., 2015). Elevated sNfL levels have been correlated with cognitive impairment and brain atrophy in conditions like Alzheimer's disease (Lehmann et al., 2023; Xiong et al., 2021). These findings suggest that sNfL could potentially serve as a biomarker for neurodegenerative processes underlying frailty.

Previous studies have reported associations between elevated sNfL levels and frailty-related conditions. Capo et al. found that NfL levels increased significantly with age, particularly in men, and were associated with decreased muscle function, including grip strength, walking speed, and chair test performance (Capo et al., 2023). Ladang et al. (2023) reported that NfL was associated with performance tests and was an independent predictor of severe sarcopenia. In this study, we demonstrated a clear association between frailty and sNfL levels in a large, representative sample across a wide age range. Our study builds on these findings by establishing a linear relationship between frailty score and sNfL levels, suggesting that neuronal damage may increase progressively with frailty severity. Subgroup analyses revealed potential sex-specific and age-dependent mechanisms linking frailty and neuronal damage, with stronger associations observed in males and older age groups. Significant associations in specific socioeconomic subgroups (e.g., those with higher education levels or lower family income) highlight the complex interplay between social determinants of health, frailty, and neurological integrity.

The negative association between eGFR and sNfL levels is consistent with previous research indicating that impaired kidney function contributes to increased sNfL levels, possibly due to reduced clearance of neurofilament proteins (Koini et al., 2021; Dittrich et al., 2023; Tang et al., 2022). Our results revealed a consistent and statistically significant negative association between eGFR (as a continuous variable) and sNfL levels across all adjusted models. However, when examining eGFR as a categorical variable (<60 vs. ≥60 mL/min/1.73m^2), a positive association with sNfL levels was observed for participants with lower eGFR, although this relationship did not reach statistical significance in the fully adjusted models. This

TABLE 3 Stratified analyses of the associations between different frailty status and sNfL levels.

Subgroups	Non-frailty	Pre-frailty	*p*-Value	Frailty	*p*-Value	P–t	P-int
Age							0.042
20–39	ref	0.443(−1.706, 2.591)	0.667	1.672(−2.508, 5.851)	0.407	0.552	
40–59	ref	3.728(−0.937, 8.394)	0.109	5.469(0.141,10.797)	0.045	0.021	
≥60	ref	0.624(−4.326, 5.574)	0.792	25.092(2.569,47.615)	0.031	0.029	
Sex							0.83
Male	ref	2.062(−1.686, 5.810)	0.259	13.353(1.355,25.351)	0.031	0.017	
Female	ref	0.841(−1.532, 3.214)	0.462	11.192(−4.258,26.642)	0.143	0.147	
BMI							0.495
<25	ref	0.534(−2.078, 3.146)	0.669	22.361(−5.594,50.316)	0.109	0.171	
25–30	ref	1.925(−0.292, 4.142)	0.084	9.749(3.398,16.101)	0.005	0.005	
≥30	ref	2.253(−1.835, 6.340)	0.258	11.076(−6.878,29.030)	0.208	0.159	
Ethnicity							0.296
Non-Hispanic White	ref	1.05(−1.030, 3.131)	0.299	14.172(−3.414,31.758)	0.106	0.073	
Mexican American	ref	−2.302(−6.956, 2.352)	0.292	6.528(−5.579,18.635)	0.254	0.894	
Non-Hispanic Black	ref	0.302(−1.594, 2.197)	0.736	7.812(−1.363,16.987)	0.089	0.083	
Other Hispanic	ref	−0.486(−4.524, 3.553)	0.799	4.445(−1.116,10.005)	0.108	0.63	
Other Race	ref	5.936(−4.185,16.058)	0.229	−9.115(−35.049,16.818)	0.463	0.948	
Education level							0.234
Less than 9th grade	ref	−0.802(−4.702, 3.099)	0.664	−3.781(−11.715, 4.153)	0.322	0.332	
9-11th grade	ref	0.605(−5.606, 6.817)	0.838	5.573(−4.852,15.998)	0.272	0.362	
High school graduate or equivalent	ref	−0.604(−3.941, 2.732)	0.705	3.64(−4.043,11.324)	0.329	0.424	
Some college or AA degree	ref	3.813(0.545, 7.081)	0.025	18.387(−6.489,43.262)	0.136	0.089	
College graduate or above	ref	1.678(−1.100, 4.457)	0.217	22.503(8.841,36.165)	0.003	0.014	
Smoking status							0.432
Never	ref	1.664(−1.143, 4.470)	0.226	8.093(0.891,15.295)	0.030	0.024	
Former	ref	1.452(−2.805, 5.709)	0.478	24.626(−11.750,61.003)	0.170	0.144	
Current smoker	ref	1.24(−5.001, 7.481)	0.678	7.806(−5.534,21.145)	0.231	0.272	
Drinking status							0.452
Never	ref	8.73(−0.678,18.139)	0.067	13.08(−1.225,27.384)	0.070	0.019	
Former	ref	−0.243(−9.568, 9.081)	0.956	20.139(−14.383,54.662)	0.233	0.22	
Current drinker	ref	0.537(−0.795, 1.869)	0.404	7.95(0.210,15.690)	0.045	0.059	
Family income							0.167
Low	ref	5.293(0.575,10.012)	0.030	8.167(0.061,16.273)	0.049	0.019	
Medium	ref	−1.116(−5.132, 2.899)	0.562	22.226(−6.603,51.054)	0.121	0.128	
High	ref	1.567(−0.916, 4.050)	0.199	7.386(−1.512,16.283)	0.097	0.103	

BMI, Body mass index. Analyses were adjusted for covariates age, sex, ethnicity, education level, marital status, family income, smoking status, drinking status, and BMI when they were not the strata variables. P–t, p for trend; P-int, p for interaction.

may be due to the relatively small number of participants with eGFR <60 mL/min/1.73m^2 associated with the study population. The mediating role of eGFR in the frailty-sNfL relationship suggests that kidney function significantly influences the relationship between frailty and neuronal damage. Impaired kidney function, which is common in frail individuals, may exacerbate neuronal damage by several mechanisms: Firstly, reduced kidney function may lead to the accumulation of neurotoxic metabolites, contributing to neuronal damage and elevated sNfL levels (Stanciu et al., 2020). Secondly, both frailty and kidney dysfunction are associated with chronic inflammation and oxidative stress, which may synergistically promote neuronal injury (Ebert et al., 2021; Gill et al., 2024). Lastly, shared risk factors and pathophysiological pathways between frailty, kidney disease, and neurodegeneration may underlie these complex relationships (Shen et al., 2017).

Our findings have significant clinical implications. The association between frailty and elevated sNfL levels suggests that sNfL could serve as a potential biomarker for frailty-related neuronal damage. This may

TABLE 4 The association between eGFR and sNfl levels, with results weighted for sampling strategy.

Unweighted no./Population size		Neurofilament light chain (pg/mL)					
		Model 1, Adjusted β (SE)	*p*-Value	Model 2, Adjusted β (SE)	*p*-Value	Model 3, Adjusted β (SE)	*p*-Value
eGFR	1782/189254495	−0.32 (0.06)	<0.0001	−0.23 (0.06)	0.004	−0.23 (0.05)	<0.001
eGFR group							
≥60 mL/min/1.73m^2	1687/180498548	Ref		Ref		Ref	
<60 mL/min/1.73m^2	95/8755947	20.95 (5.8)	0.003	14.79 (6.46)	0.05	11.88 (6.39)	0.08

SE, standard error; eGFR, estimated glomerular filtration rate; sNfl, serum neurofilament light chain. Model 1: unadjusted. Model 2: adjusted for age, sex, ethnicity. Model 3: adjusted for all the factors in Model 2 and education level, marital status, family income, smoking status, drinking status, and BMI.

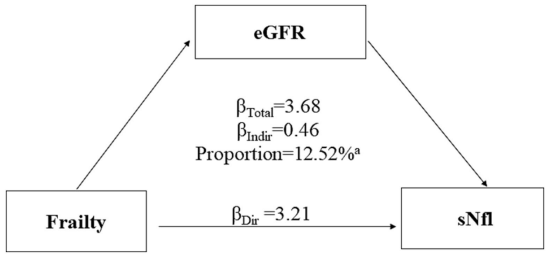

FIGURE 3
Mediation analyses of the association between frailty with serum neurofilament light chain (sNfL) levels through estimated glomerular filtration rate (eGFR). [a]*p* value <0.0001.

have important applications in early detection and monitoring of frailty, particularly in identifying individuals at higher risk of frailty-associated neurological decline. The mediating role of eGFR underscores the importance of considering kidney function in frailty assessment and management strategies. One of the strengths of our study is the large, representative sample from the U.S. population, which enhances the generalizability of our findings. Additionally, the comprehensive assessment of frailty using a 49-item frailty index provides a robust measure of frailty status. However, limitations include the cross-sectional design, which precludes establishing causality, and potential confounding factors despite adjustments in our models. The use of self-reported data for some variables may introduce recall bias.

Future research should include longitudinal studies to investigate the predictive value of sNfL for frailty progression and associated outcomes. Mechanistic studies exploring the biological pathways linking frailty, kidney function, and neuronal damage are warranted. Clinical trials evaluating interventions targeting the frailty-sNfL-eGFR relationship could provide valuable insights for frailty prevention and management strategies.

5 Conclusion

This study demonstrates a significant association between frailty and elevated sNfL levels in a representative U.S. population, with eGFR partially mediating this relationship. These findings advance our understanding of the complex interplay between frailty, neuronal damage, and kidney function in aging populations. By highlighting sNfL as a potential biomarker for frailty-related neuronal damage and emphasizing the role of kidney function, this study opens new avenues for research and clinical practice in aging neuroscience. These insights may lead to improved strategies for early detection, monitoring, and management of frailty, potentially mitigating its impact on neurological health and overall well-being in aging populations.

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 Ethics Review Board of the American National Center for Health Statistics. 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

WY: Formal analysis, Writing – original draft, Writing – review & editing. SH: Formal analysis, Writing – original draft, Writing – review & editing. HX: Funding acquisition, Methodology, Visualization, Writing – review & editing. PT: Methodology, Writing – original draft. SC: Conceptualization, Supervision, Validation, 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

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Effects of repetitive transcranial magnetic stimulation on cognitive function and hormone levels in early stroke patients with low thyroid hormone levels

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Background: This study aimed to observe the effects of repetitive transcranial magnetic stimulation (rTMS) on cognitive function and thyroid hormone levels in early older stroke patients with low thyroid hormone levels, and to investigate the correlation between the changes in thyroid hormone levels and the improvements in cognitive function after stroke.

Methods: Forty older stroke patients who met the inclusion criteria were recruited and randomized into a magnetic-stimulation group (rTMS group) and a sham-stimulation group (Sham group). The rTMS group received low-frequency true stimulation and the Sham group received low-frequency sham stimulation. Patients' cognitive scores, activity of daily living(ADL) scores, and their levels of triiodothyronine (T3), free triiodothyronine (FT3), thyroxin (T4), free thyroxine (FT4), and thyroid stimulating hormone (TSH) were assessed before the intervention, after the 4-week intervention, and after an additional 4 weeks of follow-up; Repeated measurement analysis of variance was used to compare the changes of each index in the two groups at different times and the correlations between patiens' cognitive function scores and their changing hormone levels were subsequently investigated.

Results: Thirty-one patients were included in this study: 16 patients in rTMS group and 15 patients in the Sham group. Repeated-measures ANOVA showed that patients' T3,FT3 and TSH levels tended to increase at 4-week intervention and at the follow up ($p < 0.05$), and that the rTMS group had a better effect on improving T3 than the Sham group ($F_{group} = 5.319$, $p = 0.028$); The cognitive scale at different time points in both groups showed an upward trend ($p < 0.05$), and the MoCA, DSF, DSB scores in the rTMS group were statistically higher than those in the Sham group at the end of the 4-week intervention and at the follow-up ($p < 0.05$); The changes in the levels of T3 before and after 4-week intervention were positively correlated with the changes in the MoCA scores ($r = 0.638$, $p < 0.05$). And the difference in T3 level change was positively correlated with the difference in delayed recall, attention and naming score change ($r = 0.562$, $p < 0.05$; $r = 0.562$, $p < 0.05$; $r = 0.531$, $p < 0.05$); and the difference in FT3 level change was positively correlated with the visuospatial and executive function ($r = 0.514$, $p < 0.05$).

Conclusion: Repetitive transcranial magnetic stimulation improved cognitive function and elevated T3 levels in older patients with post-stroke cognitive dysfunction who had low thyroid hormone levels. Within the normal range, increases in T3 levels are positively correlated with changes in cognitive function.

KEYWORDS

stroke, repetitive transcranial magnetic stimulation, thyroid hormone, cognitive function, HPT axis, rehabilitation

1 Introduction

Stroke is characteristic by high morbidity, mortality and disability, and is the second leading cause of death and the third leading cause of disability worldwide (Dee et al., 2020; Kefale, 2019). Post-stroke cognitive impairment (PSCI), as one of the most important dysfunctions, has an incidence rate of up to 80% (Sun et al., 2014). PSCI refers to a series of syndromes characterized by cognitive dysfunction that meet the diagnostic criteria of cognitive dysfunction through clinical symptoms and functional evaluation, especially various types of cognitive impairment that occur after stroke (Huang et al., 2022; Wang et al., 2021). PSCI is closely related to the poor functional prognosis of stroke patients, and seriously affects individual's ability to self-care and achieve re-occupation. The probability of dementia in stroke patients with cognitive impairment will increase by 4–12 times if it is not detected and treated quickly. Post-stroke dementia, greatly increases the difficulty of patient rehabilitation and seriously reduces the quality of life of patients in addition to imposing a heavy burden on individuals, families, and the society (Renjen et al., 2015; Yang et al., 2024). Therefore, early prevention and targeted mitigation of risk factors that lead to or exacerbate cognitive impairment are particularly critical.

The mechanism of PSCI occurrence is complex and has multiple influencing factors. Although it is known that damage to neuroanatomical structures related to cognitive function that is caused by stroke will directly lead to cognitive dysfunction, recent progress in brain research and the neuroendocrine mechanisms on the functional prognosis of stroke. It has been demonstrated that, as a stress event, stroke may activate the neuroprotective mechanism of the body. It can reduce the oxygen consumption and metabolic rate of the body through self-regulation of endocrine function, such as reducing the level of thyroid hormone, especially T3 level, which is conducive to the repair of the injured site. With the recovery of the disease, the serum thyroid hormone level will increase, but there will be differences between different individuals. Compared with the young people, the decrease of the physiological thyroid hormone level in the elderly after stroke may last longer resulting in dysfunction of the hypothalamic–pituitary-thyroid axis (HPT axis) which further aggravates cognitive impairment (Gkantzios et al., 2023; Lei et al., 2019; Murolo et al., 2022). Furthermore, older patients with post-stroke cognitive dysfunction who also have low thyroid hormone levels have been shown to have especially poor functional levels and worse prognoses (Li et al., 2021; Mei et al., 2022). Because there are no standardized clinical guidelines for the use of medications in patients who have abnormal thyroid hormone levels due to non-thyroidal diseases but not meeting the diagnostic criteria for hypothyroidism, it is unclear whether non-pharmacological interventions are indicated in these patients. Given the adverse effects of persistent low thyroid hormone levels in patients with post-stroke cognitive dysfunction (Gkantzios et al., 2023; Lei et al., 2019; Li et al., 2021; Mei et al., 2022; Murolo et al., 2022), here is a clinical need to identify a safe and effective way to intervene early in such patients to improve their functional prognosis and quality of survival.

As a non-invasive and safe treatment, rTMS has been increasingly recognized and accepted. It has been clinically used in the treatment of a variety of neurological and mental diseases. Existing studies have demonstrated that rTMS stimulation of Dorsal Lateral Prefrontal Cortex (DLPFC) can improve cognitive dysfunction after stroke by promoting synaptic plasticity, improving cerebral blood flow and cerebral metabolism, increasing cortical and subcortical functional connections and other neural mechanisms (Gao et al., 2023; Gong et al., 2023; Wang and Voss, 2015; Yang et al., 2015). Some studies have also found that rTMS can elevate thyroid hormone levels in healthy older adults as well as in stroke patients (Ma et al., 2021; Mei et al., 2022; Ren et al., 2017). We therefore questioned whether rTMS could similarly improve cognitive function in patients with PSCI who have low thyroid hormone levels, in addition to promoting the recovery of thyroid hormone levels. In conclusion, we aimed to observe the effects of rTMS on cognitive function and thyroid hormone levels in older patients with post-stroke cognitive dysfunction accompanied who have low thyroid hormone levels, and to provide a safe and effective therapeutic option for the clinical rehabilitation of this population.

2 Materials and methods

2.1 Patient characteristics

The patients in this study were older stroke patients who treated in the Department of Rehabilitation Medicine of Shijiazhuang People's Hospital between October 2019 and December 2020. The inclusion criteria required that patients met the following conditions: (1) they provided signed informed consent and acceptance of cooperation; (2) Based on the diagnostic criteria revised in the 4th National Conference on Cerebrovascular Disease in 1995, and at the same time, confirmed by CT or MRI for the Stroke patients with first-onset, unilateral hemispheric lesions; (3) they showed stroke recovery (14 days ≤6 months) and stable vital signs; (4) they were at least 60 years of age; (5) they were right-handed; (6) they obtained a Montreal Cognitive Assessment (MoCA) score < 26; (7) Passed the safety screening for rTMS, and met the safety criteria for participating in the rTMS interventions; and (8) their serum thyroid hormone levels were lower than the normal reference value, but did not meet the diagnostic criteria for thyroid disease (Mei et al., 2022). The exclusion criteria were as follows: (1) previous thyroid disease; (2) dementia; (3) severe functional impairment of important organs; (4) severe mental and

psychological disorders; (5) tetraplegia; (6) aphasia, hearing and comprehension disorders; (7) the presence of metal foreign bodies; (8) claustrophobia; (9) previous epilepsy; (10) severe sleep disorders; or (11) progressive exacerbation of the disease. Patients dropped out of the study if (1) they were patients who were uncooperative in completing the rTMS or sham stimulation treatment; (2) they were uncooperative in completing the cognitive assessment or (3) they withdrew from the treatment due to other reasons.

According to the random number table method, 40 patients were randomly divided into rTMS group ($n = 20$) and Sham group (using the same parameters as the rTMS group, but differently placed to not play a therapeutic role; $n = 20$) according to the order of consultation. Valid and complete data were obtained from 31 of these patients (16 patients in the rTMS group, and 15 patients in the Sham group) as 9 patients did not complete the current study due to the epidemic; among these 9 patients, 4 patients were in the rTMS group (1 patient was discharged halfway through the study, 1 patient was transferred to intensive care for clinical treatment for aggravation (not related to this study), and 2 patients could not be retested due to the impact of the epidemic), and 5 patients in the Sham group (2 patients refused to have their blood drawn for testing at the time of follow-up, 2 patients continued to undergo treatment in other hospitals for rTMS and tDCS, respectively, during the follow-up period, and 1 patient could not be retested due to the impact of the epidemic). The patient recruitment flowchart is shown in Figure 1.

2.2 Procedure

The information that was collected from all patients before the intervention included their age, gender, years of education, stroke type, disease duration, past medical history, and handedness. All enrolled patients were strictly screened with regard to the safety of repeated transcranial magnetic stimulation, and the indications and contraindications of transcranial magnetism were strictly controlled. An rTMS stimulator (manufacturer: Shenzhen Yingzhi) was then used to measure and determine each patient's motor threshold (MT) and a magnetic stimulation programme was formulated. The patients in both the rTMS and Sham groups received the same basic treatments, including conventional medication, conventional rehabilitation, and cognitive function; rTMS treatment was added to the treatments given to the rTMS group, and sham stimulation was added to the treatments given to the Sham group. Cognitive function scores, activities of daily living (ADL) scores, and thyroid hormone indexes were evaluated before the intervention, at 4 weeks (immediately after the intervention concluded), and at follow-up (4 weeks after the intervention concluded).

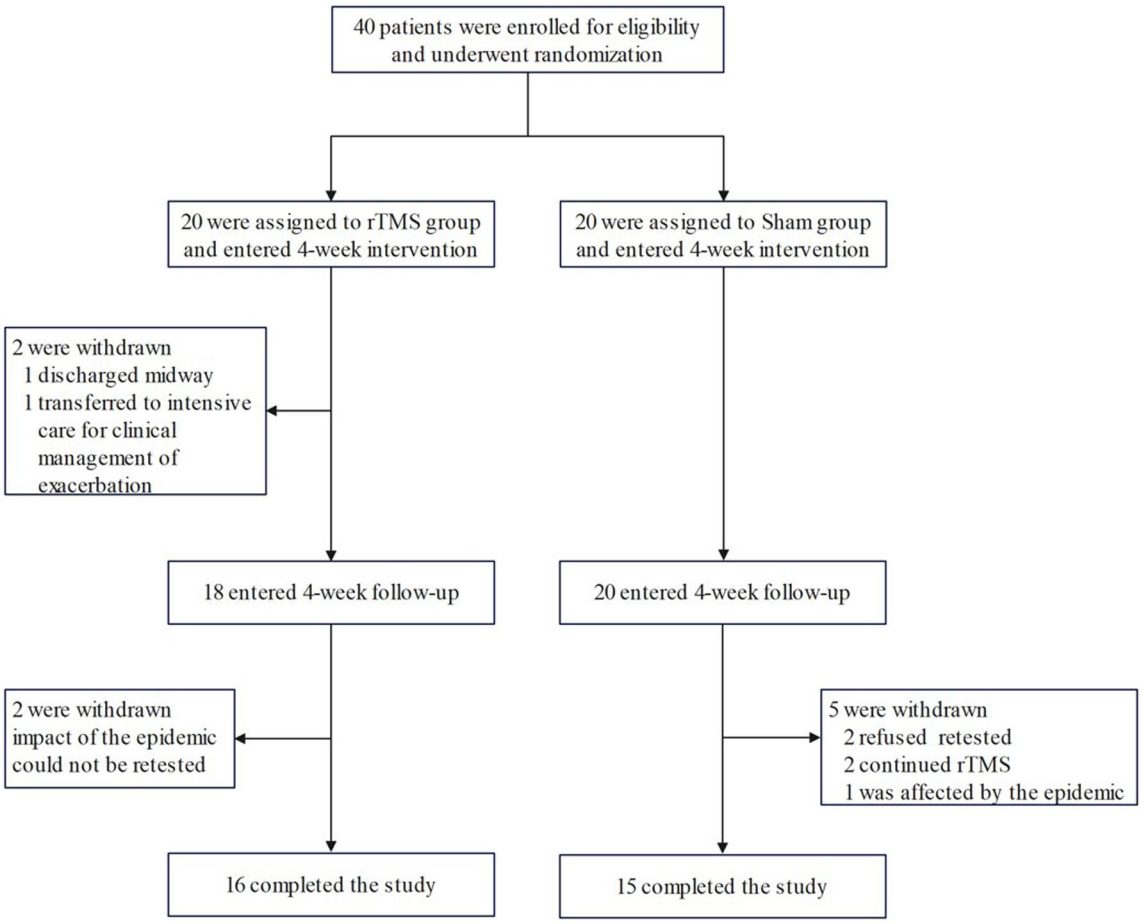

FIGURE 1
The flowchart of patient recruitment.

2.3 Conventional rehabilitation

2.3.1 Pharmacological treatment

Patients received appropriate pharmacological treatment for their underlying diseases, such as medications to manage their nerve nutrition, blood pressure, blood sugar, and blood lipids, in addition to drugs to prevent secondary injury.

2.3.2 Conventional rehabilitation therapy

Patients received therapy that used nerve facilitation technology and motor re-learning to carry out conventional rehabilitation training for the hemiplegic side limb and to help them with turning over, sitting up, standing up, weight-bearing of the affected limb, walking training, balance training, and occupational therapy (Ni et al., 2018; Pepping, 2014; Yan et al., 2018) Patients undertook one 40-min session of training per day, 5 days per week, for 4 weeks in total.

2.4 Cognitive training protocol

Routine Cognitive Function Training (Ni et al., 2018; Pepping, 2014) was provided according to patient's cognitive function at the time of consultation, targeted training is provided, which mainly included the following: (1) attention training—using visual tracking and linking games; (2) memory training using photos, pictures and auditory stimuli to repeatedly practice the processes of recognition, retelling, recall and re-recognition; (3) orientation training involved setting up a particular environmental scene and eliciting responses about time, place, people, and the location of related objects; (4) visual and spatial training - using jigsaw puzzles and object recognition; (5) executive training that involved setting up specific tasks (e. g., manual activities) and practicing independent thinking by planning, adjusting and completing them independently; (6) judgement and reasoning skills training that involved using puzzles and games and combining the background to complete the blank scenes to practice their logical reasoning ability. Patients undertook one 30-min session of training per day, 5 days per week, for 4 weeks in total.

2.5 rTMS protocol

2.5.1 Safety screening

Before the intervention, each patient was screened with regard to rTMS safety during which his or her complete clinical history, past history and epilepsy history of the patient were fully determined; the indications and contraindications for rTMS were strictly controlled. rTMS contraindications included the presence of metal objects or devices in the skull or on the scalp, cardiac pacemakers, medical implantable devices, a history of epilepsy, pregnancy, implants in the body, or claustrophobia. Strictly in accordance with the instructions for the use of transcranial magnetism for standardized operation, there was detailed communication with the patients before the intervention to ensure that they had an objective understanding and awareness of the procedure, and each patient was instructed not to move his or her head during the treatment process, so as to avoid positional shifts affecting the therapeutic efficacy (Fox et al., 2012; Lefaucheur et al., 2014).

2.5.2 Determination of motor threshold (MT)

Before the intervention began, the MT was measured and determined for each patient by applying the electrode sheet to the patient's right adductor muscle, connecting the electrode sheet to the multichannel physiological signal recorder to collect EMG signals, and then stimulating the primary motor area of the left side of the brain with a single pulse of TMS (Schecklmann et al., 2020). The motor evoked potentials that were recorded on the EMG acquisition software and the contraction of the right adductor muscle were observed, and at least five out of ten consecutive stimulations had an amplitude greater than the minimum stimulation intensity of 50 μV, which can be regarded as the motor threshold MT (Fisicaro et al., 2019; Fox et al., 2012; Lefaucheur et al., 2014).

2.5.3 Implementation of rTMS and sham interventions

Previous studies have shown that DLPFC is an effective target of rTMS for the treatment of post stroke cognitive impairment, and stimulation of this region can improve the cognitive function of stroke patients (Balconi, 2013; Fisicaro et al., 2019; Wang et al., 2024). In addition, other studies have found that stimulating the DLPFC region of older people with cognitive decline using rTMS can simultaneously improve cognitive function and thyroid hormone levels (Ma et al., 2021; Mei et al., 2022; Ren et al., 2017). So we chose DLPFC for our study. A transcranial magnetic stimulator and a standard figure-of-eight coolable coil were used, and the brain stimulation area localization method was based on the International 10–20 system of EEG and located at the Dorsal Lateral Prefrontal Cortex (DLPFC) locus (Balconi, 2013; Fisicaro et al., 2019). All parameters of the magnetic stimulation programme were set regardless of a patient's treatment group (stimulation frequency 1 Hz, stimulation intensity 90% MT, stimulation duration: 20s, interval per cycle: 3 s; this treatment was performed for 20 min once per day, 5 times per week, over 4 weeks of continuous treatment). The placement of the coil differed between the two groups: the rTMS group was treated with the coil placed across the target area of patient's healthy DLPFC, whereas the Sham group was treated with the coil placed perpendicular to the scalp to give a pseudo stimulation but had no therapeutic effect (Lefaucheur et al., 2014). The patients were told to remain relaxed, to avoid moving, and to ask and observe the patients promptly.

2.6 Outcome measures

Patients' cognitive function scores, ADL scores, and thyroid hormone levels were assessed 1 day before the intervention, 4 weeks after the intervention began, and at follow-up assessment conducted 4 weeks after the treatment intervention ended.

2.6.1 Cognition assessment

This assessment included the MoCA test, the verbal fluency test (VFT), and the digital span test.

2.6.1.1 The montreal cognitive assessment (MoCA)

The MoCA scale is one of the most commonly used scales for assessing cognitive impairment in clinical practice. It assesses various cognitive domains-including alternating connectivity test (1-A-2-B-), orientation, visuospatial and executive functions (cube, clock),

memory, attention, abstract thinking, language, naming, etc. The MoCA scale has a total score of 30, with cognitive impairment defined as a score below 26 points. When the patient's number of years of education is less than or equal to 12 years, 1 point will be added to the test results. The total time required for this assessment does not exceed 10 min (Nie et al., 2012).

2.6.1.2 The verbal fluency test (VFT)

Verbal sphere fluency was assessed using the VFT test (Henderson et al., 2023). This test requires the patient to name as many foods as possible within 1 min, and is scored according to the number of correct responses given by the subject. The instruction was given, "Now please list the names of as many foods as you can in 1 min, "was given, and a stopwatch was used to time the test, with the timing beginning after the initial instruction was given and the patient confirmed that he or she understood the instructions. The names of the foods listed by the subject were recorded sequentially; if the subject paused for more than 15 s, the instructions were repeated and then the patient was instructed to continue the list, and the time was counted. If patients stopped listing items before 1 min they were encouraged to try to continue.

2.6.1.3 Digital span testing

Digital span testing gives digital span forward (DSF) and digital span backward (DSB) (Gao et al., 2023). Starting with a short string of digits with fewer digits, the tester first reads out a string of digits at a constant speed, and then asks the patient to repeat the digits in the order in which they were read. The tester gradually increases the number of digits until the patient cannot recite the string correctly, and the patient's score is the highest number of digits that they correctly recited. DSB scores are obtained in an equivalent way but with the patients reciting the digits in the reverse order to which they were read by the tester.

2.6.2 ADL scores

The Modified Barthel index (MBI) scale was used to assess the patient's ability to perform activities of daily living (Pournajaf et al., 2023), and this was evaluated primarily on the basis of the patient's actual performance, not on the basis of what the patient might be able to do or on the results of questioning. The standard evaluation includes ten (or eleven) basic components such as eating, dressing, and walking (or using a wheelchair), and the basic rating scale allows each activity to be rated on a 5-point scale, with different levels representing different degrees of self-dependence and self-care ability, ranging from the lowest degree at level 1 to the highest degree at level 5. A total score of 100 is considered normal, a total score of ≥60 is considered as basic self-care, between 41 and 59 is considered as partially dependent, a total score 21–40 is considered as mostly dependent, and a score of 20 or below is considered as totally dependent.

2.6.3 Serum levels of thyroid hormones and thyroid stimulating hormone (TSH)

All patients had their blood collected, after fasting, on three occasions: in the morning of the day before the intervention began, 4 weeks after the intervention began, and at an 4-week follow-up visit conducted 4 weeks after the intervention concluded. Approximately 10 mL of blood was collected from the vein and injected into a procoagulant vacuum tube, which was left at room temperature for 1 h. The serum was separated by centrifugation at 3000 r/min for 10 min. During the assessment, we first checked that the relevant instruments were in good working condition, and then carried out the tests in strict accordance with the reagents' instructions. The following hormones were measured using electrochemiluminescence: T3, T4, FT3, FT4, and TSH (Ma et al., 2021; Ren et al., 2017).

2.7 Data analysis

SPSS statistical software, version 25.0 was used to perform statistical analysis. P–P Plots was used to test the normality of all continuous variables. Normally distributed variables were presented as mean ± standard and non-normally-distributed variables were presented as median (25^{th} percentile, 75^{th} percentile). Age, disease course, and years of education were compared between the two groups using two-sample independent t-test, whereas gender, lesion side, and types of stroke were compared using the Chi-squared test. Using repeated measures ANOVA to analyze the changes in various indicators between two groups at different time points and the differences between groups. Mann Whitney U test was used to compare the changes of cognitive function and thyroid hormone levels (after 4 weeks of intervention pre intervention) between the two groups. Spearman correlation analysis was performed to assess the correlation between the post-treatment change in thyroid hormone levels and cognitive function scores (posttest–pretest) in the rTMS group, p values<0.05 were considered indicative of statistical significance.

3 Results

3.1 Comparison of general data between the two groups

Data from 31 patients (16 in the rTMS group and 15 in the Sham group) were analysed in this study. Before the intervention, there were no significant differences between the rTMS and Sham groups with respect to gender, age, disease course, side of lesion, types of stroke, or years of education ($p > 0.05$) (Table 1).

3.2 Repeated measurement analysis of variance results of cognitive function between the two groups before and after intervention and at follow-up

Repeated measurement analysis of variance showed that MoCA, DSF and DSB scores had interaction between group and time ($F_{time*group} = 7.631$, $p = 0.002$; $F_{time*group} = 5.479$, $p = 0.01$; $F_{time*group} = 4.114$, $p = 0.027$). Further separate effect analysis showed that there were significant differences in MoCA, DSF and DSB scores between the two groups at different time points, and MoCA ($P_{post} = 0.044$; $P_{follow\text{-}up} = 0.038$), DSF ($P_{post} = 0.027$; $P_{follow\text{-}up} = 0.048$), DSB ($P_{post} = 0.033$; $P_{follow\text{-}up} = 0.045$) in rTMS group at the time of intervention and follow-up, which were better than those in sham group. The scores of MoCA, DSF and DSB in rTMS group after intervention and follow-up

TABLE 1 Comparative analysis of the results of the general data of the two groups of patients.

Group	N	Gender		Age	Disease course	Lesion side		Types of stroke		Years of education
		Male	Female			Left	Right	Cerebral infarction	Cerebral haemorrhage	
rTMS	16	9	7	65.38 ± 3.26	26.94 ± 9.71	6	10	11	5	9.88 ± 3.01
Sham	15	8	7	66.13 ± 4.10	24.87 ± 8.58	7	8	10	5	10.13 ± 2.75
P		1		0.572	0.535	0.722		1		0.805

rTMS, repetitive transcranial magnetic stimulation.

were significantly different from those before intervention ($p < 0.05$), and the scores of MoCA in follow-up were significantly different from those after intervention ($p < 0.05$). The scores of MoCA in sham group after intervention and follow-up were significantly different from those before intervention, and the scores of DSF and DSB after intervention were significantly different from those before intervention ($p < 0.05$). There was no interaction between VFT group and time ($F_{time*group} = 2.0410$, $p = 0.149$). Further analysis of the main effect showed that the VFT ($F_{time} = 20.486$, $P < 0.001$) score of patients showed an upward trend before intervention, 4 weeks of intervention and follow-up, but there was no significant difference between the two groups ($F_{group} = 0.254$, $p = 0.618$) (Table 2).

3.3 Repeated measurement analysis of variance results of hormone levels between the two groups before and after intervention and at follow-up

Repeated measurement analysis of variance showed that FT3 group had interaction between group and time ($F_{time*group} = 3.610$, $p = 0.04$). Further independent effect analysis showed that there was no significant difference in FT3 levels between the two groups at different time points ($p > 0.05$), but there was a significant difference in rTMS group after intervention ($p < 0.001$). There was no interaction between the group of other indicators and time. The independent effect analysis showed that the T3 level in rTMS group was significantly higher than that in sham group after intervention and follow-up ($P_{post} = 0.046$; $P_{follow-up} = 0.034$), Further main effect analysis showed that the levels of T3 ($F_{time} = 22.546$, $p < 0.001$), FT3 ($F_{time} = 6.483$, $p = 0.005$), TSH($F_{time} = 12.173$, $p < 0.001$) in patients at 4 weeks of intervention and follow-up showed an upward trend, and the effect of improving T3 in rTMS group was better than that in sham group ($F_{group} = 5.319$, $p = 0.028$) (Table 3).

3.4 Repeated measurement analysis of variance results of MBI between the two groups before and after intervention and at follow-up

Repeated measurement analysis of variance showed that there was no interaction between the group of MBI score and time ($F_{time*group} = 2.326$, $p = 0.116$). Independent effect analysis showed that there was no significant difference in MBI levels between the two groups at different time points ($p > 0.05$), but the intra-group comparison showed that MBI scores in both groups improved after intervention and at follow-up compared with those before intervention ($p < 0.05$). Further analysis of the main effect showed that the MBI ($F_{time} = 23.290$, $p < 0.001$) levels of patients before intervention, 4 weeks of intervention and follow-up showed an upward trend, but there was no significant difference between the two groups ($F_{group} = 1.999$, $p = 0.168$) (Table 4).

3.5 Comparative analysis of cognitive change values (after 4 weeks of intervention-pre-intervention) between the two groups

Mann Whitney U test was used to compare the changes of cognitive function (after 4 weeks of intervention pre intervention) between the two groups. The results showed that after 4 weeks of intervention, the differences of cognitive function and MBI scores in rTMS group were higher than those in sham group, with statistical differences ($p < 0.05$) (Table 5).

3.6 Comparative analysis of hormonal change values (after 4 weeks of intervention-pre-intervention) between the two groups

Mann Whitney U test was used to compare the changes of thyroid hormone levels (after 4 weeks of intervention pre intervention) between the two groups. The results showed that after 4 weeks of intervention, the difference of FT3 levels in rTMS group was higher than that in sham group, with statistical difference ($p = 0.024$) (Table 6).

3.7 Correlation between changes in thyroid hormone levels and cognitive function scores in rTMS group patients

(1) Correlation between the value of changes in various indicators of thyroid hormone levels and the value of changes in the scores of various indicators of cognitive function (after 4 weeks of intervention - before intervention) in patients in the rTMS group: the results of the analysis using Spearman correlation analysis showed that the value of changes in the levels of T3 in the rTMS group of patients and the value of changes in the scores of MoCA were in a positive correlation relationship after 4 weeks of intervention ($r = 0.638$, $p < 0.05$) (Table 7, Figure 2).

TABLE 2 Repeated measurement analysis of variance results of cognitive function between the two groups.

Time	MoCA				VFT				DSF				DSB			
	rTMS ($n = 16$)	Sham ($n = 15$)	F	P	rTMS ($n = 16$)	Sham ($n = 15$)	F	P	rTMS ($n = 16$)	Sham ($n = 15$)	F	P	rTMS ($n = 16$)	Sham ($n = 15$)	F	P
Pre	11.56 ± 3.63	11.73 ± 3.33	0.019	0.893	6.81 ± 3.12	7.00 ± 2.98	0.029	0.866	4.94 ± 1.57	4.93 ± 1.49	0.000	0.994	2.88 ± 0.72	2.87 ± 0.64	0.001	0.973
Post	17.25 ± 4.85aA	13.73 ± 4.40a	4.450	0.044	9.13 ± 2.78a	8.20 ± 3.82a	0.600	0.445	7.38 ± 1.78aA	5.80 ± 1.97a	5.452	0.027	4.13 ± 0.81aA	3.47 ± 0.83a	4.994	0.033
Follow-up	19.50 ± 5.50abA	14.87 ± 6.37a	4.717	0.038	9.56 ± 3.37a	8.53 ± 4.21a	0.569	0.457	7.56 ± 2.97aA	5.67 ± 2.02	4.263	0.048	4.50 ± 1.41aA	3.40 ± 1.50	4.410	0.045
F	35.776	5.370			16.901	5.182			21.048	2.171			15.219	7.996		
P	<0.001	0.02			<0.001	0.22			<0.001	0.133			<0.001	0.005		
Group (F, P)	2.796, 0.105				0.254, 0.618				3.561, 0.069				4.409, 0.045			
Time (F, P)	34.891, <0.001				20.486, <0.001				23.824, <0.001				26.018, <0.001			
Time* group (F, P)	7.613, 0.002				2.041, 0.149				5.479, 0.01				4.114, 0.027			

rTMS, repetitive transcranial magnetic stimulation; MoCA, Montreal Cognitive Assessment; VFT, verbal fluency test; DSF, digital span forward; DSB, digital Span Backward. a indicates comparisons with pre, $p < 0.05$; b indicates comparisons with post, $p < 0.05$; A indicates comparisons with the Sham group, $p < 0.05$; both two-way comparisons are Bonferroni corrected.

(2) Correlation between changes in thyroid hormone levels and changes in MoCA cognitive domain scores (after 4 weeks of intervention - before intervention) in the rTMS group: Spearman's correlation analysis showed that there was a positive correlation between changes in T3 levels and changes in naming, delayed recall, and attention scores in the rTMS group after 4 weeks of intervention ($r = 0.562$, $p < 0.05$; $r = 0.562$, $p < 0.05$; $r = 0.531$, $p < 0.05$); and the value of change in FT3 level showed a positive correlation with the value of change in visuospatial and executive function scores ($r = 0.514$, $p < 0.05$) (Table 8).

4 Discussion

There are many studies relating to thyroid hormone levels to cognitive function after stroke (Gkantzios et al., 2023; Lei et al., 2019; Li et al., 2021; Murolo et al., 2022), and it has been concluded that the majority of patients with post-stroke cognitive dysfunction have abnormal thyroid hormone levels, and that persistent low thyroid hormone levels exacerbate the dysfunction of the PSCI. However, very few studies have examined clinical interventions within this specific population. Our study aims to find a safe and effective rehabilitation method for this population to reduce the adverse effects of chronic low thyroid hormone in older patients with cognitive impairment after stroke. A large number of studies have shown that low-frequency repetitive transcranial magnetic stimulation is effective in improving cognitive dysfunction in post-stroke patients through central mechanisms (Blesneag et al., 2015; Gong et al., 2023; Wang et al., 2024; Yingli et al., 2022), and some animal studies have also found that rTMS improves endocrine hormones and cognitive function in naturally aging mice from the perspectives of synaptic plasticity and neurophysiology, suggesting that rTMS improves cognitive function through a potential neuroendocrine mechanism (Ren et al., 2017; Zhu et al., 2020). As research advances in the field of neuroendocrinology, clinical studies have demonstrated that rTMS can increase cerebral blood flow in healthy elderly people and stroke patients, in addition to increasing T3 levels in the peripheral blood, suggesting that rTMS may regulate the disorders of the hypothalamic–pituitary-thyroid axis and elevate the hormone levels to improve cognition through a potential neuroendocrine mechanisms (Ma et al., 2021; Mei et al., 2022). The results of the present study showed that rTMS significantly improved both cognition and T3 levels in PSCI patients with low thyroid hormone levels, furthermore, compared with the Sham group, the improvement effects of rTMS on cognitive function and T3 levels were statistically different at 4-week intervention as well as at follow-up, and T3, MoCA, DSF, and DSB continued to improve with rTMS at follow-up, compared with pre-intervention as well as post-intervention, suggesting that there is a sustained effect of rTMS. Based on current research advances on the central and neuroendocrine mechanisms by which rTMS improves cognitive function. We hypothesise the following possible reasons for the improvement of thyroid hormone levels and cognitive function with rTMS: on the one hand, the DLPFC, as a target area threshold that closely related to both cognitive function (Fischer et al., 2013) and is also a major area of thyroid hormone action. Stimulation of this area may affect both cognition and thyroid hormone levels; on the other hand, based on the central mechanism by which rTMS improves cognition, stimulation of the DLPFC increases cerebral blood flow and metabolic

TABLE 3 Repeated measurement analysis of variance results of hormone levels between the two groups.

Time	T3 (nmol/L)				FT3 (pmol/L)				T4 (nmol/L)				FT4 (pmol/L)				TSH (uIU/mL)			
	rTMS ($n = 16$)	Sham ($n = 15$)	F	P	rTMS ($n = 16$)	Sham ($n = 15$)	F	P	rTMS ($n = 16$)	Sham ($n = 15$)	F	P	rTMS ($n = 16$)	Sham ($n = 15$)	F	P	rTMS ($n = 16$)	Sham ($n = 15$)	F	P
Pre	0.96 ± 0.05	0.93 ± 0.07	2.638	0.115	3.82 ± 0.56	3.79 ± 0.67	0.012	0.914	118.36 ± 20.24	121.67 ± 20.64	0.203	0.656	12.30 ± 2.14	10.94 ± 2.24	2.974	0.095	1.81 ± 1.23	1.84 ± 1.08	0.004	0.95
Post	1.21 ± 0.20aA	1.07 ± 0.17a	4.327	0.046	4.49 ± 0.93a	3.91 ± 0.71	3.831	0.06	110.49 ± 14.82	115.80 ± 21.71	0.64	0.43	11.55 ± 2.66	10.79 ± 2.37	0.708	0.407	2.77 ± 1.36a	2.56 ± 1.40	0.189	0.667
Follow-up	1.37 ± 0.36abA	1.13 ± 0.24a	4.95	0.034	4.27 ± 1.16	3.96 ± 0.68	0.824	0.371	113.80 ± 20.33	122.01 ± 24.97	1.209	0.281	11.21 ± 1.99	9.68 ± 2.40	3.75	0.063	2.97 ± 1.47a	2.49 ± 1.43	0.829	0.37
F	14.505	10.628			5.304	0.728			1.437	1.278			1.354	2.3			8.66	4.056		
P	<0.001	<0.001			0.018	0.492			0.254	0.294			0.273	0.119			0.001	0.039		
Group (F, P)	5.319, 0.028				1.488, 0.232				0.839, 0.367				3.724, 0.063				0.747, 0.478			
Time (F, P)	22.546, <0.001				6.483, 0.005				2.360, 0.104				3.212, 0.050				12.173, <0.001			
Time*group(F, P)	2.092, 0.142				3.610, 0.04				0.347, 0.708				0.370, 0.682				0.747, 0.472			

rTMS, repetitive transcranial magnetic stimulation; T3, triiodothyronine; FT3, free triiodothyronine; T4, thyroxin, FT4, free thyroxine; TSH, thyroid stimulating hormone. Note: a indicates comparison with pre, $P < 0.05$; b indicates comparison with post, $P < 0.05$; A indicates comparison with Sham's group, $P < 0.05$; both two comparisons are Bonferroni corrected.

TABLE 4 Repeated measurement analysis of variance results of MBI between the two groups.

Time	rTMS ($n = 16$)	Sham ($n = 15$)	F	P
Pre	46.94 ± 8.18	44.67 ± 9.29	0.524	0.475
Post	57.75 ± 10.48[a]	50.27 ± 13.57[a]	2.975	0.095
Follow-up	61.06 ± 16.34[a]	52.13 ± 18.22[a]	2.069	0.161
F	20.666	6.585		
P	<0.001	0.010		
Group (F, P)	1.999, 0.168			
Time (F, P)	23.290, <0.001			
Time*group(F, P)	2.326, 0.116			

Unit: points. rTMS, repetitive transcranial magnetic stimulation; MBI, Modified Barthel index. a indicates comparisons with pre, $P < 0.05$; both two-way comparisons are Bonferroni corrected.

levels, promotes the release of neurotransmitters, and increases signaling, thereby enhancing the neuronal connections between the cortex and hypothalamus (Basilis et al., 2007) thus affecting the HPT axis and causing changes in THs levels. In addition, rTMS promotes the recovery of cognitive function, which will directly affect the level of other bodily functions of the organism, and overall improves the metabolic function level of the organism, which in turn affects hormone levels.

Based on the results of repeated measures ANOVA, T3 levels as well as cognitive levels were statistically different in the rTMS group compared to the Sham group, both at post-intervention and at follow-up ($P < 0.05$), our study also investigated whether changes in cognitive function scores observed after rTMS treatment were correlated with equivalent changes in thyroid hormone levels in older stroke patients with low thyroid hormone levels. These investigations showed that among patients who received rTMS treatment, increases in T3 levels were significantly and positively correlated with increases in MoCA scores that were observed after 4 weeks of rTMS treatment was delivered ($r = 0.638$, $p < 0.05$). It is appears that within a certain range, the change of T3 level in early older stroke recovery patients with cognitive dysfunction and low thyroid hormone level is correlated with the change in the MoCA score, i.e., the cognitive function of patients will be improved together with the increase of T3 level, and the increase of T3 level will, in turn, improve the cognitive function of patients with cognitive dysfunction in stroke, and that the two function will boost each other and influence each other. In addition, specific scores for naming, delayed recall, and attention functions of patients in the rTMS group improved with increasing T3 levels, and visuospatial and executive function scores improve with increasing FT3 levels. Improvements in these cognitive domain scores may have contributed to the increase in overall MoCA values. We hypothesise that there are multiple factors that are likely to have contributed to this observation: (1) In peripheral blood, 80–90% of T3 is converted from T4 by deiodinase, and the clinical stress of stroke inhibits this deiodinase conversion and thereby reduces levels of T3, which is the main thyroid hormone that exerts a wide range of biological effects, including effects on the nervous system (Bunevicius et al., 2016; Chen et al., 2016; Lamba et al., 2018; Wang et al., 2017). Reduced T3 may further exacerbate cognitive deficits and reduce an individual's abilities to be independent in daily

TABLE 5 Comparative analysis of the difference of cognitive change values (after 4 weeks of intervention-pre-intervention) between the two groups.

Group	MoCA	VFT	DSF	DSB	MBI
rTMS ($n=16$)	6 (1, 10)A	2 (−1, 5)A	2 (1, 5)A	1 (0, 3)A	9.50 (2, 25)A
Sham ($n=15$)	2 (−5, 6)	1 (−2, 4)	1 (−1, 3)	1 (-1, 1)	5.50 (-6, 21)
Z	−3.056	−2.328	−2.903	−2.139	−2.002
P	0.002	0.020	0.004	0.032	0.045

Unit: points. rTMS, repetitive transcranial magnetic stimulation; MoCA, Montreal Cognitive Assessment; VFT, verbal fluency test; DSF, digital span forward; DSB, digital Span Backward. A indicates comparison with the Sham group, $p<0.05$.

TABLE 6 Comparative analysis of the difference of hormonal change values (after 4 weeks of intervention-pre-intervention) between the two groups.

Group	T3 (nmol/L)	FT3 (pmol/L)	T4 (nmol/L)	FT4 (pmol/L)	TSH (uIU/mL)
rTMS ($n=16$)	0.21 (−0.04, 0.54)	0.53 (−0.28, 2.54)A	−8.85 (−51, 22.4)	−0.78 (−6.45, 3.97)	1.11 (−2.04, 2.86)
Sham ($n=15$)	0.13 (−0.06, 0.43)	0.11 (−0.67, 1.00)	−9.66 (−20.21, 38.29)	−0.55 (−4.23, 3.82)	0.82 (−2.04, 2.86)
Z	−1.682	−2.254	−0.514	−0.435	−0.909
P	0.093	0.024	0.607	0.664	0.363

rTMS, repetitive transcranial magnetic stimulation; T3, triiodothyronine; FT3, free triiodothyronine; T4, thyroxin, FT4, free thyroxine; TSH, thyroid stimulating hormone. A indicates comparison with the Sham group, $p<0.05$.

TABLE 7 Correlation analysis between values of hormonal changes and values of changes in cognitive scores (after 4 weeks of intervention-pre-intervention) in the rTMS group(r, *P*).

	MoCA	VFT	DSF	DSB	MBI
T3 (nmol/l)	0.638, 0.008**	0.018, 0.946	0.434, 0.093	0.242, 0.367	0.028, 0.918
T4 (nmol/l)	−0.288, 0.279	0.217, 0.419	−0.058, 0.831	−0.066, 0.809	0.396, 0.128
FT3 (pmol/l)	0.119, 0.662	0.338, 0.201	−0.031, 0.911	0.175, 0.516	0.189, 0.484
FT4 (pmol/l)	−0.014, 0.960	−0.135, 0.617	0.168, 0.534	0.128, 0.636	−0.228, 0.395
TSH (uIU/mL)	0.215, 0.425	−0.050, 0.854	0.211, 0.434	0.050, 0.854	−0.352, 0.181

**$P<0.01$. Abbreviations: rTMS, repetitive transcranial magnetic stimulation; MoCA, Montreal Cognitive Assessment; VFT, verbal fluency test; DSF, digital span forward; DSB, digital Span Backward; MBI, Modified Barthel index; T3, triiodothyronine; FT3, free triiodothyronine; T4, thyroxin, FT4, free thyroxine; TSH, thyroid stimulating hormone.

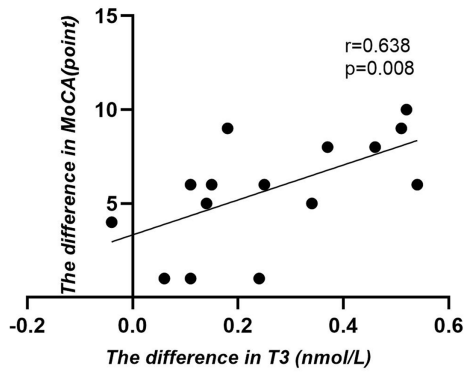

FIGURE 2
Scatter plot analysis of the correlation between T3 levels and MoCA scale (post-pre) in rTMS group.

life. (2) The cerebral cortex and hippocampus are brain regions that are closely related to cognitive function and are also the main sites of thyroid hormone action. When cerebrovascular damage to specific neural networks or circuits occurs, cognitive function will be directly affected (Chen et al., 2016; Mei et al., 2022) and, at the same time, the biological effects of thyroid hormones will be inhibited, and abnormal levels of thyroid hormones may exacerbate cognitive dysfunction. (3) It has been found that the blood–brain barrier is disrupted after stroke, which affects the level of organic anion-transporting polypeptides in epithelial cells, thus causing a decrease in the levels of peripheral thyroid hormones that are responsible for their transport, and a decrease in T3 levels in the brain. This decrease in T3 levels will affect cerebral tissue blood perfusion, energy metabolism (Zhu et al., 2020) and signal systems, in addition to interfering with the generation of synaptic long-range potentiation (Hainsworth et al., 2017; Van Heugten et al., 2017), which in turn affects cognitive function.

This study has certain limitations, such as a small sample size, incomplete evaluation methods, and a lack of in-depth exploration of the specific mechanisms by which rTMS improves cognition and thyroid hormone levels in older early stroke patients with low thyroid hormone levels. In the future, large-scale multicenter randomized controlled trials should be conducted, and more objective evaluation methods such as brain imaging technology should be used to explore the potential neuroendocrine mechanisms, and long-term tracking of the functional prognosis of this group of people is needed, which will provide new ideas for early clinical intervention in patients with low thyroid hormone levels in PSCI, and minimize the adverse effects of long-term low thyroid hormone levels.

5 Conclusion

rTMS can effectively improve the cognitive function of early stroke patients with low thyroid hormone levels in addition to

TABLE 8 Correlation analysis of hormonal indicators in the TMS group with the difference in change in MoCA scores in each cognitive domain (after 4 weeks of intervention—before intervention) (*r*, *P*).

	Visuo-spatial and executive functions	Naming	Delayed recall	Attention	Language	Abstraction thinking	Orientation
T3 (nmol/l)	0.277, 0.300	0.562, 0.024*	0.562, 0.024*	0.531, 0.034*	0.260, 0.330	0.085, 0.756	0.327, 0.216
T4 (nmol/l)	0.203, 0.452	−0.252, 0.346	−0.370, 0.158	−0.455, 0.077	0.096, 0.725	−0.270, 0.312	0.067, 0.805
FT3 (pmol/l)	0.514, 0.042*	0.308, 0.246	0.106, 0.697	0.109, 0.686	0.232, 0.387	0.428, 0.098	0.301, 0.257
FT4 (pmol/l)	−0.393, 0.133	0.196, 0.467	−0.187, 0.489	0.014, 0.960	0.205,0.446	0.162, 0.549	−0.276, 0.301
TSH (uIU/ml)	0.185, 0.492	0.028, 0.918	0.096, 0.724	0.211, 0.432	0.178, 0.510	0.333, 0.208	0.042, 0.878

*$P<0.05$. rTMS, repetitive transcranial magnetic stimulation; T3, triiodothyronine; FT3, free triiodothyronine; T4, thyroxin, FT4, free thyroxine; TSH, thyroid stimulating hormone.

elevating their low thyroid hormone levels, and the therapeutic has a sustained effect, which is superior to a single conventional cognitive training. Within the normal range, changes in T3 levels are positively correlated with changes in cognitive functioning. Moreover, there were no adverse reactions and other conditions during the whole study, suggesting that this approach is safe for clinical application. Clinical attention should be paid to older stroke patients with low thyroid hormone levels as early as possible, and timely monitoring and targeted interventions should be provided to reduce the risk that low thyroid hormone may further aggravate the degree of cognitive impairment in stroke patients.

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 in the article/supplementary material.

Ethics statement

The studies involving humans were approved by the ethics committee of Shijiazhuang People's Hospital (Approval number: 2020034). 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

HL: Writing – original draft, Writing – review & editing. JM: Writing – review & editing. ZS: Writing – original draft. XT: Writing – review & editing. YX: Writing – review & editing. FZ: 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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The association between oral health and mild cognitive impairment in community-dwelling older adults

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Background: Older adults with cognitive impairment can experience poor oral health due to reduced self-care ability, yet the impact of various oral health indicators on the cognitive ability remains unclear. We investigated the relationship between oral health indicators and mild cognitive impairment (MCI) in older adults.

Methods: A cross-sectional study of 234 older adults aged 65 years or over was performed form January to March 2023 at health screening departments of hospitals. This study used the Mini-mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Activities of Daily Living (ADL), Clinical Dementia Rating (CDR), and Hachinski Ischemic Score (HIS) to measure MCI. Two qualified dentists performed clinical oral examinations (number of teeth lost, dental caries, removable dentures, periodontitis). The other oral health status was measured by subjective assessment questionnaires, and the oral health-related quality of life (OHRQoL) was assessed by Geriatric Oral Health Assessment Index (GOHAI).

Results: Of the 234 older adults, 166 had MCI and 68 had normal cognitive ability. The univariate analyses revealed that older adults with poor oral health indicators of dental caries, mastication ability, oral and maxillofacial pain, self-perceived oral health status and OHRQoL had lower cognitive levels. The stepwise logistic regression analysis observed that higher education level (OR= 0.06, 95%CI=0.007, 0.567) and OHRQoL score (OR=0.92, 95%CI=0.878, 0.963) were negatively associated with the presence of MCI. The area under the ROC curve (AUC) of MCI was 0.675 (95% CI: 0.600, 0.749) with a low sensitivity of 41.6% and a moderate specificity of 86.8%.

Conclusion: OHRQoL was found to be associated with MCI, implying that OHRQoL may be important in cognitive decline. The GOHAI scale can be used to more easily assess the oral health of older adults, which is important for the timely detection of poor oral status to delay cognitive decline.

KEYWORDS

mild cognitive impairment, oral health, oral health-related quality of life, older adults, association

Introduction

Population aging is currently a significant concern facing the world, and with increasing aging, the health problems of older adults constantly highlighted (1). Among the diseases that endanger the health of older adults, dementia has become the fourth leading cause of death after cardiovascular disease, cancer, and stroke (2). China is one of the fastest-aging countries (3), with a prevalence of 5.56% for dementia and 10–20% for mild cognitive impairment (MCI) in adults over 65 years of age (4, 5), which will bring a serious burden to families and society.

MCI is an intermediate state between normal cognition and dementia in which one or more cognitive domains are impaired and do not yet meet the diagnostic criteria for dementia and do not interfere with the ability to perform daily activities (6). The risk of MCI turning into dementia is much higher than normal older adults, with 10–15% of MCI patients developing dementia every year (7). However, to date there is no cure for dementia (8), the stage of MCI provides a critical "window of opportunity" for the prevention and treatment of dementia (9). Early intervention at the MCI stage can effectively delay the progress of dementia, and even restore the older adults to normal cognitive state (10). Therefore, early intervention and risk management for MCI is greatly important and has become a research hot topic at home and abroad, with important academic significance and lucrative socio-economic benefits.

Oral health is a key indicator of overall health, well-being and quality of life, and poor oral health causes millions of people to suffer from devastating pain and increases the financial burden for society (11). The risk of oral diseases increases with age and can affect the cognitive function of older adults (12, 13). Tooth loss, dental caries, mastication ability, and periodontitis are common oral problems. One of the most common oral problems associated with cognitive impairment is tooth loss (14–16). The older adults with tooth loss can lead to nutritional problems such as impaired intake of micronutrients and vitamins, which can lead to affect cognitive function (17). Mastication is a predictor of cognitive impairment, with the ability to masticate decreasing with age and increasing the risk of cognitive impairment (18). The reason is that normal mastication maintains peripheral sensory input, increases blood supply to different areas of the brain, effectively transmits a large amount of sensory information to the brain, and maintains normal learning and memory functions (19). Periodontitis is also associated with cognitive decline, and the inflammatory response it induces can negatively affect the brain (20).

Although the relationships between tooth loss, mastication ability, and cognitive function have been studied, the measurements and results have been heterogeneous. The relationship between other oral health assessment indicators such as dental caries, lateral mastication, and cognitive function are poorly reported. The relationship between OHRQoL and cognitive function is unclear. Moreover, no study has included comprehensive oral health indicators in the analysis of association between the oral health and cognitive function. Information on the association between various aspects of oral health and cognitive function remains insufficient. Accordingly, this study aimed to determine whether there are associations between various aspects of oral health and cognitive function through oral examinations and electronic questionnaire assessments. The innovation of this study lies in the inclusion of comprehensive indicators and the innovative exploration of the subject by using two methods of oral examinations and questionnaire survey.

Methods

Design and participants

The sample size was calculated with reference to the preliminary study and based on the sample size calculation formula (21). The sample size was estimated using the following formula. $n = Z^2 * p(1-p)/e^2$, $Z = 1.96$, p = prevalence of MCI in Wuhan (87.8%), e = error rate = 0.05; n = 165 patients, with 15% attrition rate, making a total of 190 participants (22). Eligible participants were recruited from health screening departments at two hospitals, part of the Wuhan in China from January to March 2023. The inclusion criteria were age ≥ 65 years, having sufficient visual and auditory discrimination to undergo neuropsychological tests, willingness to participate in the study, and signing the informed consent form. Exclusion criteria were participants with mental disorders and other serious physical illnesses. The study protocol was reviewed and approved by the Medical Ethics Committee of Hubei University of Chinese Medicine (Approved No. of ethic committee: 2019-IEC-003). Participants signed the informed consent form, after due clarification concerning the study and before data collection. This study developed a data web platform specifically to screen and intervene with MCI, including detailed demographic information, neuropsychological tests, and Traditional Chinese Medicine (TCM) technical interventions, enabling direct target population identification while ensuring correct data entry and export.

Assessments of cognitive function

The cognitive function tests were developed according to the MCI diagnostic criteria of the 2018 China Dementia and Cognitive Disorders Diagnostic and Treatment Guidelines (23). To maximize measurement precision, the cognitive function tests comprised the following tests. The participant was diagnosed with "mild cognitive impairment" when all tests were met.

The mini-mental status examination

The MMSE is one of the most widely used cognitive screening tool worldwide and is used to assess the general cognitive function of participants (24). The cut-off values for this tool are related to education level and this study used education-based cut-offs for MMSE in Chinese to exclude definite dementia: illiterate, ≥17 points; primary school, ≥20 points; and junior high school and above, ≥24 points (25). The Cronbach's α of MMSE is 0.825, which has good reliability.

The Montreal cognitive assessment

The MoCA is a 30-point test given in 10 min to assess various cognitive tasks including: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. A total MoCA score of 26 is the cut-off value for MCI and older adults with a score of <26 were included in the study (26). The Cronbach's α of MoCA is 0.818, which has a good measurement characteristic.

Activities of daily living

This scale is commonly used to assess physical function and is a common indicator of the lives of people with dementia. In this study, the scale was used to exclude people with impairments in daily living skills and participants with scores <16 were included in the study (27). The scale has good reliability and validity, and the Cronbach's α of ADL is 0.966.

The clinical dementia rating

The CDR scale comprises six domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care, which is graded on a 5-point scale. MCI is defined as CDR = 0.5 (28). The reliability of the scale is 0.84.

Hachinski ischemic score

To exclude cognitive decline due to vascular dementia, participants were asked to have a HIS score of ≤4 in the study (29).

Assessments of oral health status

Oral examinations

Two well-trained dentists used probes and mouth mirrors under artificial lights to examine the number of teeth lost, the presence of dental caries, removable dentures, and periodontitis in older adults.

Oral health surveys

Geriatric Oral Health Assessment Index (GOHAI), the GOHAI is a scale developed specifically to assess oral health-related quality of life (OHRQoL), which is a 12-item questionnaire with the following response options: 1 = very often; 2 = fairly often; 3 = occasionally; 4 = hardly ever; and 5 = never, including 3 subscales of physical function, pain or discomfort, and psychosocial function. A higher total GOHAI score indicates a better OHRQoL, with a range of 12 to 60. The total score was divided into 3 levels: high (57–60 points), medium (51–56 points), and low (≤50 points) (30, 31). For this study, instead of other measurements, GOAHI was chosen, as it has been the most commonly used measurement tool for evaluating the OHRQoL of the older adults in the world. The Cronbach's α of GOHAI is 0.81, which has a good measurement characteristic. In addition, the caregivers obtained oral health conditions such as mastication ability, unilateral mastication, and oral and maxillofacial pain through interviews.

Potential covariate assessment

The following potential confounders were examined. As possible parameters associated with MCI, demographic confounders included age, gender, monthly income, and educational level.

Data analysis

In the descriptive analysis, categorical and continuous variables were shown by frequency, percentage, mean, and deviation. The comparison analysis between the MCI and normal groups was explored using the chi-squared test and fisher's exact test. If a p value was less than 0.05, it was considered statistical significance. Logistic regression was set up using those variables that were found to have a significant difference between cognitive function groups in the univariate analysis as independent variables and MCI (Yes = 1, No = 0) as dependent variables to analyze the relationship between OHRQoL and MCI. The binary logistic regression analysis was performed using the stepwise forward method to control for potential confounders. The odds ratio (OR) and 95% confidence interval (CI) were calculated. Receiver operating characteristic (ROC) curves were used to determine the ability of GOHAI score in identifying MCI. All analyses were conducted using SPSS version 25.0 (IBM Corp., Armonk, NY, United States).

Results

Comparison of participant characteristics

This research included 234 older adults, 80 male and 154 female with a mean age of 71.18 ± 4.97 years. The result showed that 65.8% of older adults had a monthly income of ≤3,999, and the education level was concentrated on junior and high school. Based on the assessment criteria for MCI, more than 70% of people had MCI. Of these, 154 were female and 80 were male, women being more likely to have the condition than men (p = 0.019). In addition, the data showed that there was an association between MCI and different economic levels (p = 0.048) and education levels (p < 0.001). MCI is more common in older adults with low-income (73.4%), and low education level (90.0%), but less common in older adults with high-income levels and high education level. In terms of oral health, dental caries (p = 0.044), mastication ability (p = 0.022), oral and maxillofacial pain (p = 0.042), and self-perceived oral health status (p = 0.002) all differed across cognitive status. MCI is more common in older adults with dental caries (76.9%), masticatory disorders (>70.0%), oral and maxillofacial pain (>60.0%), and bad self-perceived oral health status (>70.0%) (Table 1).

The correlation between GOHAI scale scores and MCI

The mean GOHAI assessment index score in this study was 47.00 ± 7.958, which was at a low level of oral health status. The mean score of 14.46 ± 3.501 for the physical function dimension, 11.12 ± 2.336 for the pain and discomfort dimension and 21.35 ± 3.138 for the psychosocial dimension, indicating that OHRQoL of older adults in the region is poor and needs to be improved. We also found a statistically significant weak negative correlation between GOHAI test scores and MCI (p < 0.001). The GOHAI scores were higher in older adults with normal cognition than in those with MCI, suggesting that MCI in older adults is associated with poorer OHRQoL (Table 2).

Oral health-related risk factors for MCI

Table 3 describes binary logistic regression analysis for MCI with risk factors. Treating MCI and normal cognition as dependent variables, the variables that were significant for the above analysis (gender, monthly income, education level, dental caries, mastication ability, oral and maxillofacial pain, self-perceived oral health status,

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TABLE 1 Comparison of participants' characteristics in MCI vs. normal group.

Variable	Normal ($n = 68$)	Mild cognitive impairment ($n = 166$)	Total	p-value
Age (years), mean ± SD	71.06 ± 9.53	71.23 ± 7.61	71.18 ± 4.97	0.612
65–69	27 (26.7%)	74 (73.3%)	10 (43.2%)	
70–74	29 (33.3%)	58 (66.7%)	87 (37.2%)	
75–79	8 (30.8%)	18 (69.2%)	26 (11.1%)	
80–84	4 (26.7%)	11 (73.3%)	15 (6.4%)	
≥85	0 (0.0%)	5 (100.0%)	5 (2.1%)	
Gender				0.019*
Male	31 (38.8%)	49 (61.3%)	80 (34.2%)	
Female	37 (24.0%)	117 (76.0%)	154 (65.8%)	
Monthly income (RMB)				0.048*
≤3,999	41 (26.6%)	113 (73.4%)	154 (65.8%)	
4,000–5,999	18 (28.1%)	46 (71.9%)	64 (27.4%)	
6,000–7,999	7 (50.0%)	7 (50.0%)	14 (6%)	
≥8,000	2 (100.0%)	0 (0.0%)	2 (0.9%)	
Education level				<0.001**
Illiteracy	1 (10%)	9 (90%)	10 (4.3%)	
Primary school	1 (7.7%)	12 (92.3%)	13 (5.6%)	
Junior high school	16 (18.4%)	71 (81.6%)	87 (37.2%)	
High school	22 (27.8%)	57 (72.2%)	79 (33.8%)	
Undergraduate and above	28 (62.2%)	17 (37.8%)	45 (19.2%)	
Number of teeth lost				0.921
0	9 (30.0%)	21 (70.0%)	30 (12.8%)	
1–5	35 (29.7%)	83 (70.3%)	118 (50.4%)	
6–10	10 (24.4%)	31 (75.6%)	41 (17.5%)	
>10	14 (31.1%)	31 (68.9%)	45 (19.2%)	
Dental Caries				0.044*
Yes	28 (21.3%)	93 (76.9%)	166 (51.7%)	
No	40 (35.4%)	73 (64.6%)	113 (48.3%)	
Removable dentures				0.771
Yes	41 (30.1%)	95 (69.9%)	136 (58.1%)	
No	27 (27.6%)	71 (72.4%)	98 (41.9%)	
Periodontitis				0.296
Yes	21 (24.4%)	65 (75.6%)	86 (36.8%)	
No	47 (31.8%)	101 (68.2%)	148 (63.2%)	
Mastication ability				0.022*
Very good	6 (75.0%)	2 (25.0%)	8 (3.4%)	
Good	22 (32.4%)	46 (67.6%)	68 (29.1%)	
Moderate	24 (30.8%)	54 (69.2%)	78 (33.3%)	
Bad	15 (20.3%)	59 (79.7%)	74 (31.6%)	
Very bad	1 (16.7%)	5 (83.3%)	6 (2.6%)	
Lateral mastication				0.648
Never	14 (35.0%)	26 (65.0%)	40 (17.1%)	
Rarely	18 (30.0%)	42 (70.0%)	60 (25.6%)	
Occasionally	11 (35.5%)	20 (64.5%)	31 (13.2%)	
More often	17 (23.9%)	54 (76.1%)	71 (30.3%)	
Frequently	8 (25.0%)	24 (75.0%)	32 (13.7%)	
Oral and maxillofacial pain				0.042*
Never	26 (37.1%)	44 (62.9%)	70 (29.9%)	
Rarely	24 (27.6%)	63 (72.4%)	87 (37.2%)	
Occasionally	16 (31.4%)	35 (68.6%)	51 (21.8%)	
More often	2 (7.7%)	24 (92.3%)	26 (11.1%)	
Frequently	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Self-perceived oral health status				0.002*
Very good	5 (71.4%)	2 (28.6%)	7 (3.0%)	
Good	27 (41.5%)	38 (58.5%)	65 (27.8%)	
Moderate	20 (26.3%)	56 (73.7%)	76 (32.5%)	
Bad	16 (20.5%)	62 (79.5%)	78 (33.3%)	
Very bad	0 (0.0%)	8 (100.0%)	8 (3.4%)	

n, number; SD, standard deviation; RMB, Chinese yuan; * < 0.05.; ** < 0.01.

and total GOHAI score) were selected as independent variables to enter into a binary logistic regression analysis. Table 3 shows that independent risk factors for MCI were education level (OR = 0.06, 95%CI = 0.007, 0.567) and OHRQoL (OR = 0.92, 95%CI = 0.878, 0.963). The higher education level reduced the risk of MCI, while the lower OHRQoL increased the risk of MCI.

ROC analyses of GOHAI score in identifying MCI

We also carried out the ROC analyses to verify the accuracy and sensitivity of GOHAI in identifying MCI. The best threshold value of GOHAI score in identifying MCI was 43.5. The area under the ROC curve (AUC) of MCI was 0.675 (95%CI: 0.60, 0.75) with a low sensitivity of 41.6% and a moderate specificity of 86.8%.

Discussion

The World Health Organization has listed oral health as one of the top 10 criteria for human health. At present, as the transformation

TABLE 2 The correlation between GOHAI scale scores and MCI.

Variable	Normal (n = 68) Mean ± SD	Mild cognitive impairment (n = 166) Mean ± SD	Total (n = 234) Mean ± SD	r	p-value
Physiological functions	15.72 ± 3.407	13.98 ± 3.395	14.46 ± 3.501	−0.228	<0.001
Pain and discomfort	11.88 ± 2.263	10.81 ± 2.308	11.12 ± 2.336	−0.208	0.001
Psychosocial functions	22.65 ± 2.520	20.89 ± 3.134	21.35 ± 3.138	−0.261	<0.001
Total score	50.25 ± 6.933	45.67 ± 7.987	47.00 ± 7.958	−0.262	<0.001

r, correlation coefficient; n, number; SD, standard deviation.

TABLE 3 Binary logistic regression analysis for MCI with risk factors.

Variable	B	SE	Odds ratio (95% CI)	p-value
Education level				
Primary school	0.242	1.498	1.27 (0.068 ~ 23.992)	0.872
Junior high school	−0.840	1.105	0.43 (0.049 ~ 3.764)	0.447
High school	−1.241	1.099	0.29 (0.034 ~ 2.489)	0.259
Undergraduate and above	−2.753	1.115	0.06 (0.007 ~ 0.567)	0.014
GOHAI score	−0.084	0.023	0.92 (0.878 ~ 0.963)	<0.001

B, unstandardized regression coefficient; SE, standard error; CI, confidence interval.

of the medical pattern and the concept of Healthy China continues to grow, oral health has become an important part of people's pursuit of health. The fourth national oral health epidemiological survey in China showed that the current oral health status of older adults in China is not optimistic, with the serious prevalence of dental caries and periodontal disease (32), and these poor oral health status may increase the risk of cognitive impairment in older adults.

However, research on the relationship between oral health status and MCI is currently limited, which is constrained by the conventional views that "dental disease is not a disease" and "losing teeth is normal aging" (33). This study assessed the relationship between oral health indicators and MCI, the results of the subjective and objective examination revealed that gender, education level, economic level, dental caries, mastication ability, oral and maxillofacial pain, self-perceived oral health status, and the OHRQoL were all correlated with cognitive status in older adults. The regression analysis showed that the GOHAI was negatively associated with cognitive status, and poor OHRQoL in older adults was an independent risk factor for MCI. ROC curves revealed the GOHAI score was determined with 41.6% sensitivity and 86.8% specificity in the prediction of MCI at a cut-off value of 43.5. This is the first study to find that poorer OHRQoL is an independent risk factor for MCI. OHRQoL is a reflection of oral health physiological function, pain and discomfort, and psychosocial function and is closely related to oral physiological dysfunction such as tooth loss, dental caries, and decreased mastication ability, which may be an indicator of true oral health problems. Despite the low sensitivity, the study results provide a certain reference to for clinical study.

Oral diseases are the main influencing factors of OHRQoL, and older adults with poor oral examination results have low OHRQoL (34). Oral diseases, including functional tooth loss, dental caries, and poor mastication function can negatively affect OHRQoL. The low OHRQoL predicts oral problems in older adults and may influence cognitive function through physiological effects (35, 36). Moreover, oral diseases damage the harmony and esthetics of the face, which restricts the social activities of the older adults and can have a detrimental effect on their mental health level. Previous studies have shown that poor OHRQoL can lead to loneliness (37), depression (38), and restriction of mobility and social participation (39). Loneliness (40), depression (41), and reduced social activities (42) have been associated with cognitive decline in older adults. The psychological influence of oral health or the negative psychological impact of OHRQoL on older adults can also affect cognitive function. Therefore, identifying and managing OHRQoL in older adults can help to relieve discomfort, improve oral problems, reduce psychological stress, and also improve cognitive status in older adults with MCI.

In the regression analysis, oral problems such as tooth loss, dental caries, and mastication impairment have not been found to be associated with MCI in older adults, which may be related to factors such as the sample size and the assessment method. Obviously, the impact of poor oral health on the OHRQoL of older adults has a negative effect on cognitive function. Oral health is an easily identifiable and modifiable risk factor. The MCI stage, where older adults retain good mobility and can take care of their oral health, is the best stage for interventions for poor oral health in older adults with cognitive disorders. The OHRQoL assess enables the detection of oral problems, which will help to slow down the decline in cognitive function. The regular objective examination of oral health often has special requirements, and GOHAI is a more comprehensive and subjective evaluation system that reflects the new medical model and view of health. The GOHAI can be used by a variety of researchers to assess the OHRQoL and to improve poor oral status, healthcare behaviors, and habits promptly, which is important for the overall health and quality of life of older adults. Therefore medical workers can adopt targeted interventions to create proper oral awareness and establish proper oral habits in older adults, which may improve their OHRQoL and improve cognitive performance.

There are some limitations in our study. First, participants were recruited through hospitals, which may have selection bias. Second, our study was designed as a cross-sectional study, it was difficult to draw conclusions about the causal relationship between oral health status and MCI. Additionally, Some oral health indicators were assessed by self-report, which may be subject to recall bias. In subsequent studies, there is a need to develop strict inspection measures, refine the classification indicators, expand the sample size and reduce confounding factors to further improve the study design, preferably through longitudinal studies to clarify the causal relationship between various oral health indicators and MCI.

Conclusion

This study intentionally developed a data web platform to screen and intervene older adults with MCI. To improve measurement accuracy and data collation, older adults with MCI were identified through multiple assessments, and their oral health was assessed through subjective and objective examinations. This is the first study to show that OHRQoL is an independent risk factor for MCI and that poor OHRQoL is associated with poor cognitive function in older adults. Therefore medical workers can focus on increasing oral health awareness, establishing proper oral hygiene habits, improving oral problems, and enhancing education about the causes and symptoms of oral problems in older adults, which may improve their OHRQoL and thus maintain and improve cognitive ability. It is also important to pay attention to the psychological impact of poor OHRQoL on older adults, and maintaining the psychological health of older adults also has a role in improving OHRQoL and cognitive ability. However, longitudinal studies with large samples on various oral health indicators are needed in the future.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the Medical Ethics Committee of Hubei University of Chinese Medicine (Approved No. of ethic committee: 2019-IEC-003). The patients/participants provided their written informed consent to participate in this study.

Author contributions

NY: Conceptualization, Writing – original draft, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – review & editing. BD: Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. HH: Conceptualization, Data curation, Funding acquisition, Project administration, Writing – review & editing. YA: Conceptualization, Data curation, Writing – review & editing. XL: Data curation, Investigation, Methodology, Writing – review & editing. SZ: Data curation, Investigation, Writing – original draft. YL: Data curation, Investigation, Writing – original draft.

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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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Neurophysiological markers of early cognitive decline in older adults: a mini-review of electroencephalography studies for precursors of dementia

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The early detection of cognitive decline in older adults is crucial for preventing dementia. This mini-review focuses on electroencephalography (EEG) markers of early dementia-related precursors, including subjective cognitive decline, subjective memory complaints, and cognitive frailty. We present recent findings from EEG analyses identifying high dementia risk in older adults, with an emphasis on conditions that precede mild cognitive impairment. We also cover event-related potentials, quantitative EEG markers, microstate analysis, and functional connectivity approaches. Moreover, we discuss the potential of these neurophysiological markers for the early detection of cognitive decline as well as their correlations with related biomarkers. The integration of EEG data with advanced artificial intelligence technologies also shows promise for predicting the trajectory of cognitive decline in neurodegenerative disorders. Although challenges remain in its standardization and clinical application, EEG-based approaches offer non-invasive, cost-effective methods for identifying individuals at risk of dementia, which may enable earlier interventions and personalized treatment strategies.

KEYWORDS

electroencephalogram (EEG), event-related potentials (ERPs), dementia prevention, neurophysiological biomarker, mild cognitive impairment, subjective cognitive decline, subjective memory complaint, cognitive frailty

1 Introduction

Rapid aging of the global population has intensified the need to extend healthy life expectancy, and dementia poses an important challenge to this goal. Alzheimer's disease (AD) and other types of dementia are characterized by cognitive decline that is distinct from that of normal aging, necessitating a deeper understanding of the underlying mechanisms. Recent research has revealed that AD-associated pathophysiological changes can begin more than a decade before the onset of clinical symptoms (Ritchie et al., 2016; Moffat et al., 2022). Although postmortem examination remains the definitive method for diagnosing dementia, important advancements in *in vivo* assessment techniques have emerged, including cerebrospinal fluid biomarkers, positron emission tomography, and magnetic resonance imaging (MRI) (Clark et al., 2018; Hojjati et al., 2018; Liu et al., 2024). However, these methods present various challenges, such as high cost, invasiveness, and limited clinical accessibility.

Electroencephalography (EEG) offers a non-invasive, cost-effective approach for detecting neurological markers of cognitive decline. Recent reviews have focused on EEG characteristics

in AD and mild cognitive impairment (MCI) (Al-Qazzaz et al., 2014; Sanchez-Reyes et al., 2021; Torres-Simon et al., 2022; Wijaya et al., 2023). EEG activity correlates with cognitive decline assessed by the Mini-Mental State Examination (MMSE), and combining these measures improves dementia prediction accuracy (Doan et al., 2021). EEG may detect subtle early functional changes. However, research on EEG markers of early precursors, such as subjective cognitive decline (SCD), subjective memory complaints (SMC), and cognitive frailty (CF), remains scarce.

This mini-review summarizes recent EEG findings used to identify a high risk of dementia in older adults, emphasizing conditions such as SCD, SMC, and CF. We explore EEG-based approaches, including event-related potentials (ERPs), quantitative EEG (qEEG) markers, microstate analysis, and functional connectivity measures. Additionally, we discuss the integration of EEG with artificial intelligence technologies for early diagnosis and prediction of dementia progression.

By focusing on pre-MCI states, we aim to increase knowledge of the early detection of cognitive decline, thus enabling earlier interventions and more effective prevention strategies. Additionally, we highlight the challenges and future directions in this field, emphasizing the need for standardized approaches and larger-scale studies to validate the clinical utility of EEG-based markers in dementia risk assessments.

2 Early cognitive decline: from normal aging to pre-MCI states

The risk of dementia in older adults is influenced by 12 modifiable risk factors (Livingston et al., 2020). Previous studies have pointed out the association between preclinical stages of AD (i.e., SMC and SCD) and these lifestyle risk factors, such as low education and hypertension (Chen et al., 2014), and depression and cigarette smoking (Ahn et al., 2021). The importance of treating these factors before cognitive decline onset or at the subjective complaint stage is increasingly emphasized (Van Der Flier et al., 2023).

The spectrum of cognitive decline ranges from normal aging to dementia, encompassing crucial intermediate stages for early detection and intervention. MCI is a high-risk state for progression to dementia, particularly AD (Arnáiz and Almkvist, 2003), and is characterized by clinical symptoms, minimal assistance needs with daily activities, and potentially reversible cognitive decline (García et al., 2021).

Recent studies have focused on earlier stages of cognitive decline. In SCD and SMC, individuals experience self-perceived cognitive decline but perform within the normal range on objective tests, and exhibit an increased risk of progressing to MCI and dementia (Kryscio et al., 2014; Bessi et al., 2018). CF represents coexisting physical frailty and MCI, and encompasses mild cognitive decline even without a diagnosed neurological disorder (Kelaiditi et al., 2013; Shimada et al., 2018; Facal et al., 2021). Kocagoncu et al. (2022) defined CF as mild cognitive decline without subjective awareness, indicating that the concept of CF is not fully established. CF is linked to increased risks of dementia, care needs, hospitalization, disability, and mortality compared with healthy aging (Lee et al., 2018; Panza et al., 2018).

Distinguishing these early stages from normal aging is challenging because differences can be subtle and not always apparent using standard cognitive assessments. EEG primarily reflects postsynaptic potentials, offering promising avenues for identifying early markers of cognitive decline. EEG may detect subtle changes in postsynaptic fields that potentially underlie cognitive dysfunction in AD and MCI (Arendt, 2009; Targa Dias Anastacio et al., 2022).

3 Contemporary ERP methodologies and their application

While EEG may reflect postsynaptic potentials and neuronal population activity, ERPs are derived from averaging electrical responses to specific stimuli or tasks, enabling identification of components related to perception and cognition. Goodin et al. (1978) first identified the P300 component as a biomarker for dementia, characterized by a positive waveform occurring 200–300 ms after an oddball task event. AD typically results in attenuated P300 amplitude and increased latency compared with normal aging (Pedroso et al., 2012; Hedges et al., 2016; Fruehwirt et al., 2019). The P300 is also sensitive to MCI; reduced P300 amplitude indicates cognitive deterioration in at-risk older adults (Newsome et al., 2013), and its latency may predict MCI progression to AD (Jiang et al., 2015).

Table 1 summarizes recent ERP studies on early cognitive decline in older adults. Evidence regarding the P300 in SCD and SMC is limited but promising. People with SMC progressing to AD show a prolonged P300 latency before AD onset (Gironell et al., 2005) and in response to stimulus–response incongruence (Cespón et al., 2018). Ulbl and Rakusa (2023) reviewed studies that demonstrated decreased N170 and P300 amplitudes in SCD, although the results across ERP components were inconsistent. The P3b is a later component of the P300, and has exhibited decreased amplitude in cognitively low-performing older adults, suggesting age-independent episodic memory decline (Porcaro et al., 2019). Additionally, P300 peak amplitude correlates with bilateral hippocampal volume in healthy older adults (Devos et al., 2021).

Mismatch negativity (MMN) reflects the automatic detection of sensory input changes. Attenuated MMN is associated with memory and psychosocial deficits (Mowszowski et al., 2012) and is decreased in AD and MCI compared with normal aging (Kazmerski et al., 1997; Papadaniil et al., 2016). The neural sources of MMN show a characteristic migration pattern with AD progression (Papadaniil et al., 2016; Tsolaki et al., 2017). Ruzzoli et al. (2016) reported distinctive patterns of auditory MMN distribution in normal aging, MCI, and AD. In SCD, magnetoencephalography (MEG)-measured MMN revealed that attenuated responses were correlated with memory function (Cheng et al., 2021). Additionally, MMN-based neurofeedback is reportedly effective for working memory training in SCD (Pei et al., 2020).

The N200 component has shown utility for differentiating MCI from AD (Papaliagkas et al., 2009b; Morrison et al., 2018) and predicting progression risk to MCI/AD in healthy older adults (Papaliagkas et al., 2009a; Howe, 2014). Although similar effects in N400 and P600 have been reported (Grieder et al., 2013; Chou et al., 2023), their usefulness remains unclear in the context of SCD, SMC, and CF.

Research on other ERP components has been limited. Tarawneh et al. (2023) reported prolonged P50 latency in amyloid-β-positive participants compared with healthy controls. Changes in ERPs during

TABLE 1 Summary of ERP studies of early cognitive decline in older adults.

Authors (Year)	Participants	ERP task	ERP component	Amplitude effects	Latency effects	Other effects
Gironell et al. (2005)	SMC ($n = 116$)	Oddball	P300	–	AD > NC, MCI, DOT	Baseline P300 latency predicted AD diagnosis
Cespón et al. (2018)	Low SMC ($n = 18$), High SMC ($n = 16$)	Simon task	P300, MFN	High SMC: larger MFN for incompatible trials	P300: longer for incompatible position	High SMC: interference from arrow direction at slow RTs
Ulbl and Rakusa (2023)	SCD, MCI, AD, NC (Review of 30 studies)	Various	P300, N170	SCD: reduced P300/N170 amplitudes in some studies	SCD: increased P300/N170 latencies in some studies	EEG: SCD showed slowing of rhythms and connectivity changes
Porcaro et al. (2019)	Young ($n = 15$), HP Old ($n = 17$), LP Old ($n = 14$)	Visual three-stimulus oddball	P3a, P3b	P3b: Young > HP > LP P3a: Young > HP, LP	P3a, P3b: Young< HP, LP	FSS improved detection of group differences; P3b amplitude distinguished HP from LP
Cheng et al. (2021)	SCD ($n = 26$), NC ($n = 29$)	Not specified	MMNm	SCD < HC in left IPL and right IFG	–	MMNm amplitudes in right IFG correlated with memory performance in SCD; No GM volume differences between groups
Pei et al. (2020)	SCD ($n = 17$)	Auditory oddball	MMN	Increased at Pz after training	–	Improved WM performance, especially in auditory tone 3-back task
Tarawneh et al. (2023)	SMC ($n = 43$), non-SMC ($n = 19$)	Auditory oddball	P50, N100, P200, N200, P300	–	P50: Aβ+ > Aβ-; P50 latency weakly correlated with MAC-Q scores	P50 latency may identify individuals at higher risk of cognitive decline
Garrido-Chaves et al. (2021)	Young SMC ($n = 28$), Young noSMC ($n = 37$), Older SMC ($n = 32$), Older noSMC ($n = 39$)	Iowa Gambling Task	FRN, P3	FRN: Losses > Wins; Older > Young; P3: Young > Older	FRN, P3: Older > Young; FRN: Older SMC > Older noSMC for losses in first block	Older SMC showed worse behavioral performance in ambiguity phase
Kocagoncu et al. (2022)	CF ($n = 26$), NC ($n = 38$), MCI ($n = 15$), AD ($n = 11$)	Cross-modal oddball	MMN	CF, NC > MCI, AD for novel and associative deviants	–	CF showed similar neurophysiological profile to NC, despite poor cognitive performance

Aβ, amyloid-β; AD, Alzheimer's disease; AERP, auditory event-related potential; CF, cognitive frailty; DOT, dementia of other type; ERP, event-related potentials; FRN, feedback-related negativity; FSS, functional source separation; GM, gray matter; HC, healthy control; HP, high performing; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; LP, low performing; MAC-Q, Memory Assessment Clinics Questionnaire; MCI, mild cognitive impairment; MFN, medial frontal negativity; MMN, mismatch negativity; MMNm, magnetic mismatch negativity; NC, normal control; RT, reaction time; SCD, subjective cognitive decline; SMC, subjective memory complaints; WM, working memory.

cognitive tasks have been reported in SMC, including prolonged feedback-related negativity latencies (Garrido-Chaves et al., 2021). Kocagoncu et al. (2022) proposed that CF is part of the normal neurocognitive spectrum, as its MMN responses resemble those of normal aging.

Cognitive function in the normal range, possibly resulting from compensatory neural mechanisms (Sala-Llonch et al., 2015; Wei et al., 2022), may contribute to low sensitivity to ERP components in SMC and SCD. Thus, EEG may offer more sensitive and valuable information regarding early cognitive decline than ERPs in SCD, SMC, and CF.

4 Exploring the frontiers of EEG research: advanced approaches to elucidating early cognitive decline as a risk for dementia

4.1 Quantitative EEG markers during precursor symptoms of AD

qEEG analyzes digital EEG signals using mathematical algorithms (Nuwer, 1997), providing insights into potential early neurobiomarkers of pathological cognitive aging (Keller et al., 2023). Unlike ERPs focusing on

time-locked responses, qEEG examines ongoing EEG activity, offering a broader view of brain function. qEEG includes linear techniques, including power spectral analysis, and nonlinear methods, including entropy measurements and fractal dimension analysis (Al-Qazzaz et al., 2014). In AD, EEG typically shows reduced alpha and beta band activity (Wada et al., 1998; Knott et al., 2000), distinct from normal aging (Babiloni et al., 2021).

Recent research focuses on differences between normal aging and prodromal AD pathophysiology, including MCI, SCD, and SMC. A key finding in MCI and AD is "EEG slowing," in which increased occipital low-frequency power and decreased frontal high-frequency power are correlated with cognitive performance (Farina et al., 2020; Medici et al., 2023). The theta/alpha ratio indicates cognitive decline, showing differences between AD, MCI, and healthy older adults (Meghdadi et al., 2021), with an increased ratio in MCI associated with higher dementia risk (Hamilton et al., 2021).

EEG slowing parameters show promise for detecting early cognitive decline in SCD and SMC (Table 2). Previous studies have reported decreased frontal EEG slowing parameters with declining cognitive scores in healthy older adults (Choi et al., 2019), increased theta power and reduced alpha reactivity in SMC (Perez et al., 2022), and altered oscillatory activity in SCD (Shim et al., 2022).

Higher education levels are correlated with higher posterior alpha rhythm amplitudes in SMC (Babiloni et al., 2020) and enhanced neural coupling between posterior alpha rhythm and thalamus-visual networks (Lopez et al., 2024), suggesting a protective role of cognitive reserve.

Several studies have demonstrated qEEG's potential for predicting progression from preclinical to AD. Engedal et al. (2020) reported moderate accuracy in predicting transition to dementia in SMC and MCI. Associations between qEEG parameters and pathological protein biomarkers suggest that resting-state EEG changes might reflect increased brain amyloid burden in AD progression (Spinelli et al., 2022; Ulbl and Rakusa, 2023).

Nonlinear methods have shown promising results in distinguishing AD patients from healthy older individuals (Abásolo et al., 2006; Pineda et al., 2020), potentially capturing complex brain dynamics not evident in linear analyses. However, studies employing nonlinear techniques for SMC and SCD have been limited, mainly using MEG (e.g., Shumbayawonda et al., 2020). The application of this approach to preclinical dementia stages faces challenges, including high computational costs and complex data interpretation (Vicchietti et al., 2023).

Although EEG biomarkers exist for SCD and SMC, research examining CF remains limited. Some studies have suggested that CF exhibits brain activity patterns related to physical conditions (Suárez-Méndez et al., 2021) linked to cognitive function (Liu et al., 2024). CF characteristics may be discerned through changes in cognitive function-related neural oscillations, microstate analysis, functional connectivity, and phase coherence analysis.

4.2 Integrating microstate and connectivity analyses for the early detection of cognitive decline

Although qEEG provides insights into frequency characteristics of resting-state brain activity, advanced techniques like microstate analysis, functional connectivity assessment, and graph theory approaches offer a deeper understanding of brain network dynamics in cognitive decline. These methods show promise for differentiating normal aging from pathological changes, including AD and prodromal AD symptoms.

Microstate analysis captures functional network dynamics with millisecond-level resolution, revealing distinct characteristics between AD and MCI. EEG microstates, brief periods of quasi-stable scalp electrical patterns typically classified into four topographies (A–D), reflect momentary global brain states and the basic units of cognitive processing (Michel and Koenig, 2018). Significant differences in microstate topographies—particularly A, C, and D—between healthy controls and AD/MCI (Britz et al., 2010; Smailovic et al., 2019; Lian et al., 2021) may reflect dysfunction in key brain networks (e.g., default mode network or frontoparietal network) associated with AD pathology.

Changes in microstate dynamics have been observed in MCI and AD. Musaeus et al. (2019, 2020) reported higher transition probabilities from microstates C and D to A, and increased occurrence frequencies and coverage of microstate A, in AD and MCI compared with healthy controls. Notably, Lassi et al. (2023) found reduced complexity of microstate transitions in MCI and SCD, indicating simpler brain network dynamics even at the SCD stage. Shi et al. (2022) reported that specific microstate transition probabilities ($C \rightarrow A - D \rightarrow A$) correlate with MMSE scores, suggesting applications for identifying potential cognitive impairment and brain activity patterns in the pre-dementia stage.

Functional connectivity analysis provides insights into SCD and MCI pathophysiology without apparent structural changes. López-Sanz et al. (2017) identified anterior network hyper-synchronization and decreased posterior network connectivity in SCD and MCI during the resting state. Cheng et al. (2020) reported increased functional connectivity within the default mode network in the delta and gamma frequency bands in SCD using MEG, potentially representing compensatory mechanisms.

Graph theory approaches have further elucidated changes in brain network organization across the cognitive decline spectrum (Rubinov and Sporns, 2010). Vecchio et al. (2014) applied graph theory to EEG analysis, revealing differences in brain networks between healthy elderly and AD patients. EEG of normal subjects showed high interaction between channels, while AD patients exhibited more random brain network structures, particularly in the alpha band. These changes correlated with cognitive decline, suggesting that EEG-based brain network analysis may be useful for early diagnosis and monitoring of dementia progression.

Task-related functional connectivity analyses have provided additional insights into cognitive decline. During working memory tasks, MCI patients exhibit altered connectivity patterns, including decreased fronto-temporal connectivity and increased fronto-occipital and parieto-occipital connectivity in theta and alpha bands (Jiang et al., 2024). Furthermore, decreased alpha band connectivity and lack of beta band modulation with increasing memory load were observed, resulting in a more centralized network structure (Fodor et al., 2021). These changes may reflect compensatory mechanisms in response to neurodegeneration in the hippocampus and surrounding regions. Table 2 summarizes EEG studies of microstate analysis and functional connectivity.

In healthy older adults, high cognitive load tasks are also associated with decreased alpha band connectivity and increased

TABLE 2 Summary of EEG studies of early cognitive decline in older adults.

Authors (Year)	Participants	EEG task	Frequency bands	Power/ amplitude effects	Functional connectivity	Other features	Main findings
Choi et al. (2019)	496 elderly (165 Male, 331 Female), age ≥ 50 years	Resting-state, eye closed	*α*, *θ*	MF, PF, TAR ↓ with lower MMSE	–	EEG from Peak Frequency (Fp1, Fp2)	(1) MDF, PF, TAR: correlated with MMSE (2) EEG slowing significantly between MMSE T2 vs. T1
Shim et al. (2022)	SMC ($n = 95$): 26 A+, 69 A−, age ≥ 65 years	Resting-state, eye closed	*δ*, θ, α1, α2, β1, β2, β3, *γ*	A+: (1) ↑ relative *δ* in F, P, O (2) ↓ relative α1 in F, C, O	↑ connections bilateral PCu in δ ↓ connections bilateral entorhinal areas in α1	19 scalp electrodes; sLORETA; DMN analysis	(1) A+: ↑δ, ↓α1 (2) ↓α1 in bilateral fusiform & inferior temporal area, ↑δ in posterior regions
Babiloni et al. (2020)	SMC ($n = 172$): 118 A−, 54 A+, age ≥ 70 years	Resting-state, eye closed	δ, θ, α1, α2, α3, β1, β2, γ	A+ high education: ↓ O α2, ↑ T α3 A− high education: ↑ P, O, T α2 & α3	–	19 scalp electrodes; IAF-based analysis	(1) A− high education: ↑ posterior α (2) A+ high education: ↑ T α3, ↓ O α2
Lopez et al. (2024)	SMC ($n = 161$): 105 A−, 56 A+, age ≥ 70 years	Resting-state, eye closed	δ, θ, α1, α2, α3, β1, β2, γ	A− high education: ↑ P, O, T α2, ↑ O α3 A+ high education: ↓ F, O α2 & α3	+ associations Thal-VN connections & posterior α3 in A− high education	68 scalp electrodes; rs-fMRI; amyPET	(1) A− high education: ↑ posterior α (2) A+ high education: ↓ posterior α
Engedal et al. (2020)	SMC ($n = 45$), MCI ($n = 88$), NC ($n = 67$), age ≥ 50 years	Resting-state, eye closed	–	–	–	qEEG using SPR method; DI (0–100)	DI predicted conversion to dementia with moderate accuracy (AUC = 0.78)
Spinelli et al. (2022)	SMC ($n = 318$): 230 A−, 88 A+, age 70–85 years	Resting-state, eye closed	δ, θ, α1, α2, β1, β2, γ	Baseline: A+ ↑ MF θ 24-month follow-up: A+ ↑ PC θ, ↓ O α1	–	256 electrodes; source-level analysis; longitudinal	(1) A+: ↑ MF θ at baseline, ↑ PC θ at follow-up (2) Suggests DMN hypoactivation in A+
Lassi et al. (2023)	SCD ($n = 57$), MCI ($n = 46$), NC ($n = 19$)	Resting-state	δ, θ, α, β	↑ δ power in MCI vs. NC in left central ROI	SWI in δ band: SCD > MCI	Microstates analysis, LZ complexity, Hurst exponent	(1) Microstate C: ↓ duration and coverage in MCI vs. NC and SCD (2) ↓ LZ complexity in MCI vs. SCD (3) Hurst exponent: NC > SCD > MCI (4) Microstate C topography different in AD-like CSF profile
Shi et al. (2022)	AD ($n = 13$), MCI ($n = 19$)	Resting-state	2–20 Hz (secondary filter)	–	–	Microstate parameters (GEV, TPs, TTPs)	(1) AD showed longer microstate durations and fewer occurrences than MCI. (2) TPC → A-D → A correlated with MMSE scores (negatively in AD, positively in MCI). (3) Using TTPs and Partial Accumulation strategy, LDA classifier achieved 93.8% accuracy in distinguishing AD from MCI

(Continued)

TABLE 2 (Continued)

Authors (Year)	Participants	EEG task	Frequency bands	Power/ amplitude effects	Functional connectivity	Other features	Main findings
López-Sanz et al. (2017)	SCD ($n = 41$), MCI ($n = 51$), NC ($n = 39$)	Resting-state	α (6.9–11.4 Hz)	–	Whole-brain FC analysis; DMN and DAN analysis	PLV, SWI	(1) SCD and MCI showed similar FC alterations: ↑ FC in anterior network, ↓ FC in posterior network. (2) MCI had more pronounced posterior FC decrease vs. SCD. (3) ↓ FC in DAN and posterior DMN for both SCD and MCI vs. HC. (4) FC changes correlated with cognitive scores and hippocampal volume.
Cheng et al. (2020)	SCD ($n = 27$), NC ($n = 26$)	Resting-state	δ, θ, α, β, γ1, γ2	–	↑ FC in DMN for SCD vs. NC in δ and γ bands	AEC, Node strength	(1) ↑δ band FC in SCD between LTC-PCC and PCu-PCC. (2) ↑γ band FC in SCD between LTC-PCC and PCu-PCC. (3) PCC node strength in δ and γ bands showed good discrimination ability for SCD vs. NC (AUC > 0.75). (4) PCC γ1 node strength correlated with cognitive complaints in SCD.
Hou et al. (2018)	Young ($n = 15$, 19–29 years), Senior ($n = 10$, 58–70 tears)	Resting-state, 0-back, 2-back	θ, α, β, γ	–	PLI	Clustering coefficient, Characteristic path length, Small-world coefficient	(1) Age-related alterations more prominent in 2-back task, especially in θ band. (2) ↑θ band FC and nodal clustering coefficient in seniors during 2-back. (3) ↓α band small-world coefficient in seniors during both *n*-back tasks. (4) Young adults showed ↑β band clustering coefficient during 2-back vs. rest; absent in seniors. (5) θ and γ band metrics correlated with working memory performance.
Kim et al. (2021)	SCD ($n = 180$), MCI ($n = 63$)	Resting-state, eyes-closed	δ, θ, α1, α2, β1, β2, β3, γ	Various power changes reported	–	Relative power, Genetic algorithm for feature selection, Multi-model ensemble	(1) SCD amyloid classification: 85.7% sensitivity, 89.3% specificity, 88.6% accuracy. (2) MCI amyloid classification: 83.3% sensitivity, 85.7% specificity, 84.6% accuracy. (3) Genetic algorithm identified optimal EEG features for classification. (4) Multi-model ensemble approach improved classification performance.

A−, amyloid PET-negative; A+, amyloid PET-positive; AD, Alzheimer's disease; AEC, amplitude envelope correlation; amyPET, amyloid positron emission tomography; AUC, area under the curve; C, central; CSF, cerebrospinal fluid; DAN, dorsal attention network; DI, dementia index; DMN, default mode network; EEG, electroencephalography; F, frontal; FC, functional connectivity; GEV, global explained variance; IAF, individual alpha frequency; LDA, linear discriminant analysis; LTC, lateral temporal cortex; LZ, Lempel–Ziv; MCI, mild cognitive impairment; MDF, median frequency; MF, midfrontal; MMSE, Mini-Mental State Examination; NC, normal control; O, occipital; P, parietal; PC, posterior cingulate; PCC, posterior cingulate cortex; PCu, precuneus; PF, peak frequency; PLI, phase lag index; PLV, phase locking value; qEEG, quantitative EEG; ROI, region of interest; rs-fMRI, resting-state functional magnetic resonance imaging; SCD, subjective cognitive decline; sLORETA, standardized low-resolution brain electromagnetic tomography; SMC, subjective memory complaints; SPR, statistical pattern recognition; SWI, small world index; T, temporal; TAR, theta-alpha ratio; Thal-VN, thalamus-visual network; TPs, transition probabilities; TTPs, time-factor transition probabilities.

theta band phase synchronization and connectivity (Hou et al., 2018). These findings suggest that graph theory-based functional connectivity analysis during cognitively demanding tasks may reveal characteristic changes in brain functional networks specific to SCD, SMC, and potentially CF.

4.3 Novel EEG methods using machine learning and deep learning algorithms

Integrating artificial intelligence with EEG analysis has emerged as a powerful approach for predicting cognitive decline progression.

Machine learning algorithms applied to EEG data have high accuracy for classifying AD patients and predicting progression from MCI to AD. For instance, studies using support vector machines and gradient-boosted trees have achieved impressive classification accuracies, reaching 95% for AD detection (Rossini et al., 2022) and 83% for MCI progression prediction in healthy older adults (Mazzeo et al., 2023a). Al-Hagery et al. (2020) improved the accuracy of AD diagnosis to 96.66% using the random forest algorithm as an ensemble method, representing a significant improvement over the single decision tree algorithm (73.33%). These results demonstrate the potential of machine learning techniques, particularly ensemble methods, in enhancing early diagnosis and prediction of dementia progression. The high accuracy achieved by these models suggests their potential clinical application, potentially enabling earlier interventions and more personalized treatment strategies for patients at risk of cognitive decline.

Multimodal approaches combining EEG with other biomarkers may enhance prediction accuracy. Maestú et al. (2019) demonstrated that integrating EEG data with other biomarkers (e.g., genotypes, cognitive tests, or brain imaging) may provide more accurate AD predictions. Kim et al. (2021) developed a model integrating EEG and apolipoprotein E genotypes to predict amyloid positron emission tomography positivity in SCD and MCI, with high accuracy in both groups (see Table 2). These advancements extend early intervention potential to preclinical stages. Mazzeo et al. (2023b) reported a protocol for a prospective cohort study of SCD patients, aiming to develop a model for predicting AD progression using machine learning by integrating multifaceted data including neuropsychological assessments, genetic analysis, EEG, and ERPs.

However, challenges remain in implementing these approaches for large-scale screening, including cost, generalizability, and invasiveness (Rossini et al., 2022). Many studies face limitations, including small sample sizes, short follow-up periods, and difficulties controlling diverse data in multimodal approaches. The variability and reproducibility of machine learning findings across facilities are also concerns. However, in SCD and SMC contexts, machine learning and deep learning models based on large-scale databases are becoming increasingly crucial for distinguishing between actual cognitive impairment and personal cognitive complaints.

5 Discussion

Herein, we reviewed the clinical implications of EEG approaches for the early screening of dementia risk in cognitively frail individuals.

Resting-state qEEG is a promising biomarker for SCD, SMC, and possibly CF. When adjusted for cognitive reserve factors, EEG slowing may detect frequency pattern changes and correlate with cognitive decline in high-risk individuals. Combining qEEG with AD pathology markers could enhance its predictive potential for AD progression (Spinelli et al., 2022).

Microstate analysis, functional connectivity analyses, and graph theory approaches may serve as early neural markers of dementia, revealing brain network alterations. These methods, especially when combined with cognitive tasks, can identify subtle functional changes before overt impairments manifest. Recent machine-learning approaches have shown promise in classifying amyloid status in SCD and MCI using EEG features (Kim et al., 2021).

ERP components, particularly P300 and MMN, may detect cognitive frailty in older adults when paired with cognitive tasks. However, their effectiveness is limited in pre-MCI states caused by subtle, multidomain cognitive decline. ERPs are more useful in detecting MCI and AD. As reviewed above, numerous studies have identified common EEG/ERP features in MCI and AD. Combining these with neuropsychological tests and AD biomarkers can improve diagnostic accuracy.

With the increase in young-onset dementia (YOD), EEG has shown potential for YOD diagnosis, particularly in early-onset AD and frontotemporal dementia. Studies highlight distinct EEG patterns, such as increased theta and delta activity in YOD, making EEG a valuable, cost-effective tool for early detection and differentiation (Lin et al., 2021; Brown et al., 2023).

However, clinical application of EEG faces methodological challenges. Evidence for EEG alone to predict dementia progression is insufficient compared with established AD biomarkers (Gouw et al., 2017; Jiao et al., 2023). The absence of standardized guidelines for dementia-specific EEG limits the comparability and generalizability of results (Monllor et al., 2021). Gender differences in dementia risk remain underexplored in EEG research on pre-dementia symptoms despite higher risk in women (Hayden et al., 2006; Chêne et al., 2015). Both EEG and fMRI alone show limited efficacy in distinguishing healthy older adults from MCI (Farina et al., 2020), suggesting the need for multimodal integration (Li et al., 2024).

To overcome these limitations, we propose multi-center collaborative research, such as the "Dementia ConnEEGtome" project (Prado et al., 2022). This approach, with 5-year follow-ups incorporating conventional diagnostic approaches, including AD pathology, could advance standardization, address methodological issues, and improve EEG's reliability as an early AD biomarker.

Author contributions

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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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Association of serum klotho with cognitive function among individuals with nonalcoholic fatty liver disease

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Introduction: This study investigated the potential link between serum klotho levels and cognitive function in patients with non-alcoholic fatty liver disease (NAFLD).

Materials and Methods: Utilizing NHANES data from 2011 to 2014, the research included 356 eligible participants. NAFLD was identified with the United States Fatty Liver Index (US-FLI), and cognition was measured by various tests including the Animal Fluency Test (AFT), Digit Symbol Substitution Test (DSST), Immediate Recall Test (IRT), and Delayed Recall Test (DRT). Weighted logistic regression and restricted cubic splines were employed to analyze the relationship between klotho levels and cognitive scores.

Results: A significant nonlinear association was observed between klotho levels and the performance in DSST and Delayed Recall Test (DRT). After controlling for confounding factors, the study found a positive association between higher serum klotho levels and improved cognitive performance in both AFT and DSST. However, there was no significant relationship between klotho levels and the IRT or DRT, regardless of whether the natural logarithm or quartile was considered.

Discussion: The findings suggest that a higher serum klotho level may be positively correlated with better cognitive performance in NAFLD patients.

KEYWORDS

NAFLD, klotho, cognitive performance, DSST, AFT

1 Introduction

Nonalcoholic fatty liver disease (NAFLD) has a high prevalence worldwide, and there is evidence suggesting that NAFLD is associated with an increased risk of dementia and cognitive decline (Weinstein et al., 2019; Kim et al., 2022). Since the discovery of klotho protein at the end of the last century, many animal studies have shown that klotho can effectively delay aging and protect cognitive function (Kuro-o, 2009). A study involving 10,949 American adults found a link negative association between NAFLD and klotho levels (Chi et al., 2023). However, the relationship between cognitive function and klotho levels in patients with NAFLD requires further exploration.

The definition of NAFLD include evidence of hepatic steatosis (HS), as well as the absence of significant alcohol consumption, and other known causes of hepatic fat accumulation (Rinella et al., 2024). Patients with NAFLD may progress to nonalcoholic steatohepatitis (NASH), leading to the development of liver fibrosis and eventually liver cancer (Thomas et al., 2024). The main feature of NAFLD is the excessive accumulation of triglycerides in liver cells. However, the reasons for the ongoing deterioration of NAFLD are still unclear (Engin, 2017). The prevalence of NAFLD in the general population of the United States was 26% according

to a 2016 survey (Younossi et al., 2016), and there is a global trend of increasing. It would be a huge burden on society (Golabi et al., 2024; Riazi et al., 2022).

NAFLD is a systemic disease closely linked to various comorbidities, including cardiovascular disease, chronic kidney disease, and several types of cancer (Duell et al., 2022; Thomas et al., 2024; Marcuccilli and Chonchol, 2016). The result that NAFLD patients has smaller total cerebral brain volume suggests a possible association between NAFLD and brain aging (Weinstein et al., 2018). NAFLD may be a risk factor for central nervous system dysfunction. The reduced peripheral clearance capacity in NAFLD patients may lead to the inability to excrete substances such as amyloid-beta peptide (Aβ), thereby resulting in brain damage (Estrada et al., 2019). A study was conducted on 4,472 adults aged 20–59 found that NAFLD was independently associated with lower cognitive performance (Seo et al., 2016).

Since the discovery of the klotho protein in 1997, it has been shown to play a crucial role in aging (Abraham and Li, 2022; Kuro et al., 1997). Currently, three types of klotho have been identified, including full-length transmembrane klotho (m-klotho), soluble klotho (s-klotho), and secreted klotho (Xu and Sun, 2015). The klotho gene is primarily expressed in the kidneys and choroid plexus of the brain (Wang and Sun, 2009, 2010). Its levels in the body gradually decrease with age. Many experiments have been conducted in animal studies, mice lacking klotho exhibit manifestations resembling premature aging that manifest universally. These mice with restricted klotho expression stop growing after 3–4 weeks of life and die prematurely at 8–9 weeks (Kuro et al., 1997). Additionally, these mice experienced rapid atrophy of the thymus, thinning of the skin, and progressive emphysema around the lungs—symptoms similar to natural aging rather than pathological changes (Kawaguchi et al., 1999; Kuro et al., 1997). Notably, these Klotho-deficient mice also exhibited signs of impaired cognitive function in new object recognition and conditioned fear tests, demonstrating deficits in visual recognition memory and associative fear memory (Nagai et al., 2003). It had been found that klotho had a protective effect on the cognitive function of animals through many ways, such as overexpression of klotho protein improved the clearance of amyloid beta in Alzheimer's mice (Zhao et al., 2020). And a study found that klotho increased Forkhead box O3a (FOXO-3a) activity and catalase levels in mouse brain astrocytes, as well as increase proteasome activity in neurons, thereby regulating brain energy metabolism and redox state (Orellana et al., 2023). The levels of klotho in the human body are associated with various diseases such as cardiovascular disease, renal fibrosis, and malignant tumors (Liu and Chen, 2023; Pei et al., 2023; Qiao et al., 2023). One study found lower levels of klotho in the cerebrospinal fluid of Alzheimer's disease (AD) patients (Semba et al., 2014), suggesting a potential link between lower klotho levels and cognitive function (Linghui et al., 2023).

Research on the association between NAFLD and klotho is still scarce. A study based on NHANES data from 2007 to 2016 found that lower levels of α-Klotho protein in the blood were associated with NAFLD, particularly in individuals under 51 years of age, females, and non-Hispanic white populations. The study also suggested that increased levels of α-Klotho might have potential benefits for the treatment of NAFLD (Chi et al., 2023).

To date, the relationship between the levels of serum klotho and cognitive function among patients with NAFLD remains unclear. Thus, we aimed to investigate the association between levels of serum klotho and cognitive function among individuals with NAFLD.

2 Materials and methods

2.1 Study design and participants

This study utilized publicly available data from the National Health and Nutrition Examination Survey (NHANES), accessible at https://www.cdc.gov/nchs/nhanes/index.htm. Data from two consecutive NHANES cycles, 2011–2014, were pooled for this study. Included participants were over 60 years of age and meet the criteria for NAFLD; individuals with missing data on serum klotho or cognitive function were excluded.

According to the selection criteria, we selected 356 participants from 19,931 participants. The screening process is as follows: first, 1,603 participants were selected based on the criterion of US-FLI ≥ 30 from the total of 19,931 participants. Then, individuals with significant alcohol consumption, as well as those testing positive for hepatitis B surface antigen, positive for hepatitis C antibody, or HCV RNA were excluded. Lastly, participants below the age of 60 and those with missing klotho data were removed, resulting in the inclusion of 356 participants who met the criteria (Figure 1).

2.2 Definition of NAFLD

The gold standard for diagnosis of nonalcoholic fatty liver disease is liver biopsy. Due to the invasive nature of liver biopsy and possible complications, non-invasive testing (NIT) is increasingly acknowledged in clinical practice. Many models have been proposed. A widely used model modified on the basis of U.S. population data is the United States Fatty Liver Index (US-FLI), whose the area under the receiver operating characteristic (ROC) curve [AUC; 95% confidence interval (CI)] was 0.80 (0.77–0.83) (Ruhl and Everhart, 2015). US-FLI was calculated based on race, age, waist circumference, blood glucose, and other indicators. NAFLD is defined when the US-FLI value is ≥30 and the participant has no other established risk factors for chronic liver diseases (Ruhl and Everhart, 2015; Sourianarayanane and McCullough, 2022) including viral hepatitis and heavy alcohol intake (≥2 drinks per day for men or ≥ 1 drink per day for women).

2.3 Measurement of cognitive performance

To assess cognitive performance in participants older than 60 years of age in the 2011–2014 NHANES survey. The interviews were conducted by trained interviewers in the Mobile Examination Center (MEC Interview) and scored after the interviews were completed. A lower score indicated poorer cognitive function, and there was no defined threshold for scoring. The Consortium to Establish a Registry for Alzheimer's disease word list learning subtest (CERAD W-L), the Animal Fluency Test (AFT) and the Digit Symbol Substitution Test (DSST) were used in the cognitive performance test. The Immediate Recall Test (IRT) and one Delayed Recall Test (DRT) of the CERAD W-L test were used in cognitive performance

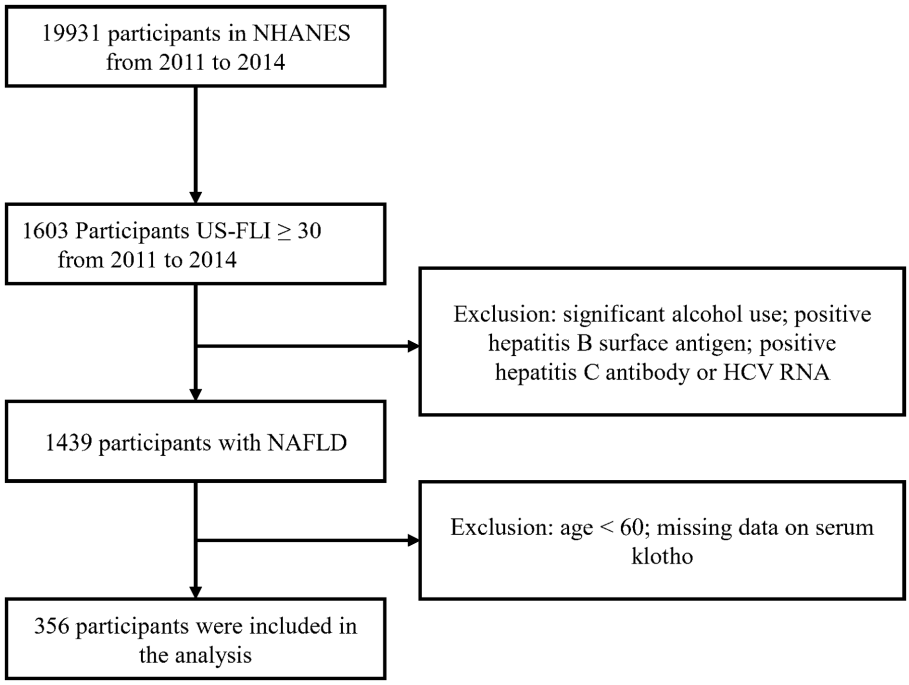

FIGURE 1
Flow chart of participants' enrollment.

evaluation to assess immediate and delayed learning abilities for new verbal information (memory domain), with a total score of 10 (Morris et al., 1989). This test has been utilized in many epidemiological studies (Fillenbaum et al., 2008; Gao et al., 2009). The AFT assesses verbal fluency by asking participants to name as many animals as possible within 1 min, earning one point for each animal named, which assesses executive function. The test scores have been shown to differentiate individuals with mild cognitive impairment from those with more severe cognitive impairment (such as Alzheimer's disease) (Fillenbaum et al., 2008; Gao et al., 2009). DSST is a test module of the Wechsler Adult Intelligence Scale (WAIS III). The exercise is conducted using a paper form that has a key at the top containing 9 numbers paired with symbols. Participants had 2 min to copy the corresponding symbols in the 133 boxes that adjoin the numbers. It relies on processing speed, sustained attention, and working memory (Tulsky et al., 2001). Detailed questionnaires and scores are available on the NHANES website.

2.4 Determination of serum klotho levels

Serum samples collected during the 2011–2014 cycles of NHANES were received on dry ice and stored at-80°C in The Northwest Lipid Metabolism and Diabetes Research Laboratories, Division of Metabolism, Endocrinology, and Nutrition, University of Washington determined klotho concentrations in these samples using an ELISA kit from IBL International, Japan. The klotho concentration in each sample was measured twice in a series, and the final value was the average of the two measurements. If the difference between the repeated measurements exceeded 10 percent, the klotho concentration was re-measured. And if the value of a quality control sample was not within the 2SD of the assigned value, the entire analytical run was rejected, and sample analyses repeated. The sensitivity of the test was 6 pg/mL. More details are available on the NHANES website.

2.5 Covariates

The following variables were included in this study, such as age (≤69, 70–79), sex (male and female), race (Mexican American, Non-Hispanic white, Non-Hispanic black, other), education (< high school, high school, > high school), the family income–poverty ratio (FMPIR) calculated as the ratio of household income to the poverty line (less than 1.0, between 1.0 and 3.0, and greater than 3.0), smoking status (never smoker, former smoker, current smoker), body mass index (BMI). Hypertension was defined as a systolic blood pressure of more than 140 mm Hg or a diastolic blood pressure of more than 90 mm Hg or having been explicitly told by a doctor to have hypertension or were taking high blood pressure medication (Beckman and Members, 2023). Depression was defined as participants who scored 10 or above on the NHANES project's Mental Health-Depression Screener (DPQ_G) (Kroenke et al., 2001). Estimated glomerular filtration rate (eGFR) was calculated based on the participants' creatinine, age, sex, and race information (Levey et al., 2009). Antipsychotics can also affect participants' cognitive status, so we also included antipsychotics as a covariate, based on whether participants were taking antipsychotics such as Amitriptyline, Bupropion, and Citalopram. Questionnaire findings (self-reported physician diagnosis of high cholesterol, diabetes, stroke), laboratory data alanine transaminase (ALT), aspartate aminotransferase (AST), total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C).

2.6 Statistical analysis

In this study, all analyses considered the complex sampling design of the NHANES. Data were presented as unweighted frequencies (weighted percentages) for categorical variables and as medians (interquartile range) for continuous variables. Differences among groups were compared using the Kruskal-Wallis test for continuous variables with non-normal distribution and the χ^2 test with the Rao and Scott second-order correction for categorical variables. Multivariable linear regression models were used to assess the association between cognitive test scores and levels of serum klotho. We constructed two models for analysis: the first was crude model. In model 2, we adjusted for age, sex, race, education level, family income-poverty ratio, smoking status, BMI, stroke, diabetes, hypertension, depression, antipsychotic, eGFR, and TG. Restricted cubic spline analysis was used to examine the nonlinear relationship between klotho protein levels and cognitive test scores. A multivariate linear regression model was used for subgroup analysis included age, sex, education level, diabetes mellitus and other variables to analyze the relationship between cognitive function score and klotho. Covariates with missing values were imputed using the multiple imputation by chained equations method R software (version 4.2.2) was used for statistical analysis in the study, and the threshold for statistical significance was set at $p < 0.05$.

3 Results

3.1 Baseline characteristics

A total of 356 participants were included in this study. The baseline characteristics of 356 participants with NAFLD according to quartile of serum klotho were summarized in Table 1. Similarities were found in the percentages of sex, race and ethnicity, education levels, family income–poverty ratio, smoking status, hypertension, depression, antipsychotic medication, high cholesterol, stroke, and the levels of ALT, AST, TC, LDL-C, HDL-Cand the score of IRT, DRT, AFT among four groups (all $p > 0.05$). Statistical significances were found in age, diabetes, TG, eGFR and DSST. The score of DSST increased from group Q1 to Q3 and decreased in group Q4 ($p < 0.05$). Age and the number of people with diabetes decreased as the klotho rating (quartile) increased (Table 1).

3.2 Association between klotho and cognitive function in NAFLD

Nonlinear relationship was found between DSST and serum klotho (p nonlinear = 0.016) in the restricted cubic splines. Similarly, a nonlinear relationship between DRT and serum klotho was also observed (p nonlinear = 0.021). However, there was no significant nonlinear relationship between serum klotho and either IRT (p nonlinear = 0.267) or AFT (p nonlinear = 0.989; both $p < 0.001$ for overall; Figure 2).

3.3 Association between serum klotho and cognitive performance

There was no significant association between serum klotho and IRT or DRT, regardless of whether the natural logarithm or quartile was taken for klotho. The β value (95% CI) of klotho (natural logarithm) and DSST in Model 1 and Model 2 were 4.05 (0.25, 7.84) and 5.47 (1.60, 9.34), and P were 0.012 and 0.040, respectively. The β value (95% CI) values for klotho (natural logarithm) and AFT in Models 1 and 2 were 1.70 (0.41, 2.98) and 2.03 (0.11, 3.96), and p were 0.012 and 0.040. In the analysis of the association between klotho actual values and cognitive scores, the second and third quartiles (Q2 and Q3) exhibited a β (95% CI) of 4.99 (0.64, 9.34) and 6 (3.06, 8.94) in comparison to the first quartile (Q1) for the DSST at model 1. In comparison to the reference group (Q1), the β value (95% CI) of AFT in Model 1 for Q4 in klotho (quartile) was 1.52 (0.05, 3.00; Table 2).

3.4 Subgroup analysis: associations of serum klotho with DSST score

We found a statistical significance between klotho (natural logarithm) and DSST when controlling for age ($p = 0.029$ for interaction). Compared with the reference group (first quartile), the DSST score β value in the third quartile for the subgroup with FMPIR >3.0 was 10.36 (95% CI: 1.96, 18.77), the DSST score β value of the fourth quartile was 9.43 (95% CI: 2.29, 16.56). In addition, we also analyzed the associations of serum klotho with scores of IRT, DRT, AFT in various subgroups. In Supplementary Table S3, we found a statistical significance between klotho (natural logarithm) and AFT when controlling diabetes ($p = 0.004$) (Table 3; Supplementary Tables S1–S3).

4 Discussion

To our knowledge, this study was the first study to examine the association between the levels of serum klotho and cognitive function (the scores of IRT, DRT, AFT, and DSST) among individuals with NAFLD. In our analysis, no statistical significances were observed between IRT and DRT scores and serum klotho levels; However, AFT scores exhibited a positive association with serum klotho levels, while DSST scores may demonstrate a non-linear relationship with serum klotho levels.

The klotho protein has long been recognized for its potential to extend lifespan and protect various organs (Kuro et al., 1997), Numerous studies have demonstrated its neuroprotective effects on the brain and nervous system, suggesting a potential role in preventing cognitive impairment." Co-incubation of klotho with glia conditioned medium + lipopolysaccharides has shown complete restoration of low-concentration glia conditioned medium—lipopolysaccharides induced neuronal toxicity (Nakao et al., 2022). Mice with klotho deficiency exhibit immature hippocampal neurons, while overexpression of klotho in the hippocampal region leads to an increase in neuron count and influences hippocampus-dependent spatial memory function (Laszczyk et al., 2017).

In previous studies, no association was found between IRT, DRT and serum klotho levels (Linghui et al., 2023; Ge et al., 2024). In our study, no statistically significant results were found, consistent with the results of previous studies. IRT and DRT are tests of the ability of short-term memory. In many animal experiments, it has been found that the expression or supplementation of klotho will improve memory, injection of a

TABLE 1 Characteristics of participants with NAFLD according to quartiles of serum klotho.

Characteristic	Overall (*N* = 356)	Serum klotho, pg/mL				
		Q1 (*N* = 91)	Q2 (*N* = 87)	Q3 (*N* = 89)	Q4 (*N* = 89)	*p*
Age, years	66.0 (63.0, 71.0)	67.0 (64.3, 71.0)	67.1 (62.7, 72.8)	65.0 (63.0, 69.7)	65.8 (62.0, 72.0)	0.031
Age (years), *n* (%)						0.371
≤ 69	212 (65.7)	53 (63.9)	50 (56.8)	56 (74.6)	53 (65.9)	
70–79	144 (34.3)	38 (36.1)	37 (43.2)	33 (25.4)	36 (34.1)	
Gender, *n* (%)						0.981
Male	186 (50.6)	45 (48.3)	53 (50.7)	45 (51.6)	43 (51.8)	
Female	170 (49.4)	46 (51.7)	34 (49.3)	44 (48.4)	46 (48.2)	
Race, *n* (%)						0.977
Mexican American	60 (6.3)	15 (5.9)	16 (7.1)	14 (5.7)	15 (6.6)	
Non-Hispanic White	175 (79.6)	48 (78.3)	39 (78.1)	46 (82.5)	42 (79.4)	
Non-Hispanic Black	43 (4.3)	13 (5.3)	8 (3.8)	8 (3.2)	14 (4.6)	
Other	78 (9.8)	15 (10.4)	24 (11.1)	21 (8.7)	18 (9.4)	
Education, *n* (%)						0.439
< High school	110 (19.4)	26 (13.3)	23 (23.3)	31 (14.8)	30 (26.7)	
High school	87 (24.8)	27 (31.5)	16 (17.6)	23 (27.1)	21 (22.1)	
Some college or above	159 (55.7)	38 (55.2)	48 (59.1)	35 (58.0)	38 (51.2)	
FMPIR, *n* (%)						0.866
< 1.0	60 (8.5)	18 (9.7)	12 (8.5)	16 (8.8)	14 (7.2)	
1.0–3.0	146 (40.0)	37 (38.2)	35 (32.8)	39 (43.3)	35 (44.7)	
> 3.0	117 (51.4)	32 (52.2)	30 (58.7)	23 (47.9)	32 (48.2)	
Smoking status, *n* (%)						0.271
Never smoker	162 (43.6)	45 (46.0)	32 (41.8)	40 (46.1)	45 (40.4)	
Former smoker	159 (46.7)	37 (45.7)	51 (56.4)	37 (42.6)	34 (43.7)	
Current smoker	35 (9.7)	9 (8.3)	4 (1.8)	12 (11.3)	10 (15.9)	
BMI, kg/m^2	33.1 (29.2, 38.0)	31.1 (27.7, 39.4)	33.6 (30.6, 38.1)	33.7 (29.5, 38.7)	31.2 (29.1, 35.1)	0.237
BMI (kg/m2), *n* (%)						0.169
< 30.0	109 (30.1)	28 (37.8)	28 (18.5)	26 (31.2)	27 (31.4)	
≥ 30.0	244 (69.9)	61 (62.2)	59 (81.5)	62 (68.8)	62 (68.6)	
Hypertension, *n* (%)						0.430

(Continued)

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TABLE 1 (Continued)

Characteristic	Overall (*N* = 356)	Serum klotho, pg/mL				
		Q1 (*N* = 91)	Q2 (*N* = 87)	Q3 (*N* = 89)	Q4 (*N* = 89)	*p*
Yes	287.0 (81.1)	76.0 (88.2)	69.0 (77.0)	68.0 (76.0)	74.0 (82.8)	
No	69.0 (18.9)	15.0 (11.8)	18.0 (23.0)	21.0 (24.0)	15.0 (17.2)	
High cholesterol, *n* (%)						0.307
Yes	223 (67.4)	62 (73.9)	54 (72.7)	53 (57.5)	54 (66.3)	
No	128 (32.6)	29 (26.1)	32 (27.3)	34 (42.5)	33 (33.7)	
Diabetes, *n* (%)						0.009
Yes	122 (32.7)	39 (49.0)	30 (32.5)	28 (30.2)	25 (19.7)	
No	234 (67.3)	52 (51.0)	57 (67.5)	61 (69.8)	64 (80.3)	
Depression						0.578
Yes	42.0 (9.1)	12.0 (9.4)	10.0 (13.2)	12.0 (8.6)	8.0 (5.8)	
No	314.0 (90.9)	79.0 (90.6)	77.0 (86.8)	77.0 (91.4)	81.0 (94.2)	
Antipsychotic						0.243
Yes	22.0 (6.7)	6.0 (9.5)	7.0 (10.8)	5.0 (5.1)	4.0 (2.2)	
No	334.0 (93.3)	85.0 (90.5)	80.0 (89.2)	84.0 (94.9)	85.0 (97.8)	
Stroke, *n* (%)						0.747
Yes	24 (6.6)	7 (8.8)	4 (4.3)	8 (7.7)	5 (5.1)	
No	332 (93.4)	84 (91.2)	83 (95.7)	81 (92.3)	84 (94.9)	
ALT, U/L	22.0 (18.0, 28.0)	21.0 (17.9, 27.0)	22.1 (20.0, 30.0)	22.0 (18.0, 27.8)	23.0 (18.4, 27.9)	0.314
AST, U/L	24.0 (20.0, 27.0)	22.0 (19.0, 26.0)	25.0 (21.0, 27.0)	23.0 (20.0, 26.0)	24.0 (21.0, 28.0)	0.175
TC, mg/dL	181.3 (155.0, 209.0)	177.6 (149.0, 203.0)	183.5 (156.7, 207.0)	187.0 (162.2, 207.8)	180.9 (154.5, 213.6)	0.716
TG, mg/dL	145.0 (101.0, 192.0)	157.7 (123.3, 215.6)	138.1 (97.0, 210.9)	153.2 (122.6, 189.8)	121.1 (91.0, 164.4)	0.008
LDL-C, mg/dL	106.0 (78.0, 129.0)	98.4 (76.0, 121.0)	103.5 (73.5, 131.0)	109.5 (91.0, 132.6)	106.5 (77.5, 134.9)	0.663
HDL-C, mg/dL	47.0 (40.0, 54.0)	46.0 (39.0, 53.0)	47.0 (41.0, 55.0)	45.0 (39.0, 53.0)	49.0 (44.8, 55.6)	0.118
eGFR, mL/min/1.73m^2	76.6 (61.7, 88.9)	70.6 (50.8, 89.5)	75.7 (59.7, 83.8)	78.8 (66.3, 90.2)	76.6 (69.5, 89.4)	0.045
IRT	20.0 (17.0, 22.0)	20.0 (17.0, 23.0)	19.7 (17.0, 22.0)	20.0 (18.0, 22.0)	19.0 (17.0, 21.0)	0.711
DRT	6.0 (5.0, 8.0)	7.0 (5.0, 8.1)	6.0 (5.0, 9.0)	7.0 (5.0, 8.0)	6.0 (5.0, 8.0)	0.885
AFT	17.0 (14.0, 21.0)	16.0 (13.0, 19.3)	16.0 (14.6, 20.0)	18.0 (14.0, 22.0)	19.6 (14.0, 20.5)	0.071
DSST	53.0 (43.0, 61.7)	50.0 (40.0, 56.4)	53.0 (42.0, 63.0)	58.4 (47.7, 63.6)	50.0 (42.9, 57.6)	0.008

Q1, Q2, Q3, Q4 are first quartile, second quartile, third quartile and max quartile; FMPIR, family income–poverty ratio; BMI, Body Mass Index; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; TC, Total Cholesterol; TG, Triglyceride; LDL-C, Low-Density Lipoprotein Cholesterol; HDL-C, High-Density Lipoprotein Cholesterol; eGFR, estimated glomerular filtration rate; IRT, Immediate Recall Test; DRT, Delayed Recall Test; AFT, Animal Fluency Test; DSST, Digit Symbol Substitution Test.

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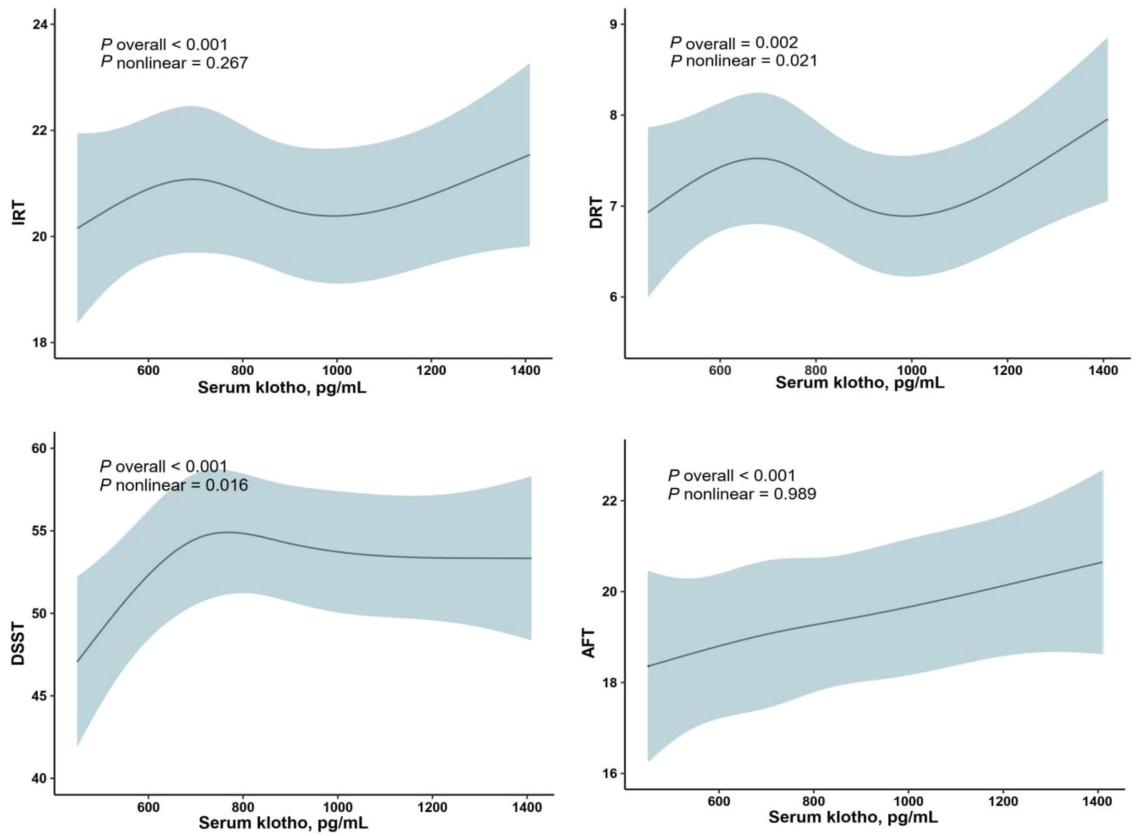

FIGURE 2
Restricted cubic spline (RCS) plot of the association between Klotho and cognitive function.

TABLE 2 Association between serum klotho and cognitive performance.

	Model	Klotho (natural logarithm)	P	Klotho (quartile), pg/mL			
				Q1 (≤ 656.6)	Q2 (656.7–801.3)	Q3 (801.4–983.7)	Q4 (> 983.7)
IRT	Model 1	0.34 (−1.80, 2.48)	0.748	Ref	0.04 (−1.49, 1.56)	0.02 (−1.81, 1.84)	−0.38 (−2.18, 1.41)
	Model 2	0.74 (−1.49, 2.98)	0.482	Ref	0.1 (−1.46, 1.65)	−0.14 (−2.2, 1.91)	−0.16 (−2.29, 1.98)
DRT	Model 1	0.11 (−1.34, 1.57)	0.873	Ref	−0.09 (−1.00, 0.81)	−0.11 (−1.20, 0.98)	−0.22 (−1.29, 0.85)
	Model 2	0.38 (−1.09, 1.85)	0.581	Ref	−0.16 (−0.96, 0.63)	−0.18 (−1.2, 0.83)	−0.08 (−1.24, 1.08)
AFT	Model 1	1.70 (0.41, 2.98)	**0.012**	Ref	0.61 (−1.33, 2.55)	1.92 (−0.01, 3.84)	1.16 (−0.05, 2.38)
	Model 2	2.03 (0.11, 3.96)	**0.040**	Ref	0.79 (−0.81, 2.38)	1.71 (−0.1, 3.52)	**1.52 (0.05, 3.00)**
DSST	Model 1	4.05 (0.25, 7.84)	**0.037**	Ref	5.32 (−0.02, 10.65)	**7.55 (2.76, 12.33)**	2.24 (−1.07, 5.56)
	Model 2	5.47 (1.6, 9.34)	**0.009**	Ref	**4.99 (0.64, 9.34)**	**6 (3.06, 8.94)**	2.89 (−0.65, 6.42)

Model 1: crude model. Model 2: adjust for age, gender, race, education levels, family income–poverty ratio, smoking status, BMI, Stroke, hypertension, antipsychotic, Depression, eGFR, Diabetes, and TG. Bold text indicates a p-value < 0.05, indicating a statistical difference between the two.

lentiviral vector capable of delivering and maintaining klotho expression in seven-month-old mice led to a significant increase in klotho expression in the brains of mice after 3 months of feeding, and the treatment reduced memory impairment and neuronal loss (Zhou et al., 2018). In another study, low doses of rhesus klotho protein administered subcutaneously to mice and older rhesus monkeys enhanced memory function, but no lasting cognitive effects were observed in rhesus monkeys similar to the high doses of klotho protein in mice, this may be due to the more complex brain structure of primates (Castner et al., 2023). The study did not find a significant association between klotho levels and human memory performance, possibly due to the consistent maintenance of a certain level of klotho in humans. The specific mechanism needs to be further studied.

In the analysis between individual factors and klotho, DSST obtained statistically significant results in the comparison with klotho. It can be seen from our results that the DSST score increases with the increase of serum klotho, but the DSST score does not continue to increase at the fourth quartile level of the serum klotho, instead of a downward trend. This nonlinear relationship has been less frequently

TABLE 3 Associations of serum klotho with DSST score in various subgroups.

Characteristic	Serum Klotho, pg/mL				
	Q1 (≤656.6)	Q2 (656.7–801.3)	Q3 (801.4–983.7)	Q4 (≥ 983.8)	P interaction
Age, years					
< 70	Ref	**10.44 (3.4, 17.49)**	**8.6 (4.47, 12.73)**	5.42 (−0.77, 11.62)	0.076
≥ 70	Ref	0.67 (−6.06, 7.4)	3.27 (−4.45, 10.99)	0.94 (−9.01, 10.89)	
Gender					
Male	Ref	5.35 (−0.42, 11.12)	5.5 (−0.14, 11.13)	1.24 (−3.94, 6.43)	0.819
Female	Ref	4.86 (−0.7, 10.42)	**7.22 (2.32, 12.12)**	5.21 (−1.78, 12.2)	
Education					
≤ High school	Ref	**7.75 (0.9, 14.6)**	**7.26 (1.4, 13.13)**	4.17 (−1.18, 9.52)	0.436
Some college or above	Ref	3.19 (−2.94, 9.31)	**4.88 (0.7, 9.05)**	−0.41 (−6.93, 6.12)	
FMPIR					
≤ 3.0	Ref	1.34 (−5.42, 8.1)	3.15 (−1.66, 7.96)	2.56 (−2.12, 7.24)	**0.029**
> 3.0	Ref	**10.36 (1.96, 18.77)**	**9.43 (2.29, 16.56)**	5.37 (−5.49, 16.24)	
Smoking status					
Never	Ref	4.5 (−5.58, 14.57)	6.45 (−1.01, 13.92)	6.9 (−0.78, 14.59)	0.368
Former or current	Ref	**7.24 (1.22, 13.27)**	**5.67 (1.19, 10.14)**	1.2 (−2.53, 4.92)	
BMI					
< 30.0	Ref	−0.85 (−9.58, 7.89)	4.99 (−3.61, 13.59)	−4.67 (−12.73, 3.4)	0.508
≥ 30.0	Ref	5.91 (−0.12, 11.94)	**5.85 (0.72, 10.97)**	4.76 (−0.72, 10.25)	
Diabetes					
Yes	Ref	2.38 (−7.19, 11.95)	6.75 (−1.55, 15.04)	2.94 (−5.64, 11.51)	0.371
No	Ref	**7.52 (2.28, 12.77)**	**6.33 (1.47, 11.18)**	2.91 (−2.72, 8.54)	

NAFLD, Nonalcoholic fatty liver disease; BMI, body mass index; NHANES, National Health and Nutrition Examination Survey. Data are presented as β value (95% CI). Adjust for age, gender, race, education levels, family income–poverty ratio, smoking status, BMI, Stroke, hypertension, antipsychotic, Depression, eGFR, Diabetes, and TG. The strata variable was not included when stratifying by itself. Bold text indicates a p-value < 0.05, indicating a statistical difference between the two.

reported in previous similar studies. A comparable association was observed in a study on the association between serum klotho concentration and cognitive ability in elderly patients with nephropathy and proteinuria, which also demonstrated an initial increase followed by a subsequent decrease (Zhang and Zhang, 2023). However, the decline in the later stage was more pronounced than that observed in this study. These findings suggest a strong relationship between lower klotho levels and lower cognitive performance in the NAFLD population.

The levels of klotho are closely associated with stress responses which plays a role in reducing inflammation. A decrease in klotho concentration is linked to an increase in oxidative stress response (Lin and Beal, 2006; Kuro-o, 2009). Research data suggested a strong association between klotho and depression, which may be attributed to oxidative stress (Gold et al., 2013). Additionally, literature also suggested a relationship between klotho, cognitive function, and stress response (Gao et al., 2021). In the "double-hit" hypothesis of NAFLD, inflammation mediated by oxidative stress is considered as the "second hit" (Chitturi and Farrell, 2001). Further investigation is needed to explore whether stress response may also play a significant role in the association between klotho levels and cognitive function in NAFLD.

In our subgroup analysis, when controlling for diabetes variables, we identified a statistical significance between klotho and AFT scores ($p = 0.004$). Compared with the reference group (first quartile), a statistical significance was observed in AFT scores within the third quartile of the diabetes subgroup, with a β value of 4.74 (95% CI: 1.12, 8.35; Supplementary Table S3). Previous studies on diabetes have shown similar results, indicating a positive correlation between the levels of klotho and cognition in patients with diabetes (Zhang et al., 2023). Some statistically significant results in the diabetes variable were also found in the subgroup analysis between DSST scores and klotho, but in people without diabetes (shown in Table 3). And these results suggest that having lower klotho levels or klotho proteins may have a greater impact on cognitive function in patients with comorbidities.

It should be noted that this study has certain limitations. First, it is a cross-sectional study, which precludes any causal inferences. Second, the sample size of study participants who were screened and ultimately included in the analysis was relatively small. Third, as the cognitive score test was only administered to participants over the age of 60, caution is required when attempting to generalize the findings to other age groups with NAFLD.

In the future, more in-depth studies should be conducted to explore the association in the NAFLD patient population, including prospective studies across different countries, races, regions, and a wider age group, to further verify the predictive value of klotho levels in the cognitive function of NAFLD patients.

5 Conclusion

In conclusion, a statistical significance exists between klotho and the scores of AFT and DSST, indicating a higher serum klotho level may be positively correlated with better cognitive performance in NAFLD patients. Our study suggests that routine testing of serum klotho can be considered in NAFLD patients for early detection of cognitive decline.

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/s.

Ethics statement

The studies involving humans were approved by National Center for Health Statistics (NCHS) Ethics Review Board. Each participant/patient signed an informed consent prior to participating in the test. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

FW: Data curation, Formal analysis, Methodology, Visualization, Writing – original draft, Writing – review & editing. JP: Data curation, Formal analysis, Methodology, Visualization, Writing – review & editing. MC: Investigation, Project administration. XL: Project administration, Methodology. YG: Project administration. LP: Project administration. LY: Conceptualization, Funding acquisition, Writing – review & editing, Methodology, Visualization.

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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.2024.1487182/full#supplementary-material

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Trajectories of cognitive function and frailty in older adults in China: a longitudinal study

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Background: Cognitive impairment and frailty are common issues in older adults. Understanding the co-development trajectories of these conditions can provide valuable sights for early detection and intervention in high-risk individuals.

Objectives: This study aims to identify the co-development of cognitive function and frailty and explore the associated characteristics.

Methods: We analyzed data from 8,418 individuals aged 55 years and above who participated in the China Health and Retirement Longitudinal Survey between 2011 and 2018. Group-based dual trajectory modeling and logistic regression were used to identify trajectory groups and assess associations with risk factors.

Results: Two distinct dual trajectories were identified: "Consistently Robust" group (76.12%) and "Consistently Severe" group (23.88%). Factors such as being female, older age, lower levels of education, residing in rural areas, being unmarried, and having comorbidities such as hypertension, diabetes, complete tooth loss, vision impairment, or hearing impairment were associated with a higher likelihood of being assigned to the "Consistently Severe" group.

Conclusion: Our findings suggest a co-development pattern between cognitive function and frailty in Chinese older adults aged 55 years and above. While cognitive impairment may be irreversible, frailty is a condition that can be potentially reversed. Early detecting is crucial in preventing cognitive decline, considering the shared trajectory of these conditions.

KEYWORDS

cognitive function, frailty, dual trajectories, older adults, aging

1 Introduction

China's population is aging rapidly. By the end of 2022, the number of individuals aged 60 and above had reached 280.04 million, accounting for approximately 19.8% of the total population (Affairs MoC, 2023). With this demographic shift, the prevalence of cognitive impairment and frailty among older adults has increased, significantly affecting their quality of life and placing a considerable economic and caregiving burden on their families.

A growing body of research has explored the relationship between frailty and cognitive impairment in older adults. For example, a longitudinal study conducted in South Korea among older adults aged 65 and above found that individuals who remained frail or transitioned from non-frail to frail had higher likelihood of lower cognitive function (Nari et al., 2021). Similarly, a prospective study in Japan revealed that frailty was associated with

cognitive decline in older adults over a two-year period (Chen et al., 2018). These findings are further supported by several studies demonstrating that frail older adults are at greater risk of experiencing cognitive impairment compared to their non-frail counterparts (Li et al., 2023; Kim et al., 2014). Conversely, there is evidence that cognitive decline also serves as a risk factor for developing frailty (Mulero et al., 2011; Doba et al., 2012; Yuan et al., 2021). For example, Li et al. (2023) study revealed that older adults with cognitive impairment have an estimated 19.5% higher one-year incidence of frailty compared to those without cognitive impairment (Belleville et al., 2022).

Despite substantial evidence, the causal relationship between frailty and cognitive impairment remains complex and not fully understood. A review by Robertson et al. (2013) discusses how frailty and cognitive decline interact within a cycle of age-associated decline, suggesting a bidirectional nature of this relationship. Furthermore, some researchers propose that frailty and cognitive impairment may develop simultaneously, sharing common biological causes (Buchman et al., 2007; Buchman et al., 2014). The oxidative stress theory suggests that the brain's vulnerability to oxidative damage can lead to cognitive impairment (Mulero et al., 2011), while reactive oxygen species contribute to frailty (Kregel and Zhang, 2007). As a result, researchers are starting to investigate the co-occurrence of cognitive decline and frailty at the population level. Group-based dual trajectory modeling (GBDTM) has emerged as a powerful analytical tool for examining these parallel developments, allowing for a better understanding of how frailty and cognitive impairment influence each other over time.

GBDTM is an extension of Nagin's Group-Based Trajectory Model (GBTM). While GBTM assumes that the population consists of multiple unobserved subgroups, each with its own trajectory, and uses finite mixture modeling to estimate these groups, GBDTM focuses on modeling the developmental trajectories of two related outcomes (Nagin and Odgers, 2010). It enhances GBTM by incorporating polynomial models of time (age) and using maximum likelihood estimation to assign individuals to subgroups (Nagin and Tremblay, 2001). Unlike GBTM, GBDTM allows for statistical associations between trajectories, enabling the exploration of their co-relationships. It employs simultaneous models to estimate the trajectories of two variables, with relationships that can vary across subgroups. These relationships can be linear or nonlinear, capturing the complex dynamics between variables. A key strength of GBDTM is its ability to identify natural subgroups within a population based on joint changes in the two variables, with these subgroups emerging from the data rather than being predefined (Nagin and Tremblay, 2001; Muthén and Muthén, 2000; Curran and Hussong, 2003).

GBDTM has proven effective in identifying dual trajectories, making it well-suited for exploring common trends in cognitive function and frailty over time. For example, a longitudinal study in the U.S. showed that 20% of older adults exhibited concurrent trajectories of "persistent frailty" and "persistent severe cognitive impairment" (Yuan et al., 2022). Similarly, another study identified four distinct trajectories of frailty and cognitive functioning, with 6.5% of older adults showing a pattern of cognitive frailty (Liu et al., 2018). In Mexico, a longitudinal study revealed that 63% of older adults with an increasing frailty index experienced rapid cognitive decline, while 68% of those with no frailty changes maintained cognitive stability (Howrey et al., 2020). In Milan, 4.3% of old adults showed continuous decline in both cognitive and physical functioning (Ferraro et al., 2021). These studies, based on GBDTM, highlight the common trajectories of frailty and cognitive impairment, though the patterns vary across countries.

While some studies have been conducted in Europe and America, our research focuses on a population that has been underrepresented in the literature. The unique cultural, lifestyle, and demographic factors in China may lead to different dual trajectories of cognitive function and frailty compared to those observed in Western populations. By exploring this specific context, we aim to provide valuable insights into how these dual trajectories manifest and to identify distinct associated factors. Our findings could help determine whether these dual trajectories are universal or context-specific, ultimately contribute to a more comprehensive understanding of cognitive and frailty dynamics.

2 Materials and methods

2.1 Data

The data for this study were obtained from the China Health and Retirement Longitudinal Study (CHARLS), which is a large-scale interdisciplinary longitudinal survey project conducted by the National Development Research Institute of Peking University and implemented by the China Social Science Survey Center of Peking University. The baseline survey was conducted in 2011, covering 150 counties and 450 communities (villages) across 28 provinces, autonomous regions, and municipalities in China, targeting individuals aged 45 and above. Subsequent nationwide follow-up surveys were conducted in 2013, 2015, 2018 and 2020.

This study used data from the 2011 CHARLS cohort, along with newly recruited participants in 2013 as the baseline, resulting in a total of 21,131 individuals. The inclusion criteria for the study were: (1) participants aged 55 and above at baseline; and (2) participants who completed at least two follow-up waves in 2013, 2015, and 2018. The exclusion criteria included: (1) missing data for key variables. After excluding participants younger than 55 years old, 11,210 participants remained. Further exclusion of individuals with missing key variables resulted in a final sample of 8,814 older adults leading to an attrition rate of 21.37%.

2.2 Measures

2.2.1 Cognitive function

In this study, we focused on the memory dimension to ensure consistent measurement of cognitive function from 2011 to 2018. Memory was assessed using both immediate memory and delayed memory tests (Yuan et al., 2022). Immediate memory involved presenting participants with a set of 10 words, which they were then asked to recall within a two-minute period with scores ranging from 0 to 10. Delayed memory was evaluated by assessing participants' recall of the same 10 words after testing their depression, calculation ability, and visuospatial ability. Scores for delayed memory also ranged from 0 to 10. Therefore, the combined score for immediate and delayed memory ranged from 0 to 20, with lower scores indicating poorer cognitive function.

2.2.2 Frailty

The frailty status of the individuals was assessed using the Frailty Index (FI), which evaluates the degree of frailty by calculating the cumulative number or proportion of health deficits. This is typically represented as the ratio of cumulative health deficit count to the total number of health items included, with total score ranging from 0 to 1; higher scores indicating a more severe frailty status (Liu et al., 2018). In this study, the FI included 38 health indicators, including 6 activities of daily living (ADL), five instrumental activities of daily living (IADL), nine physical function limitations, 12 chronic diseases, five mental health indicators, and one self-rated health indicator (Supplementary Table 1).

2.2.3 Covariates

We included several covariates in our analysis, including age, gender, residence, marital status, education, annual household expenditure, chronic disease, current drinking status, visual and hearing impairment, and complete tooth loss. Annual personal expenditure was categorized as "Lower than the average" and "Higher than the average" in comparison to the annual personal expenditure of Chinese residents in 2010. Vision impairment was defined as meeting one of the following criteria: self-reported poor vision, near vision impairment, or distance vision impairment (Howrey et al., 2020). Hearing impairment was defined as meeting one of the following criteria: having problems with deafness or partial deafness, wearing a hearing aid (Ferraro et al., 2021), or self-reporting poor hearing (Nagin, 1999). The coding of variables is presented in Supplementary Table 2.

2.3 Statistical analysis

We provided an overview of the participants' baseline characteristics, as well as their cognitive function and frailty status for each wave. We then conducted trajectory analysis, which involved the following steps:

First, we performed separate group-based trajectory modeling (GBTM) for cognitive function and frailty. GBTM identifies unobserved heterogeneous subgroups within the sample population and develops trajectories based on their trends (Nagin, 1999). Individuals are assigned to the most likely subgroups based on the largest posterior probability (Huang et al., 2013).

Second, we used group-based dual trajectory modeling (GBDTM) for cognitive function and frailty, treated these as dependent variables with year as the time variable. A dual development trajectory was fitted to assign similar individuals to different subgroups. To determine the most appropriate number of trajectories for GBDTM, we tested separate GBTM for cognitive function and frailty with two or more trajectory groups. In GBDTM, the number of dual trajectory groups and slope parameters in each group were set according to the results from GBTM.

We evaluate model fit using the Bayesian Information Criterion (BIC), entropy, the smallest group size (SG%) including at least 5% of the sample, and an average posterior probability of assignment (APPA) >0.70.

Finally, logistic regression analyses were conducted to determine the association between the potential associated factors and the dual trajectories of cognitive function and frailty. Group differences were considered significant if $p < 0.05$ (two- tailed).

3 Results

3.1 Sociodemographic and health characteristics

In this study, a total of 8,814 participants were included, with a mean age of 62.6 ($SD \pm 6.5$) years. Among them, males accounted for 50.52 and 49.48% for females. Most participants were literate (71.24%), residing in rural areas (62.29%), married (87.12%). Only 11.04% of the participants had annual personal expenditure higher than the average. And 66.38% of the participants reported never drinking alcohol. In terms of health conditions, with regard to missing data, at least 27.39% had hypertension, 6.51% had diabetes, 10.40% had experienced complete tooth loss, 43.65% had vision impairment, 17.57% had hearing impairment (Table 1).

3.2 Identifying dual trajectories of cognitive function and frailty among Chinese older adults

In the GBDTM models, we determine the number of dual trajectory groups and the slope parameters for each group based on the outcomes derived from the GBTM models for both cognitive function and frailty (Table 2) (Liu et al., 2018). Two dual trajectories were identified and labeled as follows (Supplementary Table 3): "Consistently Robust" group [Group 1 (G1); 76.12%] and "Consistently Severe" group [Group 2 (G2); 23.88%]. G1 demonstrated a high initial value and stable trend in cognitive function (slope = −0.29, $p < 0.001$), a low initial value and stable trend in frailty (slope = 0.00, $p < 0.05$) over time. Whereas G2 demonstrated a decline in cognitive function (slope = −0.30, $p < 0.001$) and an increase in frailty level (slope = 0.01, $p < 0.001$).

Figure 1 illustrates the levels and shapes of change of these dual trajectories. Participants in G1 exhibited better cognitive function than those in G2, despite a decline over time. By the end of the follow-up, G1 participants maintained relatively stable cognitive and were physically robust throughout the study. In contrast, participants in G2 experienced a continuous deterioration in both frailty and cognitive function, with changes occurring at a greater magnitude than in G1.

3.3 Examining associated factors of identified dual trajectories of cognitive function and frailty

Multivariate analyses of dual trajectories indicated that participants aged 65 to 74 at baseline were 1.71 times more likely to experience deteriorating cognition and frailty [OR: 1.71; 95%CI: 1.51–1.93]. Those aged 75 and older had 1.66 times higher likelihood of falling into the "Consistently Severe" category [OR: 1.66; 95%CI: 1.32–2.08]. Women were also at increased risk, with a likelihood 1.59 times greater [OR: 1.59; 95%CI: 1.39–1.81]. Conversely, literate

TABLE 1 Baseline characteristics distribution of participants (N = 8,814).

	Characteristics	Number of participants (n)	Percentages (%)
Gender	Male	4,453	50.52
	Female	4,361	49.48
Age	55–64	5,937	67.36
	65–74	2,353	26.70
	≥75	524	5.94
Education	Illiterate	2,535	28.76
	Literate	6,278	71.23
	Missing	1	0.01
Residence	Rural	5,490	62.29
	Urban	3,324	37.71
Marriage	Unmarried	1,135	12.88
	Married	7,679	87.12
Annual personal expenditure (compare to the average)	Lower	7,841	88.96
	Higher	973	11.04
Drinking	Still drinking	2,316	26.28
	Abstinence	647	7.34
	Never drinking	5,850	66.37
	Missing	1	0.01
Hypertension	No	5,445	61.78
	Yes	2054	23.30
	Missing	1,315	14.92
Diabetes	No	6,989	79.29
	Yes	487	5.53
	Missing	1,338	15.18
Complete tooth loss	No	6,751	76.59
	Yes	784	8.89
	Missing	1,279	14.51
Vision impairment	No	4,503	51.09
	Yes	3,488	39.57
	Missing	823	9.34
Hearing impairment	No	7,262	82.39
	Yes	1,548	17.56
	Missing	4	0.05

individuals had a lower probability of being assigned to the "Consistently Severe" group [OR: 0.72; 95%CI: 0.63–0.82]. Similarly, those living in urban areas [OR: 0.61; 95%CI: 0.54–0.69] and those who were married [OR: 0.74; 95%CI: 0.63–0.87] also showed lower likelihoods of experiencing continuous cognitive and frailty decline.

Additionally, older adults with chronic diseases at baseline were more likely to be in the "Consistently Severe" group. Specifically, participants with hypertension were 2.59 times more likely to experience worsening cognition and frailty [OR: 2.59; 95%CI: 2.30–2.92], those with diabetes were 2.43 times more likely [OR: 2.43; 95%CI: 1.98–2.97], and participants with vision impairment were 2.02 times more likely [OR: 2.02; 95%CI: 1.80–2.26]. Furthermore, the probability of being assigned to the "Consistently Severe" group was 30% higher [OR: 1.30; 95%CI: 1.09–1.54] for individuals with complete tooth loss compared to those without, and 69% higher [OR: 1.69; 95%CI: 1.47–1.93] for those with hearing impairment.

Above results can be found in Table 3. Additionally, the results of the logistic regression analyses conducted separately for cognitive function and frailty can be found in Supplementary Tables 4, 5.

4 Discussion

In this longitudinal study, we observed two distinct dual trajectories of cognitive function and frailty among older adults in China. One group exhibited better cognitive function and lower levels

TABLE 2 Model search process in GBTM models of cognitive function and frailty.

Number of trajectories	Cognitive function				Number of trajectories	Frailty			
	BIC	APPA	SG%	Entropy		BIC	APPA	SG%	Entropy
GBTM									
2	−77040.69	>0.91	49.77	0.71	2	34960.52	>0.94	23.16	0.91
3	−76291.91	>0.83	21.60	0.68	3	37612.81	>0.91	7.41	0.88
4	−76063.55	>0.79	11.07	0.66	4	38838.85	>0.87	2.67	0.86
5	−75951.43	>0.65	8.07	0.65	5	39259.81	>0.84	1.56	0.83

Final number of trajectory groups was determined				
GBDTM				
Number of dual trajectory groups	BIC	APPA	SG%	Entropy
2	−44961.65	>0.94	24.12	0.90
3	−42195.22	>0.91	7.69%	0.88
4	−40279.65	>0.86	4.37%	0.81

BIC, Bayesian information criteria; APPA, average posterior probability of assignment; SG%, the smallest group %.

of frailty compared to the other group. This finding is consistent with previous studies conducted in both institutionalized (Yuan et al., 2022) and non-institutionalized (Howrey et al., 2020) American older adults, which also identified consistent developmental trends in cognitive function and frailty. The correlation between changes in cognitive function and frailty may contributed to common underlying mechanisms. Previous research has highlighted the influence of vascular changes, hormones, vitamin D levels, inflammation, insulin resistance, and nutrition on both cognitive function and frailty in older individuals (Halil et al., 2015). Moreover, dysregulated HPA stress response, imbalanced energy metabolism, mitochondrial dysfunction, oxidative stress, and neuroendocrine dysfunction have been proposed as shared etiological factors for the concurrent occurrence of frailty and cognitive decline (Ma and Chan, 2020). This consensus was reflected in a 2013 conference held by the International Association of Nutrition and Aging and the International Association of Gerontology and Geriatrics, which coined the term "cognitive frailty" to describe the coexistence of cognitive impairment and frailty (Kelaiditi et al., 2013). Identifying individuals at a high risk of experiencing rapid declines in cognitive function and escalating frailty is crucial, given the heightened threat of mortality and disability associated with this condition (Ma et al., 2021).

We observed that certain characteristics, such as being female, older, illiterate, residing in rural areas, and unmarried were more prevalent among individuals assigned to the "Consistently Severe" group. These individuals also displayed worse overall health compared to those in the "Consistently Robust" group, including a higher prevalence of conditions such as diabetes, hypertension, hearing impairment, vision impairment, and complete tooth loss. The association between increasing age and being assigned to the "Consistently Severe" group is likely attributable to the natural deterioration of organ functions with aging. On the other hand, married older adults were more likely to be categorized into the "Consistently Robust" group, possibly due to their engagement in social activities and greater social support. We found that older adults residing in rural areas had a higher likelihood of being assigned to the "Consistently Severe" group, which aligns with findings from other research (Liu et al., 2021). However, we did not find a significant impact of alcohol consumption on cognitive function changes in older adults. The relationship between alcohol consumption and cognition remains inconclusive. While some studies suggest a connection (Fein et al., 2006; Montejo and Rico-Villademoros, 2008; García-Marchena et al., 2020), our findings are in line with the results of Linglong et al. (2021), who found no impact of alcohol consumption on different cognitive function trajectories among adults aged 65 and above in China. To further investigate this association accurately, future research is recommended to include additional specific variables related to alcohol consumption, such as the type of alcohol consumed, dosage, and other relevant factors.

Identifying potential factors that contribute to assigning individuals into high-risk groups allows for targeted interventions aimed at delaying cognitive function decline and frailty. In our research, we identified modifiable health factors suitable for intervention, including hypertension, diabetes, visual impairment, hearing impairment and complete tooth loss. Previous studies have suggested an association between hypertension and both cognitive function and frailty (Belessiotis-Richards et al., 2021; Ma et al., 2020; Emiliano Albanese et al., 2013; Farron et al., 2020; Qiu et al., 2005). A review has indicated that higher blood pressure may increase the risk of dementia in the future, particularly in cases of untreated hypertension (Qiu et al., 2005), potentially aligning with our finding that hypertensive patients are more likely to be assigned to the "Consistently Severe" group.

Our study also found that diabetes was associated with poorer cognition and frailty, which is consistent with a review examining the impact of diabetes on brain function and structure over the past two decades (Moheet et al., 2015). However, prior research on the relationship between diabetes and cognitive function remains inconclusive. For instance, a cross-sectional study in India found that self-reported diabetes is linked to better cognitive performance (Belessiotis-Richards et al., 2021). In addition, a review emphasized that managing diabetes and reducing complications may lower the risk of cognitive impairment, with a stronger association observed in

TABLE 3 Associated factors of dual trajectories.

Variables	Group 2/Group 1 (ref)	
	OR	95% CI
Age		
55–64 (ref)		
65–74	1.71***	1.51–1.93
≥75	1.66***	1.32–2.08
Education		
Illiterate (ref)		
Literate	0.72***	0.63–0.82
Gender		
Male (ref)		
Female	1.59***	1.39–1.81
Residence		
Rural (ref)		
Urban	0.61***	0.54–0.69
Average annual personal expenditure		
Low (ref)		
High	1.11	0.93–1.33
Marriage		
Unmarried (ref)		
Married	0.74***	0.63–0.87
Drinking		
Still drinking (ref)		
Abstinence	0.93	0.71–1.20
Never drinking	1.43***	1.22–1.66
Hypertension		
No (ref)		
Yes	2.59***	2.30–2.92
Diabetes		
No (ref)		
Yes	2.43***	1.98–2.97
Complete tooth loss		
No (ref)		
Yes	1.30**	1.09–1.54
Vision impairment		
No (ref)		
Yes	2.02***	1.80–2.26
Hearing impairment		
No (ref)		
Yes	1.69***	1.47–1.93

OR, odds ratio; 95% CI, 95% confidence interval; ref, reference group; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

type 2 diabetes patients compared to those with type 1 diabetes (Kodl and Seaquist, 2008).

Furthermore, our study revealed that older adults without complete tooth loss exhibited better cognitive and frailty outcomes, aligning with numerous previous research findings (Hoeksema et al., 2017; Yun et al., 2020; Zhang et al., 2022; Zhang et al., 2022). To reduce the likelihood of tooth loss, various measures can be taken, including early screening for oral health, treatment of periodontal disease, and maintenance of good oral hygiene practices. For older adults experiencing tooth loss, obtaining conventional prostheses as early as possible is advisable to prevent complications arising from the simultaneous exacerbation of cognitive function and frailty resulting from having fewer or no teeth (Yun et al., 2020).

Sensory impairments, such as hearing impairment and vision impairment, are prevalent among older adults. In our study, we found that 17.56% of older adults had hearing impairments, while and even higher proportion, 39.57%, had vision impairments. Age-related hearing loss is associated with changes in both the central and peripheral auditory systems and is characterized by difficulties in understanding words in noisy environments, which may contribute to late-life cognitive disorders (Panza et al., 2018). Similarly, hearing impairment can lead to psychosocial stress, social isolation, and the onset of depression (Johnson et al., 2015), mirroring the mechanisms observed in visual impairments (Reyes-Ortiz et al., 2005; Liljas et al., 2017). Both hearing and vision impairments have been linked to cognitive decline and dementia. Older adults with impaired vision and hearing may face challenges in accessing social support, which is crucial for preventing cognitive decline and frailty. Undetected and untreated impaired vision and hearing can have significant impacts on patients, their loved ones, and society as a whole.

Considering that cognitive decline is irreversible while frailty can be reversed (Baolin et al., 2021), and since both share common trajectories, controlling and intervening in the frailty of older adults can help prevent or slow down their cognitive decline. These findings provide valuable insights for the care of older adults.

Given that many predictors for assigning into the "Consistently Severe" group are preventable, and frailty is reversible, it is crucial to identify older adults at high risk through regular health monitoring and implement interventions as soon as possible. Early detection and intervention can significantly improve the overall health and quality of life for older adults. We recommend that community healthcare centers closely monitor the risk factors identified in the health checks of older adults and identify high-risk populations. By doing so, better management of the health status of them can be achieved, implementing appropriate intervention measures to address these factors. This will be beneficial in delaying or preventing cognitive decline and frailty.

5 Strengths and limitations

This study represents a pioneering application of GBDTM to explore the heterogeneity in co-development trajectories of cognitive function and frailty among older adults in China, using longitudinal data. Furthermore, we identified potential factors that increase the likelihood of older adults being classified into the "Consistently Severe" group, characterized by a higher rate of decline in both cognitive function and frailty.

However, it is important to acknowledge the limitations of this study. Firstly, due to data limitation, our assessment of cognitive function focused primarily on immediate and delayed memory, without considering other dimensions such as executive function

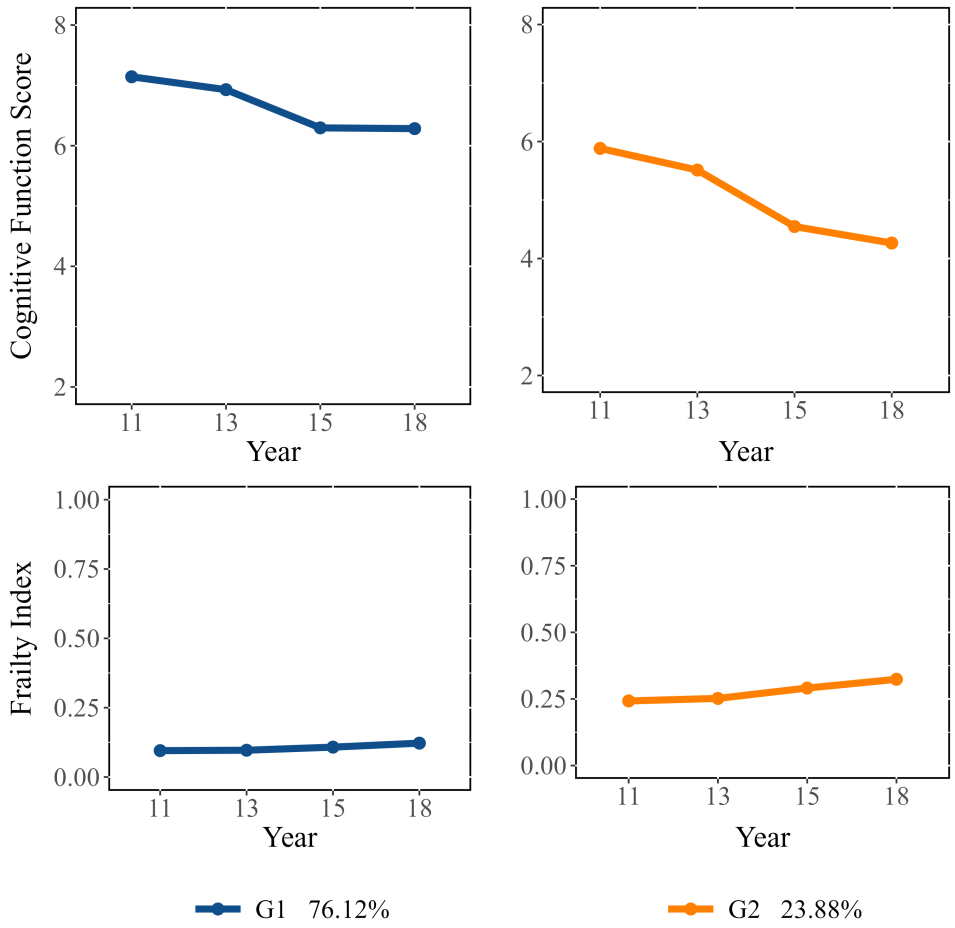

FIGURE 1
Dual trajectories of cognitive function (represented by cognitive function score) and frailty (represented by frailty index).

or orientation function. While it is true that the memory is a highly relevant dimension in relation to dementia, the exclusion of other cognitive dimensions may limit the comprehensive understanding of cognitive function in our findings. Secondly, in our study, several items, particularly those related to chronic diseases, sensory impairment and physical activities, were self-reported by participants. The use of self-reporting introduces the potential for recall bias, as participants may not accurately remember or report their behaviors or conditions. This may impact the validity and reliability of the collected data. However, it is worth noting that self-report of medical conditions has been widely used in studies involving community-dwelling older adults. Additionally, previous research has demonstrated consistency between self-reporting and objective measurements (Yuan et al., 2022; Howrey et al., 2020; Ma et al., 2020; Reyes-Ortiz et al., 2005; Liljas et al., 2017). Despite the limitations of self-reporting, it remains a valuable and commonly employed method for gathering data in this context. Thirdly, it is important to note that while the CHARLS recruited a representative sample in China, it did not include individuals from minority groups residing in regions such as Tibet and Xinjiang. As a result, the findings of this study may not be directly applicable to minority populations. It is recommended that future research should specifically investigate the co-development trajectories of cognition and frailty among these minority populations to ensure a more comprehensive understanding of the topic.

6 Conclusion

In this longitudinal study, one group showed better cognitive function and lower levels of frailty, while the "Consistently Severe" group exhibited poorer cognitive function and higher levels of frailty. Several characteristics were associated with being in the "Consistently Severe" group, including being female, older, illiterate, residing in rural areas, and being unmarried. Additionally, individuals in this group reported worse overall health and a higher prevalence of conditions such as diabetes, hypertension, hearing impairment, vision impairment, and complete tooth loss.

While cognitive impairment may be irreversible, frailty is a reversible condition. Therefore, early detection of frailty is crucial for preventing cognitive decline, given their share trajectory. Furthermore, many predictors for being in the "Consistently Severe" group are preventable, highlighting the importance of regular health monitoring and timely interventions.

Community healthcare centers should closely monitor the risk factors identified in the annual health checks for older adults. This

enables the development of targeted interventions to address these factors, which may help delay or prevent cognitive decline and frailty.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found at: http://charls.pku.edu.cn/en.

Author contributions

XJ: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. YuW: Conceptualization, Data curation, Methodology, Software, Writing – original draft. ZG: Methodology, Supervision, Validation, Writing – review & editing. ZZ: Supervision, Validation, Writing – review & editing. KW: Methodology, Writing – review & editing. SY: Writing – review & editing. YaW: Supervision, Writing – review & editing. PQ: Conceptualization, Methodology, Project administration, Resources, 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.

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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.2024.1465914/full#supplementary-material

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Risk factors analysis of cognitive frailty among geriatric adults in nursing homes based on logistic regression and decision tree modeling

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Objective: To investigate the risk factors associated with cognitive frailty among older adults in nursing homes using logistic regression and decision tree modeling, and to compare the predictive performance of these methods.

Methods: A cross-sectional study was conducted involving 697 participants aged 60 and older residing in eight nursing homes in Sichuan province, China. Participants were recruited using convenience sampling. Data were collected through questionnaires administered to the older adults. Logistic regression and decision tree modeling were employed to construct models predicting cognitive frailty.

Results: Logistic regression analysis identified age, education degree, exercise, intellectual activities, number of chronic diseases, nutritional status, sleep quality, and depression as significant predictors of cognitive frailty (all $p < 0.05$). The final decision tree model consisted of three layers and 17 nodes. Six factors were identified as significant predictors: sleep quality, number of chronic diseases, depression, education level, nutrition, and exercise. Receiver operating characteristic (ROC) curve analysis revealed that the area under the curve (AUC) for the logistic regression model was 0.735 (95% *CI*: 0.701–0.767) with a sensitivity of 0.58 and specificity of 0.75. The AUC for the decision tree model was 0.746 (95% *CI*: 0.712–0.778) with a sensitivity of 0.68 and specificity of 0.70.

Conclusion: Age, education level, exercise, intellectual activities, sleep quality, number of chronic diseases, nutritional status, and depression are significant risk factors for cognitive frailty in older adults residing in nursing homes. Both logistic regression and decision tree models demonstrated comparable predictive performance, with each offering distinct advantages. The combined use of these methods can enhance predictive accuracy and provide valuable insights for clinical practice and policy development.

KEYWORDS

cognitive frailty, risk factors, logistic regression, decision tree, nursing homes

Introduction

Frailty is a clinical condition characterized by an individual's increased vulnerability to stressors due to the cumulative decline of multiple physiological systems associated with aging. This decline encompasses physical, cognitive, psychological, and social dimensions (Clegg et al., 2013; Kolle et al., 2023). According to the World Health Organization (WHO) Health Statistics Report 2021, approximately one in 10 of the global population is elderly (Li et al., 2022b). The growing aging population has become a significant public health concern. The increasing number of older adults poses substantial challenges for the global community, particularly regarding their health. Aging can lead to both physical frailty and cognitive decline (Li et al., 2022b). Recent studies have demonstrated a close association between physical frailty and cognitive decline, often occurring simultaneously during the aging process (Sugimoto et al., 2022). To comprehensively define this condition and expand the concept of multiple dimensions of frailty, the International Consensus Group from the International Academy of Nutrition and Aging (IANA) and the International Association of Gerontology and Geriatrics (IAGG) introduced the concept of cognitive frailty (CF). CF is a heterogeneous clinical manifestation that coexists with physical frailty and cognitive impairment but excludes Alzheimer's disease and various types of dementia (Kelaiditi et al., 2013; Li et al., 2022b). In contrast to other forms of cognitive impairment, the international consensus group emphasized that CF is primarily caused by physical conditions rather than neurodegenerative diseases. Moreover, cognitive frailty may serve as a precursor to neurodegenerative processes (Sugimoto et al., 2022).

Since its introduction, the concept of cognitive frailty has garnered significant attention and has been extensively researched in a relatively short period. A systematic review of 51 studies conducted in 10 countries revealed that the overall prevalence of cognitive frailty among older adults worldwide was 16% (Zhang et al., 2021). Additionally, studies have shown that the incidence of cognitive frailty increases with age, rising from 4% in the 60–69 age group to 7% in the 70–79 group, then sharply to 29% for those 80 and older, culminating in a striking 50.3% for individuals aged 90 and above (Hao et al., 2018; Liu et al., 2023). Given the accelerating pace of aging and the increasing number of older adults, addressing cognitive frailty in geriatric populations is essential to prevent falls, disability, hospitalization, and other adverse outcomes (Huang J. et al., 2023).

Nursing homes, as primary care settings for older adults, play a crucial role in identifying, preventing, and managing cognitive frailty (Chen et al., 2023). Growing evidence suggests the importance of focusing on cognitive frailty among older individuals in nursing homes. For instance, a recent study (Huang J. H. et al., 2023) found a higher prevalence of cognitive frailty in nursing homes (49.07%) compared to communities (14.20%). Another study (Guo et al., 2023) conducted a meta-analysis and reported a prevalence of cognitive frailty among older adults in nursing homes of 24%, which exceeded that in the community (22%) and hospital (9%). When frail older individuals experience cognitive dysfunction combined with other health problems that impede their ability to manage daily activities, and family caregivers are unable to provide adequate support, placement in a nursing home may become necessary or even the only viable option (Seiger Cronfalk et al., 2017). However, older adults in nursing homes often face multiple health challenges, including advanced age, disability, dementia, and comorbid conditions (Gentili et al., 2022). Furthermore, the specialized management and living environment of nursing homes can limit physical activity, interpersonal communication, and emotional support with the outside world (Pastor-Barriuso et al., 2020). These complex factors contribute to poorer physical function, cognitive function, psychological well-being, and a higher risk of cognitive frailty among older adults in nursing homes.

Due to declining health, increased life expectancy, and decreased self-care abilities, an increasing number of older adults are opting to reside in nursing homes to receive professional care (Liu et al., 2022). The International Association of Gerontology and Geriatrics has emphasized the need for more research within nursing home settings (Liau et al., 2021), making cognitive frailty among older individuals in nursing homes a particularly worthy area of focus. While existing studies have primarily examined the prevalence and adverse outcomes of cognitive frailty, there is a growing emphasis on identifying modifiable risk factors. For instance, a meta-analysis explored modifiable risk factors of cognitive frailty in community-dwelling older adults (Yuan and Zhang, 2024). Besides, some studies have analyzed the risk factors of cognitive frailty in older patients with chronic diseases, such as diabetes (Deng et al., 2023), chronic kidney disease (Luo et al., 2022), chronic obstructive pulmonary disease (Wu et al., 2024), or cancer (Li et al., 2024). However, there remains a dearth of research focusing on the risk factors leading to cognitive frailty in older adults residing in nursing homes. Therefore, it is crucial to investigate the risk factors associated with cognitive frailty in this population to provide valuable insights and opportunities for early interventions to prevent cognitive frailty and mitigate the healthcare and financial burdens it imposes (Lee et al., 2023).

Understanding the factors that influence the development of CF among older adults in nursing homes is essential. Studies have demonstrated that logistic regression analysis models, in conjunction with decision tree models, can be valuable tools for analyzing risk factors and enhancing analytical efficacy (Rosenblatt and Yanez, 2022; Wang et al., 2024). This study aimed to investigate the risk factors associated with cognitive frailty in older adults residing in nursing homes using logistic regression analysis and decision tree models. The findings of this research can provide valuable insights for healthcare professionals to implement targeted interventions to prevent cognitive frailty in this population.

Materials and methods

Research design

A cross-sectional study was conducted from December 2021 to February 2022 in eight nursing homes located in Sichuan Province, China. Convenience sampling was employed to recruit participants. The sample size was determined based on the requirements for cross-sectional studies (Wan and Liu, 2007), resulting in a minimum sample size of 691 cases.

Participants

Face-to-face investigations were conducted among older adults residing in nursing homes between December 2021 and February

2022. Participants were included if they were aged 60 or older, had resided in a nursing home for at least 3 months, exhibited clear consciousness and good language expression abilities, and volunteered to participate in the study. Exclusion criteria included severe visual impairment, hearing impairment, mental disorders, inability to complete physical function tests, Alzheimer's disease or other types of dementia, and current participation in other clinical research trials.

Ethical statement

This study adhered to the principles outlined in the Declaration of Helsinki. All participants provided informed consent, and the study was approved by the Jinniu District People's Hospital Ethics Committee of Chengdu (No. QYYLL-2022-011).

Research tools

General information questionnaire

Demographic information, life behavior habits, health conditions, and current medications were collected during the survey process. Demographic information included age, sex, education level, personal monthly income, marital status, frequency of family visits, pre-retirement occupation, and living environment. Life behavior habits encompassed smoking and drinking status, exercise frequency, and engagement in intellectual activities. Health conditions and current medications included the use of walking aids, self-rated health status, history of stress in the past year, type of medication, and the number of chronic diseases.

Physical frailty

The physical frailty status of participants was assessed using the Frailty Phenotype (FP) (Fried et al., 2001). This tool evaluates physical frailty based on five traits: weight loss, exhaustion, low physical activity, slow walking speed and low grip strength. Each trait was answered with "Yes/no." A "yes" answer was worth 1 point, and a "no" answer was worth 0 point. The total score was 0–5 points. Participants were categorized as frail (≥3 points), pre-frail (1–2 points), or non-frail (0 points) according to their FP scores (Wu et al., 2022). The Cronbach's α of the FP in this study was 0.858, indicating good internal consistency.

Cognitive function

The cognitive function of older adults was assessed using the Chinese version of the Mini-Mental State Examination (MMSE) (Wang et al., 2024). The MMSE comprises five dimensions: orientation, memory, attention and calculation, recall, and language ability, with a total of 30 items. Scores range from 0 to 30, with lower scores indicating poorer cognitive function. Individuals with an MMSE score of ≤21 (illiterate), ≤24 (primary school education), or ≤27 (secondary school education and above) are considered to have mild cognitive impairment. The Cronbach's α of MMSE in this study was 0.779.

Cognitive frailty

According to the previous study (Alqahtani and Alenazi, 2023), CF was defined as a Frailty Phenotype (FP) score of ≥3 and an MMSE score of 18 to <24 in the absence of dementia.

Sleep quality

The sleep quality of participants was assessed using the Athens Insomnia Scale (AIS), a validated instrument with a Cronbach's α of 0.83 and a test–retest reliability of 0.94 (Soldatos et al., 2003). The AIS consists of eight items with a total possible score ranging from 0 to 24. In our study, the Cronbach's α of the AIS was found to be 0.858. The AIS scoring scale classifies sleep disorders as follows: a score below 4 indicates no sleep disorder, a score between 4 and 6 suggests suspected insomnia, and a score above 6 confirms a diagnosis of insomnia.

Nutritional status

The nutritional status of participants was assessed using the Mini Nutritional Assessment Short Form (MNA-SF), a six-item scale with a Cronbach's alpha of 0.828 in this study. The MNA-SF evaluates eating behavior, weight change, activity level, recent illness or psychological trauma, mental and psychological well-being, and body mass index. A total score of 0–14 points is assigned, with 0–7 indicating malnutrition, 8–11 indicating risk of malnutrition, and 12–14 indicating normal nutrition (Rubenstein et al., 2001).

Depression

The Geriatric Depression Scale-15 (GDS-15) is a widely used instrument for assessing depressive symptoms in older adults. It demonstrates good reliability, with a Cronbach's alpha of 0.793 and a test–retest reliability of 0.728 in the Chinese elderly population (Tang, 2013). In the present study, the GDS-15 exhibited a Cronbach's alpha of 0.823, further confirming its reliability. This 15-item scale measures negative emotions experienced in the past week, with a total score ranging from 0 to 15 points. A score of 8 or higher indicates the presence of depressive symptoms, and a higher score signifies more severe depression.

Anxiety

The Generalized Anxiety Disorder 7 (GAD-7) scale, a seven-item tool used to assess anxiety symptoms in older adults, has a total score ranging from 0 to 21 points. A score of 5 or higher indicates the presence of anxiety symptoms, with higher scores reflecting more severe anxiety. The Chinese version of GAD-7 has demonstrated Cronbach's α of 0.898 and test–retest reliability of 0.856 (He et al., 2010). In the current study, the GAD-7 scale exhibited a Cronbach's α of 0.796.

Social support

The Social Support Rating Scale (SSRS), with a Cronbach's α of 0.808 in our study, was used to measure the social support level of participants. The scale consists of 10 items with a total score of 66 points. Higher scores indicate higher levels of social support, with scores ≤22 classified as low, 23–44 as medium, and 45–66 as high. Previous research has established the reliability and validity of the Chinese version of the SSRS (Liu et al., 2008).

Statistical analysis

To mitigate selection bias and control for potential confounders, we established clear inclusion and exclusion criteria to ensure sample representativeness. In the statistical analysis, cognitive frailty served as the dependent variable, while statistically significant independent

variables ($p < 0.05$) identified in univariate analysis were included in the multivariate logistic regression and decision tree models to analyze factors influencing cognitive frailty in nursing home residents. The decision tree model was constructed using the Classification and Regression Tree (CART) algorithm with a minimum of 50 cases for the parent node and 20 cases for the child node. In addition, considering that the meaning of exercise and education degree in the independent variables overlapped with that of FP (the item of physical activities) and MMSE (the evaluation results depended on the education degree) in assessing cognitive frailty, respectively, we excluded exercise and education degree in the independent variables for sensitivity analysis and analyzed the stability of the results. Receiver operating characteristic (ROC) curves of both models were generated using MedCalc 20.1 software, with AUC, specificity, and sensitivity employed to evaluate their predictive performance. Statistical analyses were conducted using SPSS 23.0 software, incorporating descriptive statistics for general information (frequency counts, constitutive ratios, means, and standard deviations).

Results and discussion

Results

Description of each indicator

In this study, 720 questionnaires were distributed, resulting in 697 valid responses, yielding a recovery rate of 96.81%. Of the participants, 225 (32.28%) were classified as having cognitive frailty, while 472 (67.72%) were classified as not having cognitive frailty.

Comparison of the characteristics between CF and non-CF older people in nursing homes

Participants were categorized into two groups based on the presence or absence of CF: the CF group ($n = 225$) and the non-CF group ($n = 472$). This classification revealed a prevalence of CF in nursing homes at 32.28%. A comparison of general information, physical functions, psychological health, and social support between the two groups revealed statistically significant differences in age, education level, personal monthly income, pre-retirement occupation, smoking history, exercise, intellectual activities, use of walking aids, self-assessed health status, type of medication, number of chronic diseases, nutritional status, sleep quality, depression, and social support ($p < 0.05$), as presented in Table 1. No significant differences were observed in terms of sex, marital status, dwelling environment, frequency of family visits, drinking history, history of stress in the past year, and anxiety ($p > 0.05$).

Multivariate logistic regression analysis

When cognitive frailty was used as the dependent variable (no = 0, yes = 1), 15 factors were found to be statistically significant in univariate analysis and were subsequently included as independent variables in the multivariate logistic regression model: age, education degree, personal monthly income, pre-retirement occupation, smoking history, exercise, intellectual activities, use of walking aids, self-assessment of health status, type of medication, number of chronic diseases, nutritional status, sleep quality, depression, and social support. Multivariate logistic regression revealed that age, education degree, exercise, intellectual activities, number of chronic diseases, nutritional status, sleep quality, and depression were significant risk factors for cognitive frailty among older adults in nursing homes ($p < 0.05$), as shown in Table 2.

Decision tree modeling analysis of factors influencing cognitive frailty in nursing-homes older adults

The Chi-squared Automatic Interaction Detection (CHAID) algorithm was employed to construct a decision tree, with a significance level of 0.05 for branch splitting. The minimum sample size for parent and child nodes was set at 50 and 20, respectively. The variables included in the decision tree analysis were consistent with those used in the multivariate logistic regression analysis. As illustrated in Figure 1, the resulting decision tree comprised three levels, one terminal node, 10 child nodes, and identified six variables associated with cognitive frailty among older adults in nursing homes: sleep quality, number of chronic diseases, depression, education level, nutritional status, and exercise.

Sensitivity analysis

After we deleted the exercise and education degree to conduct the sensitivity analysis, the results of logistic regression analysis showed that the remaining factors of age, intellectual activities, number of chronic diseases, nutrition status, sleep quality, and depression still the risk factors of CF among the older adults in nursing homes. And results of the decision tree model analysis indicated that the sleep quality, number of chronic diseases, depression, and nutritional status were also still associated with CF in nursing homes. Besides, it suggested that sleep had the most significant effect on CF and was the most important influencing factor, which was consistent with previous results (Table 3 and Figure 2).

Comparison of the predictive efficiency of the decision tree model and logistic regression model

As depicted in Figure 3, ROC curves were plotted based on the influencing factor models constructed using logistic regression and decision tree modeling. The area under the ROC curve (AUC) for the logistic regression model was 0.735 (95% *CI*: 0.701–0.767, $p < 0.001$), with a sensitivity of 0.582 and a specificity of 0.748. The AUC for the decision tree model was 0.746 (95% *CI*: 0.712–0.778, $p < 0.001$), with a sensitivity of 0.680 and a specificity of 0.703. Moreover, no significant difference ($Z = 0.465$, $p = 0.642$) was observed in the AUC between the two models (Table 4).

Discussion

This study initially analyzed the influencing factors of cognitive frailty among older adults in nursing homes. Unlike previous research (Liu et al., 2022; Zhang et al., 2024), our analysis encompassed a broader range of factors using both logistic regression and decision tree modeling. This approach provides a more comprehensive understanding of the quantitative relationships between these factors and cognitive frailty, addressing the importance of individual factors and their interactions through systematic learning of attribute features and the visualization of results in tree diagrams (Shen et al., 2024). Furthermore, given the ongoing debate about the predictive accuracy of logistic regression and decision tree models (Nusinovici et al., 2020;

TABLE 1 Comparison of the occurrence of CF among older adults in nursing homes with different characteristics.

Variable		Cognitive frailty [*n* = 225(%)]	Non-cognitive frailty [*n* = 472(%)]	Prevalence (totally = 32.28%)	χ^2/Z	*P*
Age	60 ~ 69	20 (8.89%)	77 (16.31%)	20.62%	−6.260[b]	<0.001
	70 ~ 79	44 (19.56%)	123 (26.06%)	26.35%		
	80 ~ 89	79 (35.11%)	219 (46.40%)	26.51%		
	≥90	82 (36.44%)	53 (11.23%)	60.74%		
Sex	Men	104 (46.22%)	221 (46.82%)	32.00%	0.022[a]	0.882
	Women	121 (53.78%)	251 (53.18%)	32.53%		
Education degree	Illiteracy	71 (31.56%)	57 (12.08%)	55.47%	−6.264[b]	<0.001
	Secondary schools	68 (30.22%)	133 (28.18%)	33.83%		
	Middle school (Junior/High/ Secondary)	64 (28.44%)	194 (41.10%)	24.81%		
	College and above	22 (9.78%)	88 (18.64%)	20.00%		
Marital status	Married with spouse	51 (22.67%)	125 (26.48%)	28.98%	1.176[a]	0.278
	Unmarried/divorced/widowed	174 (77.33%)	347 (73.52%)	33.40%		
Monthly personal income	<1,000	64 (28.44%)	30 (6.36%)	68.09%	−5.795[b]	<0.001
	1,000 ~ 2,999	73 (32.44%)	178 (37.71%)	29.08%		
	3,000 ~ 4,999	61 (27.11%)	179 (37.92%)	25.42%		
	≥5,000	27 (12.00%)	85 (18.01%)	24.11%		
Living environment	Single room	43 (19.11%)	65 (13.77%)	39.81%	3.762[a]	0.152
	Double room	125 (55.56%)	268 (56.78%)	31.81%		
	Multi-room apartment	57 (25.33%)	139 (29.45%)	29.08%		
Pre-retirement occupation	Mental labor is the mainstay	71 (31.56%)	188 (39.83%)	27.41%	4.468[a]	0.035
	Physical labor is the mainstay	154 (68.44%)	284 (60.17%)	35.16%		
Frequency of family visits (times/month)	0	5 (2.22%)	4 (0.85%)	55.56%	−1.389[b]	0.165
	<1	81 (36.00%)	147 (31.14%)	35.53%		
	1 ~ 3	98 (43.56%)	231 (48.94%)	29.79%		
	≥4	41 (18.22%)	90 (19.07%)	31.30%		
Smoking history	Yes	104 (46.22%)	167 (35.38%)	38.38%	7.535[a]	0.006
	No	121 (53.78%)	305 (64.62%)	28.40%		
Drinking history	Yes	86 (38.22%)	149 (31.57%)	36.60%	3.019[a]	0.082
	No	139 (61.78%)	323 (68.43%)	30.09%		
Exercise	Never	44 (19.56%)	27 (5.72%)	61.97%	38.516[a]	<0.001
	Occasionally	98 (43.56%)	189 (40.04%)	34.15%		
	Frequently	83 (36.89%)	256 (54.24%)	24.48%		

(Continued)

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TABLE 1 (Continued)

Variable		Cognitive frailty [*n* = 225(%)]	Non-cognitive frailty [*n* = 472(%)]	Prevalence (totally = 32.28%)	χ^2/Z	*P*
Intellectual activities	Never	43 (19.11%)	52 (11.02%)	45.26%	8.976[a]	0.011
	Occasionally	108 (48.00%)	236 (50.00%)	31.40%		
	Frequently	74 (32.89%)	184 (38.98%)	28.68%		
Use of walking aids	Yes	118 (52.44%)	208 (44.07%)	36.20%	4.294[a]	0.038
	No	107 (47.56%)	264 (55.93%)	28.84%		
Self-assessed health status	Well	46 (20.44%)	142 (30.08%)	24.47%	18.444[a]	<0.001
	General	87 (38.67%)	210 (44.49%)	29.29%		
	Bad	92 (40.89%)	120 (25.42%)	43.40%		
History of stress in the past 1 year	Yes	80 (35.56%)	201 (42.58%)	28.47%	3.129[a]	0.077
	No	145 (64.44%)	271 (57.42%)	34.86%		
Type of medication	0	29 (12.89%)	77 (16.31%)	27.36%	−2.320[b]	0.020
	1 ~ 2	66 (29.33%)	153 (32.42%)	30.14%		
	3 ~ 4	72 (32.00%)	161 (34.11%)	30.90%		
	≥5	58 (25.78%)	81 (17.16%)	41.73%		
Number of chronic diseases	0	21 (9.33%)	78 (16.53%)	21.21%	−3.640[b]	<0.001
	1 ~ 2	61 (27.11%)	139 (29.45%)	30.50%		
	3 ~ 4	69 (30.67%)	161 (34.11%)	30.00%		
	≥5	74 (32.89%)	94 (19.92%)	44.05%		
Nutrition status	Normal nutrition	43 (19.11%)	133 (28.18%)	24.43%	−3.895[b]	<0.001
	Risk of malnutrition	90 (40.00%)	214 (45.34%)	29.61%		
	Malnutrition	92 (40.89%)	125 (26.48%)	42.40%		
Sleep quality	No sleep disorders	45 (20.00%)	154 (32.63%)	22.61%	−4.077[b]	<0.001
	Suspected insomnia	87 (38.67%)	185 (39.19%)	31.99%		
	Insomnia	93 (41.33%)	133 (28.18%)	41.15%		
Depression	Yes	79 (35.11%)	117 (24.79%)	40.31%	8.033[a]	0.005
	No	146 (64.89%)	355 (75.21%)	29.14%		
Anxiety	Yes	49 (21.78%)	94 (19.92%)	34.27%	0.324[a]	0.569
	No	176 (78.22%)	378 (80.08%)	31.77%		
Social support	Low level	78 (34.67%)	103 (21.82%)	43.09%	−3.228[b]	0.001
	Mid-level	101 (44.89%)	246 (52.12%)	29.11%		
	High level	46 (20.44%)	123 (26.06%)	27.22%		

[a]χ^2 test; [b]Mann–Whitney *U* test.

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TABLE 2 Multivariate logistic regression analysis of factors influencing cognitive frailty in elderly people in nursing homes.

Variables	*β*	*SE*	Wald value	*p*-value	OR value	95% CI
Age (years old) (reference: 60~69)						
70 ~ 79	0.380	0.364	1.088	0.297	1.462	0.716 ~ 2.984
80 ~ 89	0.798	0.316	6.380	0.012	2.222	1.196 ~ 4.129
≥90	1.331	0.351	14.392	<0.001	3.786	1.903 ~ 7.532
Education degree (reference: illiteracy)						
Secondary schools	−0.203	0.267	0.579	0.447	0.816	0.483 ~ 1.377
Middle school	−0.597	0.260	5.267	0.022	0.551	0.331 ~ 0.917
College and above	−1.106	0.333	11.027	0.001	0.331	0.172 ~ 0.636
Exercise (reference: never)						
Occasionally	−0.366	0.307	1.421	0.233	0.694	0.380 ~ 1.266
Frequently	−0.671	0.305	4.842	0.028	0.511	0.281 ~ 0.929
Intellectual activities (reference: never)						
Occasionally	−0.506	0.273	3.449	0.063	0.603	0.353 ~ 1.028
Frequently	−0.617	0.281	4.839	0.028	0.539	0.311 ~ 0.935
Number of chronic diseases (reference: 0)						
1 ~ 2	0.380	0.331	1.319	0.251	1.462	0.765 ~ 2.797
3 ~ 4	0.701	0.322	4.739	0.029	2.015	1.072 ~ 3.786
≥5	1.180	0.344	11.79	0.001	3.253	1.659 ~ 6.379
Nutrition status (reference: normal nutrition)						
Risk of malnutrition	0.602	0.264	5.196	0.023	1.826	1.088 ~ 3.064
Malnutrition	0.838	0.261	10.333	0.001	2.312	1.387 ~ 3.853
Sleep quality (reference: no sleep disturbance)						
Suspected insomnia	0.732	0.249	8.663	0.003	2.078	1.277 ~ 3.383
Insomnia	1.334	0.289	21.35	<0.001	3.795	2.155 ~ 6.682
Depression (reference: no depression)						
No	0.799	0.224	12.678	<0.001	2.223	1.432 ~ 3.450

Miyazaki et al., 2024), we conducted a comparative analysis of their efficiency using the AUC value.

Our findings revealed that both logistic regression and decision tree modeling identified sleep quality, number of chronic diseases, depression, educational level, nutrition, and exercise as significant influencing factors of cognitive frailty among older adults in nursing homes. Furthermore, logistic regression analysis indicated that age and intellectual activity were additional influencing factors. However, the decision tree analysis did not highlight the influence of these two factors. This discrepancy may be attributed to the logistic regression model's ability to capture correlations between variables, while the decision tree model accounts for interactions and relationships among variables, providing a detailed functional form for each subcategory and offering a wealth of information (Zhang et al., 2022).

Regarding the comparative efficiency of logistic regression and decision tree modeling, the results demonstrated that both methods achieved AUC values exceeding 0.7, indicating strong classification performance for predicting the risk factors of cognitive frailty among older adults in nursing homes. Moreover, logistic regression exhibited high specificity, while decision tree analysis demonstrated high sensitivity. Therefore, the combined application of these two methods can enhance the analysis of factors influencing cognitive frailty in older adults residing in nursing homes.

Influence of sociodemographic factors on cognitive frailty among elderly people in nursing homes

In our study, the logistic regression model identified age as a risk factor for CF among older adults in nursing homes, while the decision tree model did not. This discrepancy may be attributed to the decision tree's comprehensive analysis of interactions between different factors. Compared to other factors, the relative effect of age on cognitive frailty was relatively small and deemed less important, leading to its exclusion as an interfering factor in the analysis. Despite this, considering the existing research evidence, we suggest retaining age as a risk factor for cognitive frailty among older adults in nursing homes. For example, studies have demonstrated a strong association between age and cognitive decline (Furtado et al., 2020), with older individuals, particularly those over 80 years old, at greater risk of cognitive frailty (Zhang et al., 2024). Several investigations have explored the relationship between frailty, cognitive impairment, and cognitive frailty,

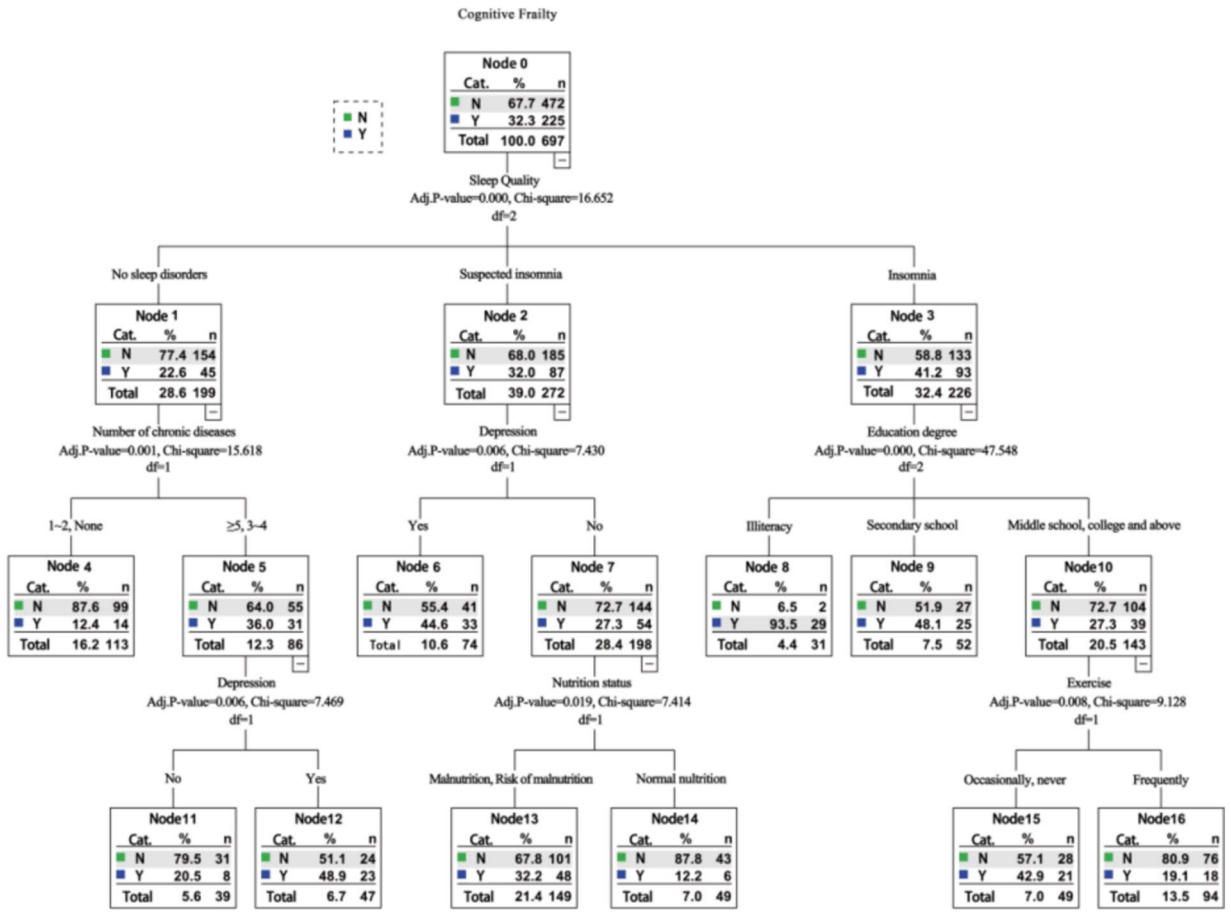

FIGURE 1
Decision tree model analysis of factors influencing cognitive frailty among old adults in nursing homes.

highlighting the role of aging in their development (Godin et al., 2017). Aging can lead to the dysfunction of multiple systems, reducing the body's physiological reserves and increasing vulnerability to frailty (Arai et al., 2018). Additionally, age-related hearing loss and hippocampal shrinkage contribute to a gradual decline in brain function, suggesting that brain aging may be a pathological mechanism underlying cognitive decline (Panza et al., 2018).

Consistent with the literature (Setiyani and Iskandar, 2022), the results of both logistic regression and decision tree analysis revealed a significant association between education level and cognitive function among nursing home residents. Older individuals with higher education levels often engage in activities such as reading books and newspapers, maintaining a relatively active state of their brain cells for extended periods. This enhanced brain activity can improve the brain's compensatory abilities for pathological aging, thereby reducing the risk of cognitive dysfunction (Maharani et al., 2023). This finding further elucidates why a low education level is a risk factor for cognitive frailty in our study. Elderly individuals with higher education levels tend to possess a stronger sense of health and are more likely to proactively seek health-related information and engage in health-promoting behaviors, consequently decreasing the risk of cognitive frailty (Bakker et al., 2017). Moreover, the decision tree analysis in our study indicated that the prevalence of cognitive frailty was highest among older adults with insomnia and illiteracy, suggesting that these factors may increase the risk of cognitive frailty among nursing home residents.

Influence of life behavior habit factors on cognitive frailty among elderly people in nursing homes

The findings of this study, utilizing logistic regression and decision tree modeling, indicate that exercise is a significant factor influencing cognitive frailty among older adults in nursing homes. Various types of exercise have been shown to mitigate adverse outcomes in nursing home residents, including falls (Dyer et al., 2023), frailty (Sahin et al., 2022), and cognitive decline (Hirt et al., 2024). Given the high prevalence of physical inactivity among Chinese nursing home residents, reaching 88.46%, tailored interventions are essential to promote physical activity in this population (Shi et al., 2024). A previous study (Angulo et al., 2020) has demonstrated that exercise can regulate bone metabolism, enhance skeletal muscle contractile function, and delay age-related bone loss and muscle strength decline, thereby maintaining better physical function and reducing the incidence of frailty. Additionally, exercise can increase brain blood circulation through complex neural reflex pathways, reshaping

TABLE 3 Sensitivity analysis results of multivariate logistic regression analysis of factors influencing cognitive frailty in elderly people in nursing homes.

Variables	*β*	*SE*	*P*-value	95% CI
Age (reference: 60~69)				
70 ~ 79	0.209	0.351	0.552	0.619 ~ 2.454
80 ~ 89	0.795	0.309	0.010	1.208 ~ 4.058
≥90	1.370	0.343	<0.001	2.007 ~ 7.710
Intellectual activities (reference: never)				
Occasionally	−0.598	0.268	0.026	0.325 ~ 0.931
Frequently	−0.721	0.276	0.009	0.283 ~ 0.835
Number of chronic diseases (reference: 0)				
1 ~ 2	0.379	0.322	0.239	0.777 ~ 2.749
3 ~ 4	0.687	0.312	0.028	1.078 ~ 3.669
≥5	1.122	0.334	0.001	1.596 ~ 5.908
Nutrition status (reference: normal nutrition)				
Risk of malnutrition	0.624	0.258	0.016	1.125 ~ 3.095
Malnutrition	0.882	0.255	0.001	1.466 ~ 3.983
Sleep quality (reference: no sleep disturbance)				
Suspected insomnia	0.722	0.243	0.003	1.278 ~ 3.315
Insomnia	1.174	0.278	<0.001	1.877 ~ 5.575
Depression (reference: no depression)				
Yes	0.887	0.218	<0.001	1.582 ~ 3.724

brain function, delaying brain atrophy, and slowing cognitive decline (Angulo et al., 2020). The decision tree analysis further revealed that regular exercise can reduce the prevalence of cognitive frailty in individuals with insomnia and at least a secondary school education, while occasional or no exercise may increase the risk. These findings highlight the crucial role of regular exercise in mitigating cognitive frailty among older adults in nursing homes, particularly those with lower educational levels.

While logistic regression and decision tree models identified differing influences of intellectual activities on cognitive frailty in nursing homes, with decision tree analysis indicating a lack of association, previous research (Li et al., 2022a) has highlighted the positive impact of intellectual activities on cognitive function. Effective cognitive stimulation through intellectual activities can promote continuous brain activity, enhance brain cell function, and strengthen neural network connections, thereby delaying cognitive decline. A recent study suggested that intellectual activities may have varying moderating effects on the relationship between age and memory performance (Karsazi et al., 2024), emphasizing the importance of nursing institutions in encouraging older adults to actively participate in exercise and intellectual activities to prevent or slow down the onset of cognitive frailty.

Influence of physical health factors on cognitive frailty among elderly people in nursing homes

Sleep quality, number of chronic diseases, and nutrition emerged as significant factors influencing cognitive frailty among older adults in our study's nursing homes. Notably, decision tree analysis revealed sleep quality as the most strongly correlated and influential factor. Previous research has highlighted the potential for long-term sleep disorders to induce cardiovascular, cerebrovascular, or degenerative neurological diseases, known risk factors for physical frailty. Furthermore, sleep disorders can impair cognitive function through mechanisms such as inflammation and vascular lesions (Nakakubo et al., 2018; Hu et al., 2021), suggesting that improving sleep quality could be a valuable target for mitigating cognitive frailty in nursing home residents. A study (Liu et al., 2022) demonstrated a significant association between poor sleep quality and long nap duration with a higher risk of cognitive frailty, suggesting that reducing nap time might be beneficial in reducing the incidence of cognitive frailty. The prevalence of chronic diseases is often elevated among older adults, with studies indicating that 55–98% of elderly individuals suffer from multimorbidity (Anderssen-Nordahl et al., 2024). Our findings revealed a higher prevalence of cognitive frailty among older adults with more chronic diseases. Chronic diseases can exacerbate the decline of various organ functions in the elderly, increasing their susceptibility to physical frailty (Zazzara et al., 2019). Additionally, common chronic diseases like hypertension and diabetes can synergistically damage vascular endothelial cells, leading to brain hypoxia and oxidative damage, ultimately contributing to cognitive decline (Chu et al., 2022). According to a recent survey (Liu et al., 2020), a significant proportion of nursing home residents in China (5.1 and 55.6%, respectively) were malnourished or at risk of malnutrition, highlighting the prevalent poor nutritional status among this population. Multiple studies have demonstrated that inadequate nutrition predisposes individuals to cognitive frailty (Gómez-Gómez and Zapico, 2019). Malnutrition can lead to weight loss and muscle tone decline, both important physical frailty indicators (Lorenzo-López et al., 2017). Moreover, deficiencies in specific nutrients, such as vitamins and micronutrients, can contribute to cognitive decline (Scarmeas et al., 2018).

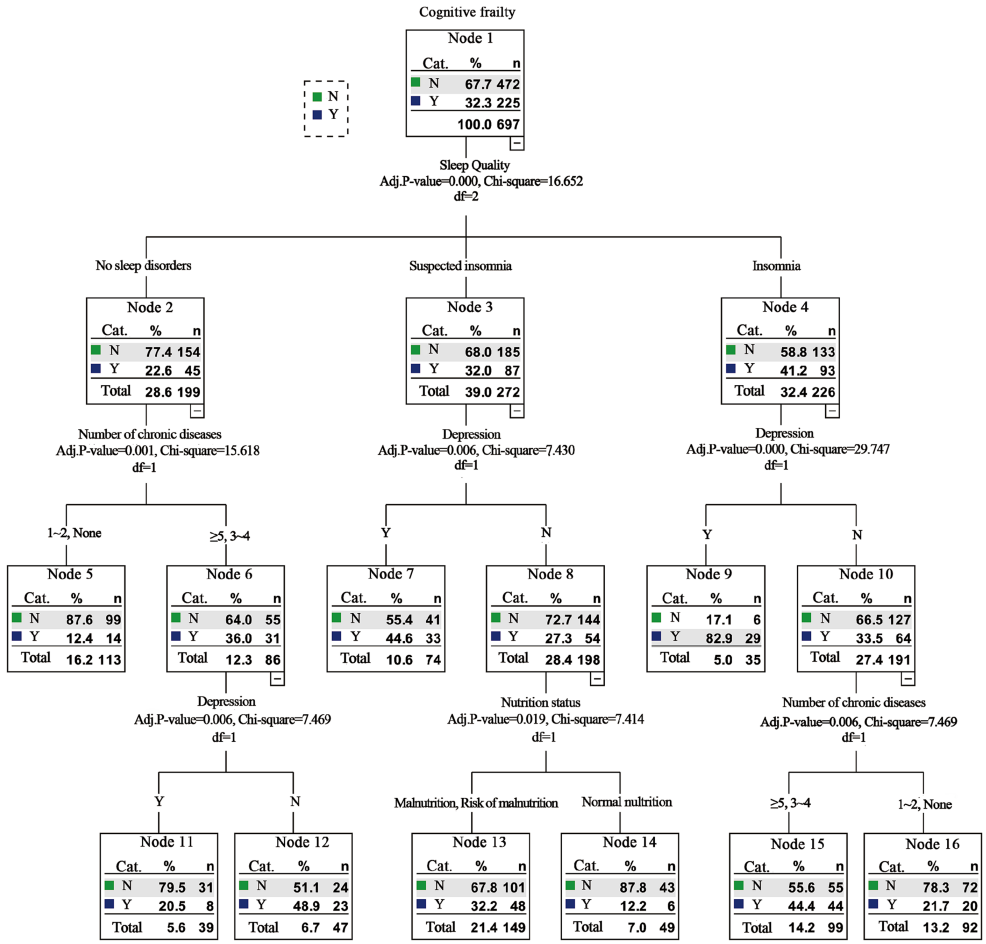

FIGURE 2
Sensitivity analysis results of decision tree model analysis of factors influencing cognitive frailty among old adults in nursing homes.

Influence of social psychological factors on cognitive frailty among elderly people in nursing homes

Consistent with the literature (Zou et al., 2023), depression emerged as a factor influencing cognitive frailty among older adults in nursing homes. A recent study (Ruan et al., 2020) suggested that depression can elevate levels of chronic inflammatory factors in the body. These inflammatory factors not only directly affect the musculoskeletal system but can also cross the blood–brain barrier, leading to an increase in amyloid protein in the brain and subsequent impairment of cognitive function. Furthermore, the decision tree analysis in this study revealed an interaction between suspicious insomnia and depression. In individuals with suspicious insomnia, depression was associated with a higher prevalence of cognitive frailty.

This study employed logistic regression and decision tree modeling to investigate the influential factors of cognitive frailty among older Chinese adults residing in nursing homes. The findings may offer novel insights into the prevention of cognitive frailty in this population. However, certain limitations should be acknowledged. Firstly, the cross-sectional study design precludes the establishment of a causal relationship between cognitive frailty and the identified risk factors. Secondly, the relatively limited scope of the investigation may restrict the

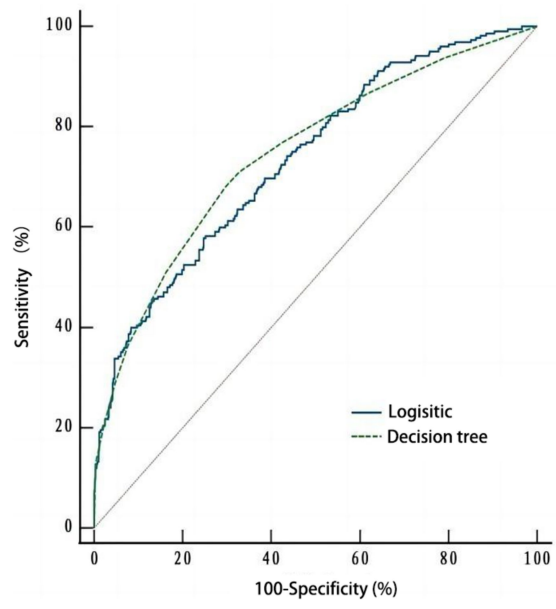

FIGURE 3
The ROC curves of the logistic regression model and decision tree model.

TABLE 4 Comparison of classification effects of the logistic regression and decision tree models.

Model	*AUC*	*SE*	95% CI	*P*	Specificity	Sensitivity
Logistic regression	0.735	0.020	0.701 ~ 0.767	<0.001	0.748	0.582
Decision tree	0.746	0.020	0.712 ~ 0.778	<0.001	0.703	0.680

generalizability of the research conclusions to other regions. Thirdly, the reliance on self-reported data and the exclusion of participants with missing values could introduce information and selection biases. Future research could address these limitations by expanding the sample size, conducting multi-center studies, and incorporating paraclinical investigations such as blood work and brain imaging. These measures would enhance the generalizability and clinical significance of the findings.

Conclusion

Overall, our study identified age, education level, exercise, intellectual activity, sleep quality, number of chronic diseases, nutrition, and depression as factors influencing cognitive frailty among older adults in nursing homes. Among these, sleep quality emerged as the most significant factor. Based on these findings, we propose several recommendations: first, nursing institutions should prioritize the assessment and early screening of cognitive frailty, particularly among older adults with low education levels. Second, nursing institutions should actively promote exercise and intellectual activities, encouraging older adults to participate regularly to prevent or delay cognitive decline. Third, healthcare professionals in nursing homes should address sleep and nutrition issues, creating a conducive sleep environment and implementing scientifically sound dietary nutrition programs to improve the sleep and nutritional status of older adults. For individuals with multiple chronic diseases, collaboration with relevant medical institutions to develop tailored treatment, nursing, and rehabilitation programs can enhance health management abilities and potentially delay or improve cognitive decline. Finally, greater attention should be paid to psychological evaluation and targeted health education for older adults with poor sleep quality to prevent or delay the onset of cognitive decline.

The results of the logistic regression and decision tree models were consistent, efficient, and demonstrated distinct advantages. Logistic regression analysis, after controlling for confounding factors, explored the linear relationship between independent and dependent variables. The output odds ratio (OR) values provided quantitative insights into the dependency between independent variables and the risk of cognitive frailty (Chen et al., 2022), offering a clearer understanding of the influence of various factors. In contrast, decision tree analysis generated a tree graph that directly visualized the importance of each risk factor in predicting cognitive frailty. Both methods effectively identified risk factors for cognitive frailty among older adults in nursing homes, as evidenced by AUC values greater than 0.7. The combined application of logistic regression and decision tree models can leverage their complementary strengths, providing a more comprehensive understanding of the factors influencing cognitive frailty in older adults in nursing homes. Healthcare professionals should actively monitor these factors, identify high-risk groups early, and implement targeted and holistic preventive interventions to prevent or delay the onset of cognitive decline, thereby improving the quality of life for older adults in their later years.

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

This study was based on the principles of the Declaration of Helsinki. All participants provided informed consent, and the study was approved by the Jinniu District People's Hospital Ethics Committee of Chengdu (No. QYYLL-2022-011).

Author contributions

JG: Data curation, Formal analysis, Methodology, Visualization, Writing – original draft. DB: Data curation, Investigation, Methodology, Writing – original draft. HC: Data curation, Investigation, Methodology, Writing – original draft. XC: Data curation, Writing – original draft. HL: Data curation, Writing – original draft. WJ: Conceptualization, Investigation, Methodology, Supervision, Writing – review & editing. CH: Conceptualization, Funding acquisition, Investigation, 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.

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A study of the correlation between sarcopenia and cognitive impairment in older individuals over 60years: cross-sectional and longitudinal validation

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Objective: To validate the correlation between sarcopenia and cognition, and explore cognitive subdomains affected by sarcopenia.

Methods: A case–control study was designed to recruit 90 individuals aged 60 and above from June to October 2023 in the same community, all individuals meeting the inclusion criteria were categorized according to the 2019 Asian criteria for sarcopenia and divided into the sarcopenia group and non-sarcopenia group at baseline. After a 12-week follow-up recording, individuals were classified into the aggravation group and alleviation group based on the change of sarcopenia severity. Sarcopenia tests including muscle mass, calf circumference, grip strength and physical function assessment, using Montreal Cognitive Assessment (MoCA) of nine dimensions for cognitive assessment.

Results: (1) There was a significant positive correlation between cognitive function and grip strength in males ($r = 0.42$, $p < 0.05$). (2) There was a moderate correlation between sarcopenia grading and MoCA score ($r = -0.4$, $p < 0.001$). (3) Individuals with sarcopenia had significantly lower MoCA total scores and sub-scores in executive function, fluency, calculation and delayed recall compared to non-sarcopenia group ($p < 0.05$). (4) After 12 weeks, the mean value of the change in fluency in the alleviation group increased by 0.33 points, while the aggravation group decreased by 0.2 points ($W = 128$, $p < 0.05$).

Conclusion: There is a correlation between sarcopenia and cognitive function, individuals with sarcopenia performing poorly in overall cognition as well as refined dimensions. The degree of cognition like fluency degenerates over time with increasing severity of sarcopenia.

KEYWORDS

sarcopenia, cognitive function, aging frailty, fluency, memory

Highlights

- The relationship between sarcopenia and cognition is reflected in physical mobility and brain function.
- Cognitive function is impaired in older adults with sarcopenia.

- Some dimensions of cognition can change as muscle atrophy worsens.
- The slowing speed caused by sarcopenia could be reflected in cognitive expression.

1 Introduction

Sarcopenia is an aging-related, progressive and generalized skeletal muscle loss disorder characterized by decreased muscle mass, decreased muscle strength, and/or reduced somatic functions (Cesari and Kuchel, 2020), and it is associated with frailty (Gielen et al., 2023), heart disease (Sasaki and Fukumoto, 2022), diabetes (Guerrero et al., 2016; Umegaki et al., 2017), and many other chronic conditions. The definition and diagnosis of sarcopenia continues to evolve, in 2019 the Asian Working Group for Sarcopenia (AWGS) proposed defining muscular dystrophy as "sarcopenia" as well (Chen et al., 2020), which means that sarcopenia is no longer a disease in the traditional sense, but rather a state of muscle atrophy that accompanies aging. Similarly, cognitive decline is a pathological condition that includes a range of cognitively related symptoms. Frailty is a multidimensional syndrome including physical, social, and cognitive aspects, among which physical and cognitive decline are fundamental dimensions (Arai et al., 2018; Kelaiditi et al., 2013).

Current findings in Asia and Europe have found that sarcopenia was associated with the incidence of neurological disorders such as cognitive dysfunction, Alzheimer's disease and depression (Yang et al., 2022; Lee et al., 2018), and was even a predictor of Alzheimer's disease, mild cognitive impairment (MCI) and cognitive decline (Beeri et al., 2021). Sarcopenia and cognitive dysfunction not only share many common pathogenic mechanisms of myokines, endocrine and inflammatory markers, but also have some external influencing factors such as lifestyle of lack of physical activity and poor nutritional habits (Cannataro et al., 2021; Sui et al., 2020). Evidence suggests that muscle loss increases the risk of cognitive decline, such as reduced handgrip strength and gait speed (Basile and Sardella, 2021; Chou et al., 2019).

The diagnosis of sarcopenia in early stages has positive implications for the prevention of cognitive dysfunction (Peng et al., 2020). The presence of early motor dysfunction has been suggested as a potential predictor of further cognitive impairment, such as the motoric cognitive risk syndrome (MCR)(Basile and Sardella, 2021). At the same time, separate diagnostic indicatorss of sarcopenia have been associated with cognitive dysfunction (McGrath et al., 2020). Better cognition was associated with a lower risk of developing sarcopenia and could explain some of the potential pathways contributing to sarcopenia (Hu et al., 2024). Studies in the US, Spain, Brazil, Saudi Arabia, and Japan reported a range of MCI prevalence between 6.5 and 38.6% (Lu et al., 2021), compared with 20.8% reported by the Chinese National Centre for Prevention and Control of Chronic and Non-communicable Diseases (Jia et al., 2014), that early recognition of cognitive deterioration is essential to prevent further deterioration of cognitive impairment, especially to prevent MCI turning into dementia. A study based on the China Health and Retirement Longitudinal Study (CHARLS) showed that the incidence of MCI in non-sarcopenia, possible sarcopenia, and sarcopenia groups was 10.1%, 16.5%, and 24.2%, this not only confirms the cross-sectional association between the two, but also suggests the progression of muscle atrophy will accelerate cognition decline.

Although several studies have been conducted to assess potential associations, most of them focused on cognition in general and did not analyze subdomains in detail, and previous studies have demonstrated significant differences in age (Hu et al., 2022; Salinas-Rodriguez et al., 2021; Sugimoto et al., 2022). Considering whether sarcopenia contributes to cognitive decline, we delve into the cognitive profiles of individuals with sarcopenia, with particular emphasis on specific cognitive domains. Subsequently, we assess the evolution of muscle atrophy and cognitive abilities over a 12-week period to explore whether the process of muscle atrophy is accompanied by cognitive function decline.

2 Methods

2.1 Study population

The study population was recruited in Yanda Retirement Community in June 2023, Langfang, Hebei, China. Inclusion criteria: (1) aged 60 and above; (2) education level of college and above; (3) participation in annual health checkups; (4) clear consciousness without communication barriers; (5) reasonable medication and stable physical condition; (6) having signed an informed consent form. Exclusion criteria: (1) patients with serious diseases or multiple diseases; (2) severe neurological disorders such as dementia; (3) unable to move independently; (4) hospitalized or exit during the experiment.

2.2 Study design

At baseline, case–control was used to classify individuals into non-sarcopenia and sarcopenia groups, consisting of 90 individuals aged 60 to 95, including 43 males and 57 females. Followed by a 12-week follow-up intervention in which all older adults participated in the exercise program to varying degrees and recorded, and were classified into the aggravation group and the alleviation group, based on the change in the progression of sarcopenia relative to baseline after 12 weeks. A total of 108 people were surveyed at baseline and 90 completed the entire process and recorded their performance, and 68 completed the recording after 12 weeks. The detailed flow chart of the sample selection is shown in Figure 1. The study protocol was approved by the Sport Science Ethics Committee of Beijing Sport University (No. 2020082H).

2.3 Measurement

2.3.1 Screening for sarcopenia

Sarcopenia was evaluated according to the AWGS guidelines, including calf circumference, muscle strength, skeletal muscle mass (ASM) and physical performance (Chen et al., 2020).

Calf circumference was measured using a long tape measure. Muscle mass of the upper and lower extremities was obtained by Inbody (230, Korea), and the total skeletal muscle mass of the extremities was summed to obtain the appendicular skeletal muscle mass index (ASMI), which was calculated by the formula: total skeletal muscle mass of the extremities (kg)/height^2 (m^2). ASMI below 7.0 kg/m^2 in male and 5.7 kg/m^2 in female in community were considered as low muscle mass.

Grip strength was assessed using a grip strength meter (Jamar Inc., USA) tested with individuals in a standing position using the

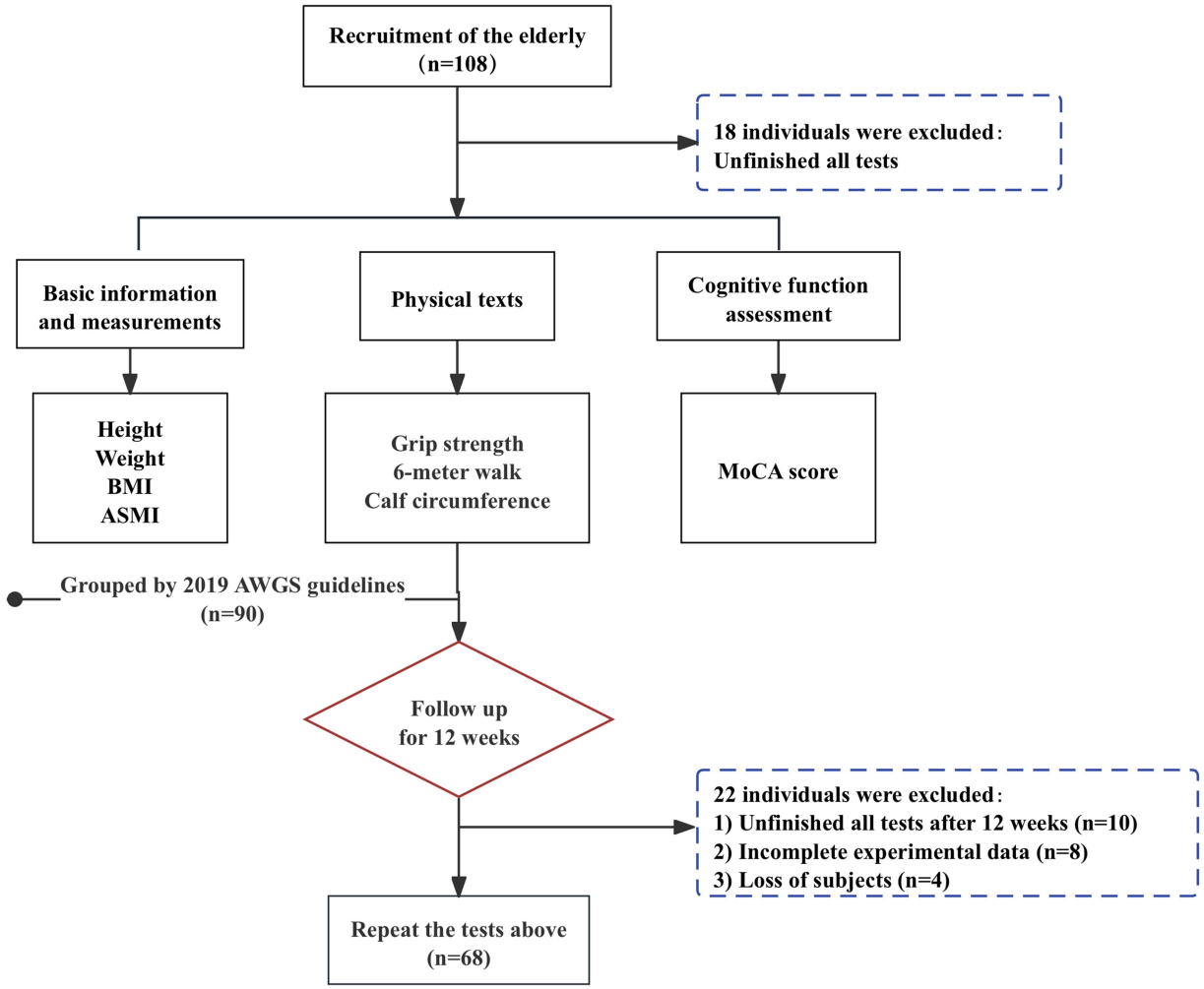

FIGURE 1
Flowchart of the experiment.

dominant hand and squeezing the grip strength meter with maximum force 2 times at 1-min intervals, the maximum values were chosen. Grip strength below 28 kg for male and 18 kg for female was considered low muscle strength.

Somatic mobility function was assessed using the 6-m walking tests, which required subjects to walk along a straight with step speed of on their usual, and the time taken to walk 6 m was recorded by a stopwatch to calculate the average speed. The test was performed twice and the minimum value was included. A 6-m walking speed of less than 1.0 m/s was considered as low physical performance.

Accordingly, the sarcopenia group was categorized into 3 parts. The group of possible sarcopenia was defined as low muscle strength or low physical performance, the group of sarcopenia was defined as low muscle mass and low muscle strength/low physical performance, the group of severe sarcopenia was defined as low muscle mass, low muscle strength and low physical performance (Chen et al., 2020). The screening groupings for sarcopenia are shown in Figure 2.

2.3.2 Cognitive function assessment

The MoCA was used to assess the cognitive functioning of the older. Nine domains including executive function, fluency, orientation, calculation, abstract thinking, delayed recall, visuospatial functions, naming and attention. The full scale value is 30, ≥26 being normal, 18–25 being MCI and 10–17 being moderate cognitive impairment, and less than 10 being severe cognitive impairment. The MoCA is an alternative to the MMSE (MiniMental State Examination), but compared to the MMSE, it was more consistent with the screening test standards for MCI in the older over 60 (Ciesielska et al., 2016), and also easier to detect the risk of dementia in patients with cognitive impairment (Dong et al., 2012). A study in Chinese middle-aged and older population also proves that ceiling effect for MCI was less frequent using MoCA versus MMSE (Jia et al., 2021). Overall, the MoCA is a better choice for screening cognitive impairment in community-dwelling older people.

2.3.3 Potential covariates

Considering sociodemographic characteristics and health-related factors in our study. Sociodemographic characteristics included age and gender, and other relevant factors collected through questionnaires included acute inflammation in 3 months, alcohol consumption, and common chronic diseases of the older (hypertension, hyperlipidemia,

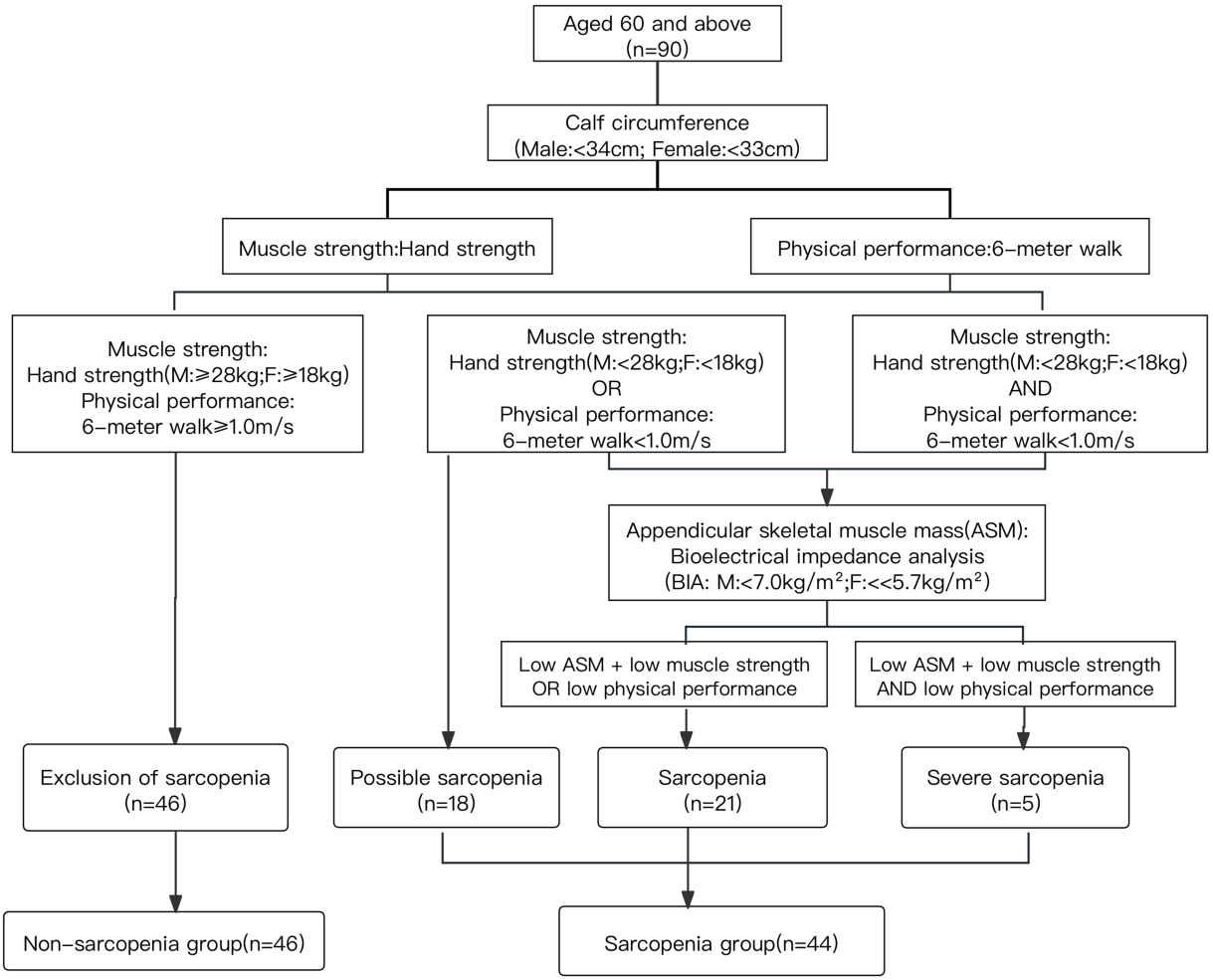

FIGURE 2
Screening groupings for sarcopenia.

diabetes, cancer, respiratory diseases, liver diseases, heart disease, stroke, urinary system diseases, digestive system diseases, nervous system diseases, and bone and joint diseases). Height and weight were measured using standardized procedures, and body mass index (BMI) was calculated as weight (kg) /height^2 (m^2). The diagnostic criteria for obesity were based on the Chinese and World Health Organization (WHO) standards. According to the Chinese BMI classification (Pan et al., 2021; Zhou, 2002), underweight was defined as <18.5 kg/m^2, normal weight was 18.5 to <24 kg/ m^2, overweight was 24 to <28 kg/ m^2, and obesity was ≥28 kg/m^2.

2.4 Statistical analysis

Data processing was performed using the RStudio (version 4.3.1). Quantitative data that satisfied normality were expressed as mean ± standard deviation, and independent samples *t*-tests were used for between-group comparisons; quantitative data that were not normal were expressed as median [interquartile spacing] and nonparametric tests were used for between-group comparisons. For categorical variables the individual number (percentage) was used for representation and chi-square test was used for comparison between groups. Spearman correlation analysis was used for correlation analysis between MoCA score and severity of sarcopenia. The effect sizes of the correlation coefficient *r* were classified as below: < 0.25 for weak correlation, 0.25–0.5 for moderate correlation, 0.5–0.75 for strong correlation, and ≥ 0.75 for extremely strong correlation, the statistical significance was set at $p < 0.05$.

3 Results

3.1 General data on baseline measurements of study subjects

Table 1 shows the baseline data of the population. There was no difference in basic information about age, gender, weight and BMI between the non-sarcopenia and sarcopenia groups, and the height of the older was 160.4 ± 7.1 cm in the non-sarcopenia group and 155.7 ± 7.6 cm in the sarcopenia group ($p = 0.003$). The total MoCA cognitive score was 27.5 [26.3, 28.8] in the non-sarcopenia group, and 25.0 [24.0, 27.0] in the sarcopenia group, which was a significant difference between the two groups ($p < 0.001$). The cognitive assessment included 9 domains of

TABLE 1 Baseline essential measurements.

Item		Level	Non-sarcopenia group (n = 46)	Sarcopenia group (n = 44)	p-value
Sarcopenia grade, n (%)		Non-sarcopenia	46 (100%)	0 (0%)	
		Possible	0 (0%)	18 (40.9%)	
		Sarcopenia	0 (0%)	21 (47.7%)	
		Severe	0 (0%)	5 (11.4%)	
Age (year), M [P25,P75]			82.0 [78.3, 86.8]	84.5 [81.0, 88.0]	0.059
Gender, n (%)		Male	17 (37.0%)	16 (36.4%)	0.961
		Female	29 (63.0%)	28 (63.6%)	
Height (cm), M ± SD			160.4 ± 7.1	155.7 ± 7.6	0.003
Weight (kg), M ± SD			61.1 ± 9.5	59.5 ± 9.3	0.425
BMI (kg/m^2), M ± SD			23.7 ± 2.9	24.5 ± 3.1	0.222
Grip strength (kg), M ± SD			25.2 ± 5.3	18.6 ± 5.6	<0.001
Calf circumference (cm), M [P25,P75]			33.0 [31.7, 35.8]	33.0 [31.6, 35.1]	0.478
6-meter pace (m/s), M [P25,P75]			0.3 [0.2, 0.3]	0.4 [0.3, 0.4]	<0.001
ASMI (kg/m^2), M ± SD			6.5 ± 0.1	6.1 ± 0.1	0.033
MoCA score, M [P25,P75]			27.5 [26.3, 28.6]	25.0 [24.0, 27.0]	<0.001
Cognitive level, n (%)		Normal	38 (82.6%)	19 (43.2%)	<0.001
		MCI	8 (17.4%)	21 (47.7%)	
		Moderate	0 (0%)	4 (9.1%)	
Obesity (kg/m^2), n (%)		Underweight (<18.5)	0 (0%)	2 (4.5%)	0.406
		Normal (18.5 to <24)	28 (60.9%)	20 (45.5%)	
		Overweight (24 to <28)	15 (32.6%)	16 (36.4%)	
		Obese (≥28)	3 (6.5%)	6 (13.6%)	
Acute inflammation in 3 months, n (%)		No	35 (76.1%)	37 (84.1%)	0.493
		Yes	11 (23.9%)	7 (15.9%)	
Chronic diseases	Alcohol consumption, n (%)	No	39 (84.8%)	36 (81.8%)	0.925
		Yes	7 (15.2%)	8 (18.2%)	
	Chronic diseases, n (%)	No	22 (47.8%)	20 (45.5%)	0.989
		Yes	23 (50.0%)	24 (54.5%)	
	Hyperlipidemia, n (%)	No	24 (52.2%)	33 (75.0%)	0.319
		Yes	17 (37.0%)	11 (25.0%)	
	Diabetes mellitus, n (%)	No	33 (71.7%)	35 (79.5%)	0.538
		Yes	13 (28.3%)	9 (20.5%)	
	Cancer, n (%)	No	45 (97.8%)	42 (95.5%)	0.969
		Yes	1 (2.2%)	2 (4.5%)	
	Respiratory diseases, n (%)	No	42 (91.3%)	40 (90.9%)	1.000
		Yes	4 (8.7%)	4 (9.1%)	
	Liver diseases, n (%)	No	45 (97.8%)	43 (97.7%)	1.000
		Yes	1 (2.2%)	1 (2.3%)	
	Cardiovascular diseases, n (%)	No	33 (71.7%)	32 (72.7%)	1.000
		Yes	13 (28.3%)	12 (27.3%)	
	Stroke, n (%)	No	41 (89.1%)	41 (93.2%)	0.761
		Yes	5 (10.9%)	3 (6.8%)	
	Urinary diseases, n (%)	No	45 (97.8%)	40 (90.9%)	0.331
		Yes	1 (2.2%)	4 (9.1%)	
	Digestive diseases, n (%)	No	40 (87.0%)	39 (88.6%)	1.000
		Yes	6 (13.0%)	5 (11.4%)	
	Neurological diseases, n (%)	No	45 (97.8%)	40 (90.9%)	0.331
		Yes	1 (2.2%)	4 (9.1%)	
	Bone and joint diseases, n (%)	No	27 (58.7%)	24 (54.5%)	0.854
		Yes	19 (41.3%)	20 (45.5%)	
	Other diseases, n (%)	No	35 (76.1%)	34 (77.3%)	1.000
		Yes	11 (23.9%)	10 (22.7%)	

BMI, body mass index; ASMI, appendicular skeletal muscle mass index; MCI, mild cognitive impairment; MoCA score, testing scores of Montreal cognitive assessment; M ± SD, mean ± standard deviation; M [P25, P75], median [25th percentile, 75th percentile]; n (%), individual number (percentage).

executive function, fluency, orientation, calculation, abstract thinking, delayed recall, visuospatial functions, naming and attention. The baseline basic measurements of the study subjects are shown in Table 1.

3.2 Relationship between cognitive function and diagnostic indicators of sarcopenia

The total population did not show a significant correlation. But in males, there was a significant positive correlation between cognitive function and grip strength ($r = 0.42$, $p < 0.05$), as shown in Figure 3A, no significant correlation between cognitive function and 6-m step speed ($p = 0.065$), calf circumference ($p = 0.74$) and SMI ($p = 0.38$). In females, there was no significant correlation between cognitive function and grip strength ($p = 0.063$), 6-m step speed ($p = 0.082$), calf circumference ($p = 0.083$) and SMI ($p = 0.52$).

3.3 Differences in cognitive function with different sarcopenia degrees

The total MoCA scores of individuals with different degrees of sarcopenia were further analyzed. According to the guidelines of AWGS of Figure 2, the non-sarcopenia group remained unchanged ($n = 46$), the population in the sarcopenia group was subdivided into possible sarcopenia ($n = 18$), sarcopenia ($n = 21$) and severe sarcopenia ($n = 5$). Compared to the non-sarcopenia group, the MoCA score progressively decreased with decreasing muscle mass and increasing muscle atrophy. There was a moderate correlation between the grade of sarcopenia and MoCA score ($r = -0.4$, $p < 0.001$), as shown in Figure 3B, indicating that individuals with severe sarcopenia are more likely to experience cognitive dysfunction.

3.4 Relationship between sarcopenia and cognitive dimension

Figure 3C shows the differences in terms of the total cognitive score and the 9 subitems. The MoCA scores of the sarcopenia and non-sarcopenia groups were 27.5 [26.3, 28.7] and 25.0 [24.0, 27.0] respectively, the MoCA scores were lower in the sarcopenia group ($p < 0.05$). Among the 9 subitems, the scores of 4 subitems of executive function, fluency, calculation and delayed recall in the sarcopenia group had a proportion of low scores in the distribution, with statistically significant differences ($p < 0.05$). The differences in orientation, abstract thinking, visuospatial perception, naming and attention were not statistically significant in the sarcopenia group relative to the non-sarcopenia group ($p > 0.05$).

3.5 Cognitive deterioration in the progression of muscle atrophy

After 12 weeks of naturalistic observation, there was a change in the degree of sarcopenia and cognitive functioning, the two groups were analyzed for potential influencing factors such as age, level of physical activity, as shown in Table 2. According to the 4 grades grouping of Figure 2, those who showed a progressing severity of muscle atrophy at the end of the 12 weeks were considered as the aggravation group ($n = 15$), and those who showed a relieving in grading was the alleviation group ($n = 12$). Although the two groups did not show a significant difference in the total MoCA scores, there was a significant change in the cognitive subdomains of fluency, as shown in Figure 4. The mean value of the change in fluency for alleviation group was an increase of 0.33 points, whereas the change of aggravation group was a decrease of 0.2 points, which was a statistically significant difference ($p = 0.038$).

4 Discussion

Through a cross-sectional and longitudinal study, we validated the correlation between sarcopenia and cognitive function, revealing changes in several cognitive subdomains. We demonstrated a moderate positive relationship between cognitive scores and grip strength in older males, suggesting grip strength as a reliable predictor of cognitive impairment. However, no significant differences were observed with calf circumference and muscle mass. Individuals with sarcopenia exhibited lower total MoCA cognitive, particularly in executive function, fluency, calculation and delayed recall. Cognitive ability further declined with increasing severity of muscle atrophy. The progression of muscle atrophy was associated with significant deterioration in cognitive functions, such as fluency.

More research confirmed that cognitive function was related to muscle strength rather than muscle mass (Moon et al., 2016; Menant et al., 2017), while cross-sectional studies have shown an association between overall cortical atrophy and low skeletal muscle mass in patients with cognitive impairment (Abellan van Kan et al., 2012). Both the AWGS and the Chinese Expert Consensus emphasize grip strength as an important indicator for screening and diagnosing sarcopenia (Chen et al., 2020). Grip strength was reliable and consistent with MCI and dementia, making it a useful tool for exploring the sarcopenia-cognition relationship (McGrath et al., 2020; Dudzińska-Griszek et al., 2017). A systematic evaluation revealed that six out of seven studies documented a significant correlation between grip strength, hand dexterity, and cognitive function in older adults (Kobayashi-Cuya et al., 2018). Recent research by Vancampfort et al. (2019) reported that lower grip strength in middle-aged and older adults was associated with an increased likelihood of MCI. Others have shown correlations between grip strength and cognitive subdomains such as MMSE (Dudzińska-Griszek et al., 2017), information processing speed and executive function (Hooghiemstra et al., 2017), stroop task performance and 6-item cognition test scores (Ramnath et al., 2018). This suggests that delaying cognitive decline is just as important as maintaining physical mobility. Therefore, we suggest that perhaps more attention should be paid to muscle work and daily mobility than to musculature.

The worsening of sarcopenia has been found to lead to poorer cognitive functioning, particularly in specific dimensions. Previous studies indicate that Chinese elderly with more severe sarcopenia have higher rates of MCI compared to those with possible sarcopenia (Hu et al., 2022). These findings suggest that the severity of sarcopenia increases the likelihood of cognitive impairment and negatively

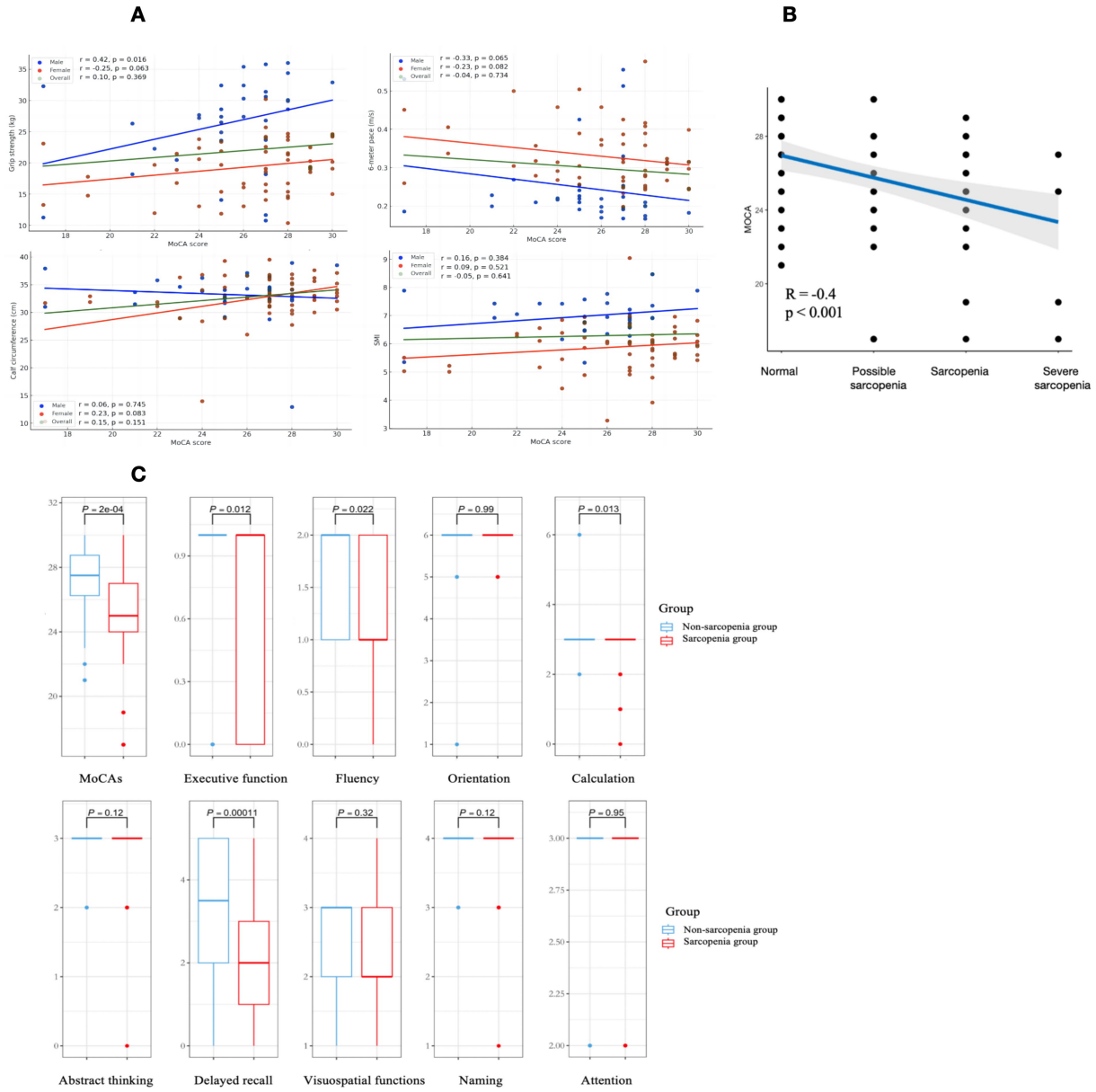

FIGURE 3
Graphical representation of data analysis images are labeled (A–C). (A) Demonstrates the relationship between cognitive function and diagnostic indicators of sarcopenia in the total population, males and females. Green, blue, and red are used to represent the overall population, males and females respectively. (B) Demonstrates the variation and correlation of the total MoCA score with those with different degrees of sarcopenia, with a significant negative correlation. (C) Demonstrates the differences between sarcopenia and healthy elderly on the cognitive subitem, with sarcopenia group performing worse on the executive function, fluency, calculation and delayed recall.

impacts cognitive function. Analyses from the CHARLS database showed associations between sarcopenia and cognitive functions such as orientation, memory, calculation and drawing (Hu et al., 2022). Other studies also reported correlations between sarcopenia and verbal fluency and recall abilities (Salinas-Rodriguez et al., 2021; Szlejf et al., 2019). Similar to these results, fluency and delayed recall were also significantly worse in our results, and we believe that fluency is associated with recall and expression, which explains why dementia and Alzheimer's disease occur at higher rates in people with sarcopenia (Beeri et al., 2021; Waite et al., 2021). Computational ability and logical agility were related to thought integration, it is thought that people with sarcopenia have reduced responsiveness and poorer executive performance, explaining their motor speed such as poor gait speed and decreased balance (Bahureksa et al., 2017).

The association between sarcopenia and cognitive impairment could be explained from physiological and functional links. Neuromuscular junction dysfunction (Moreira-Pais et al., 2022), neuronal hyperexcitability, dopaminergic dysfunction, muscle-brain axis (Arosio et al., 2023) and brain atrophy are among the regulatory processes associated with the pathophysiology of sarcopenia. Secondly, changes in the structure and function of the neuromuscular

TABLE 2 Longitudinal information for the aggravation group and alleviation group.

	Level	Alleviation group (n = 12)	Aggravation group (n = 15)	p value
Level of physical activity, n (%)	1/week	4 (33.3%)	4 (26.7%)	0.446
	2/week	2 (16.7%)	4 (26.7%)	
	3/week	5 (41.7%)	3 (20.0%)	
	4/week	1 (8.3%)	4 (26.7%)	
Age, M ± SD		83.8 ± 5.5	86.5 ± 4.1	0.143
Gender, n (%)	Male	4 (33.3%)	7 (46.7%)	0.759
	Female	8 (66.7%)	8 (53.7%)	
Height, M ± SD		156.1 ± 5.8	157.4 ± 10.2	0.708
Weight, M ± SD		59.4 ± 4.5	58.3 ± 11.3	0.753
BMI (kg/m^2), M ± SD		24.5 ± 3.0	23.4 ± 3.3	0.363
Degree of muscle atrophy at baseline, n (%)	Non-sarcopenia	0 (0%)	11 (73.3%)	0.001
	Possible	5 (41.7%)	0 (0%)	
	Sarcopenia	6 (50.0%)	4 (26.7%)	
	Severe	1 (8.3%)	0 (0%)	
Degree of muscle atrophy at 12 weeks, n (%)	Non-sarcopenia	9 (75.0%)	0 (0%)	0.001
	Possible	2 (16.7%)	7 (46.7%)	
	Sarcopenia	1 (8.3%)	3 (20.0%)	
	Severe	0 (0%)	5 (33.3%)	
Baseline MoCA, M ± SD		25.7 ± 2.3	25.7 ± 2.9	0.948
12-week MoCA, M [P_{25},P_{75}]		26.5 [25.0, 27.3]	25.0 [23.5, 27.5]	0.376
Difference of MoCA, M [P_{25},P_{75}]		0.5 [−1.0, 2.0]	0 [−2.5, 1.0]	0.302

BMI, body mass index; MoCA score, testing scores of Montreal cognitive assessment; M ± SD, mean ± standard deviation; M [P25, P75], median [25th percentile, 75th percentile]; n (%), individual number (percentage).

system. A prospective study in 2021 found moderate to severe parietal lobe atrophy, overall cortical atrophy, and medial temporal lobe atrophy were more common in the sarcopenia group compared to the non-sarcopenia group (Hsu et al., 2021). In the same year, a Korean longitudinal study involving 1,284 individuals over four years using magnetoencephalography found a greater decrease in gray matter volume in the sarcopenia group (Yu et al., 2021). This finding suggests that sarcopenia accelerates gray matter atrophy, low muscle mass is linked to reduced frontal, parietal, and occipital gray matter volumes, with significant parietal gray matter atrophy in sarcopenic patients. Finally, in terms of functional performance, older individuals with sarcopenia are more prone to falls as they experience a decline in balance, in turn the poorer the muscle control and balance of body, less active and more susceptible to sarcopenia, producing a slower gait speed (Kim and Won, 2019), decreased balance (Basile and Sardella, 2021), and psycho-emotional functioning (Lee et al., 2018; Ohta et al., 2019; Scisciola et al., 2021).

Although the causal relationship have not been confirmed, most studies have shown that the deterioration of physical function precedes cognitive function decline, such as gait speed and suffering from MCR (Basile and Sardella, 2021; Skillbäck et al., 2022). Therefore, strengthen physical activity are commended, which will not only improve muscle performance (Billot et al., 2020), but also affect cognition through the muscle-brain axis, such as L-6, which increases 100-fold during physical exercise (Pedersen and Febbraio, 2008). Post-exercise blood circulation also regulates brain functions and protects neurons from damage, increases neurogenesis and plasticity in the hippocampus, enhances the function of the prefrontal cortex (Scisciola et al., 2021; Nuzum et al., 2020). These can also be maintained through nutritional supplementation, creatine monohydrate supplementation may confer beneficial effects on cognitive function particularly in the domains of memory, attention time, and processing speed (Xu et al., 2024), Vitamin D and the Mediterranean diet can also help prevent dementia when providing the body with adequate nutrition (Cannataro et al., 2021; Psaltopoulou et al., 2013). We propose that sarcopenia aggravates cognitive impairment, lifestyle factors such as exercise and diet may improve the progressive aggravation.

Several limitations are in this study. First, although age and chronic diseases have been controlled, the baseline habitual physical activity of the participants was not assessed. In this study, only diagnostic indicators of sarcopenia were evaluated, using scales for cognitive function rather than objective indicators, such as brain imaging. Second, the causal relationship between muscle atrophy and cognitive impairment is difficult to explain. Last, the number of samples retained during the secondary collection was small. These need to be further refined in subsequent studies.

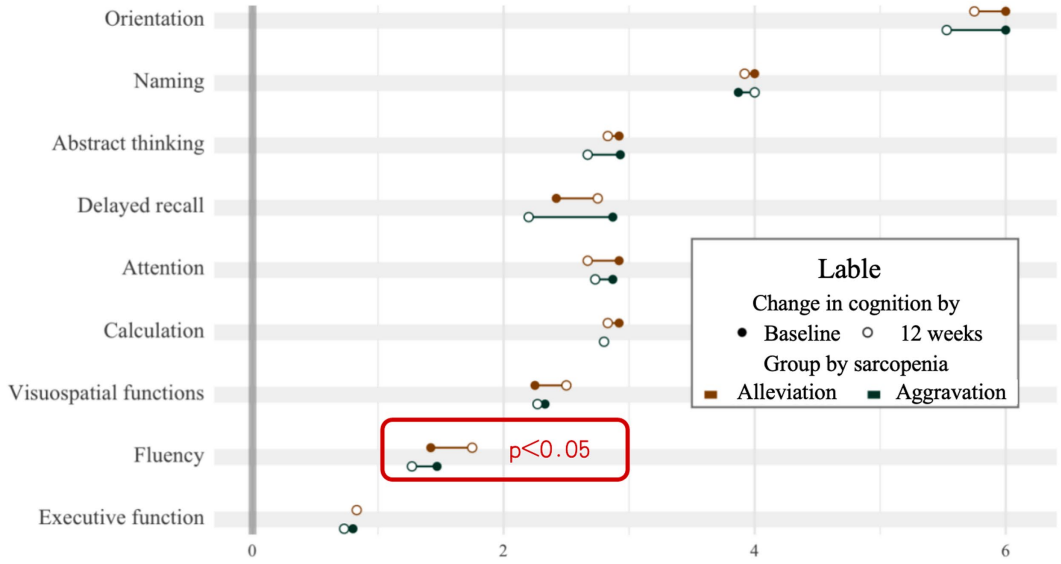

FIGURE 4
Changes in cognitive subdomains (baseline to 12 weeks).

5 Conclusion

There is a correlation between sarcopenia and cognitive function, with older individuals in sarcopenia performing worse in overall cognition as well as in executive function, fluency, calculation and delayed recall. Muscle atrophy was accompanied by cognitive decline after the exclusion of intervening factors such as age, chronic diseases and physical activity, particularly affecting verbal fluency. Sarcopenia and decreased muscle function may have dual implications for the exacerbation of cognitive impairment.

Data availability statement

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

Author contributions

XD: Investigation, Writing – original draft, Formal analysis, Writing – review & editing. YY: Conceptualization, Writing – review & editing. JL: Methodology, Writing – review & editing. XC: Investigation, Writing – review & editing. WS: Writing – review & editing. HY: Writing – review & editing. YL: 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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Development and validation of a nomogram for predicting motoric cognitive risk syndrome among community-dwelling older adults in China: a cross-sectional study

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Background: Motoric cognitive risk (MCR) syndrome is characterized by slow gait speed and subjective cognitive complaints (SCC) and increases the risk of dementia and mortality.

Objective: This study aimed to examine the clinical risk factors and prevalence of MCR in community-dwelling older adults, with the goal of developing and validating a nomogram model for developing prevention strategies against MCR.

Methods: We enrolled community-dwelling participants aged 60–85 years at Guangwai Community Health Service Center between November 2023 and January 2024. A total of 1,315 older adults who met the criteria were randomly divided into a training set ($n = 920$) and a validation set ($n = 395$). By using univariate and stepwise logistic regression analysis in the training set, the MCR nomogram prediction model was developed. The area under the receiver operator characteristic curve (AUC), calibration plots, and Hosmer-Lemeshow goodness of fit test were used to evaluate the nomogram model's predictive performance, while decision curve analysis (DCA) was used to evaluate the model's clinical utility.

Results: Education, physical exercise, hyperlipoidemia, osteoarthritis, depression, and Time Up and Go (TUG) test time were identified as independent risk factors and were included to develop a nomogram model. The model exhibited high accuracy with AUC values of 0.909 and 0.908 for the training and validation sets, respectively. Calibration curves confirmed the model's reliability, and DCA highlighted its clinical utility.

Conclusion: This study constructs a nomogram model for MCR with high predictive accuracy, which provides a reference for large-scale early identification and screening of high-risk groups for MCR.

KEYWORDS

motoric cognitive risk syndrome, gait, dementia, older adults, logistic regression, nomogram

1 Introduction

Due to the aging of the global population, there has been a steady rise in the number of older adults suffering from neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease, which emerged as a significant public health issue (1). China has around 25% of the global dementia population, resulting in heavy burdens on families and the healthcare system (2). Currently, there are no clinical treatments that will either cure or prevent the progressive course of dementia, although medication can delay the progression of dementia for some individuals (3). Therefore, it is crucial to focus on early identification of dementia and implement the preventive measures.

Motoric cognitive risk syndrome (MCR) is characterized by slow gait speed and subjective cognitive complaints in individuals without dementia or the absence of daily activity ability (4). Multiple studies have shown that slow gait speed and memory loss are common symptoms seen during the primary phases of dementia (5, 6). A large-scale survey of Japanese community-dwelling older adults revealed that the presence of MCR at baseline significantly increased the risk of developing dementia (7). Meanwhile, slow walking speed and MCR were also linked to a higher risk of death in the medium and long term (8). Therefore, considering MCR as a pre-dementia syndrome in older adults can identify timely older adults with high risk of dementia and implement appropriate intervention efforts to mitigate the rising incidence of dementia.

Numerous current studies have identified several clinic characteristics as risk factors that may predict the MCR risk, such as age, obesity, physical inactivity, hypertension, diabetes, and depression (9, 10). In a multi-center study, poor sleep, hearing, weak grip, and multiple falls were revealed as new connections with MCR (11). There are variations in the risk variables associated with MCR between high-income and middle-or low-income countries. In low-income areas of Malaysia, women residing in rural regions who had obesity, diabetes, heart disease, and cancer were shown to be more susceptible to MCR syndrome (12). In economically developed areas such as Mexico, older age, poor education level, having two or more comorbidities, and diabetes mellitus were related to the high risk of MCR (13).

However, the current literature has primarily concentrated on incidence and risk factors associated with MCR among older adults, merely a few studies have focused on developing a risk prediction model for MCR based on the large-scale sample in China (14). A nomogram is a graphical prediction model that is based on regression analysis and is capable of integrating multiple variables to estimate the probability of an event occurring and visually representing the results (15). Therefore, this study aimed to explore the factors associated associated with MCR and develop a risk prediction model based on a nomogram. This nomogram model will provide valuable evidence for the early identification of MCR syndrome and adopt early intervention and even reduce the incidence of dementia.

2 Materials and methods

2.1 Study design

The study is an cross-sectional investigation. The reporting of predictive model development and validation was standardized in accordance with Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TPIPOD) statement (16).

2.2 Setting and participants

This study recruited 1,780 community-dwelling older adults via convenience sample from November 2023 to January 2024 in the Guangwai community health service center in Xicheng District, Beijing City, China. The selection of sample size for clinical prediction modeling is typically conducted using the 10 events per variable (10 EPV) method (17). In other words, the required sample size is to ensure at least 10 events for each predictor variable. This study included 34 independent variables, and considering the 20% non-response rate, the minimum required sample size should be 408 cases. Ultimately, we surveyed a total of 1,780 older adults for this study to guarantee the precision of the prediction model and prevent issues like overfitting.

The inclusion criteria were as follows: (1) aged 60–85 years; (2) possessed normal hearing, reading, and writing abilities to complete cognition assessment; and (3) walked without assistive devices (e.g., wheelchairs, crutches). The exclusion criteria were as follows: (1) experienced rapid changes in body function within 30 days (e.g., falls, syncope, or delirium); (2) had dementia, severe cognitive impairment, or mental disorders; (3) the lack of electronic health records, cognitive function assessments, and motor function assessments. As shown in Figure 1, 465 participants were excluded as follows: loss of electronic health record (n = 358); lack of assessment of subject cognitive complaints (n = 62) or motor function (n = 32); diagnosis of dementia using the Mini-Mental State Examination (n = 13). We ultimately included and analyzed 1,315 participants.

This study was approved by the ethical review committee of Beijing Rectum Hospital (Beijing Er Long Lu Hospital) before collecting data (2024ELLHA-004-01). All participants provided their written informed consent to participate in this study.

2.3 Diagnosis of MCR syndrome

According to the original criteria proposed by Verghese et al. (4), MCR was defined as individuals with subjective cognitive complaints and slow gait speed, but without dementia or mobility disability. In our study, dementia was screened for through a combination of self-report, prior diagnostic history from health records, and the Mini-Mental State Examination (MMSE) (excluding individuals with an MMSE score of ≤17 points in the illiterate group, ≤20 points in the elementary school group, and ≤ 24 points in the junior school and above group) (18). Additionally, subject cognitive complaints were assessed using a self-reported question from the Geriatric Depression Scale-15: "Do you feel that your memory is poorer than that of your peers?" (19). A positive response to this question indicates the presence of subjective cognitive complaints. Gait speed was measured by the average time participants took to walk over a straight 3-meter path three times. Participants were asked to complete the gait test at their normal walking speed. The cutoff slow gait speed was 1.0 standard deviations or below age-and sex-appropriate mean values of gait speed in our study. In this study, the cut-off values for defining slow gait speed for different age groups (60–69, 70–79, and ≥ 80 years

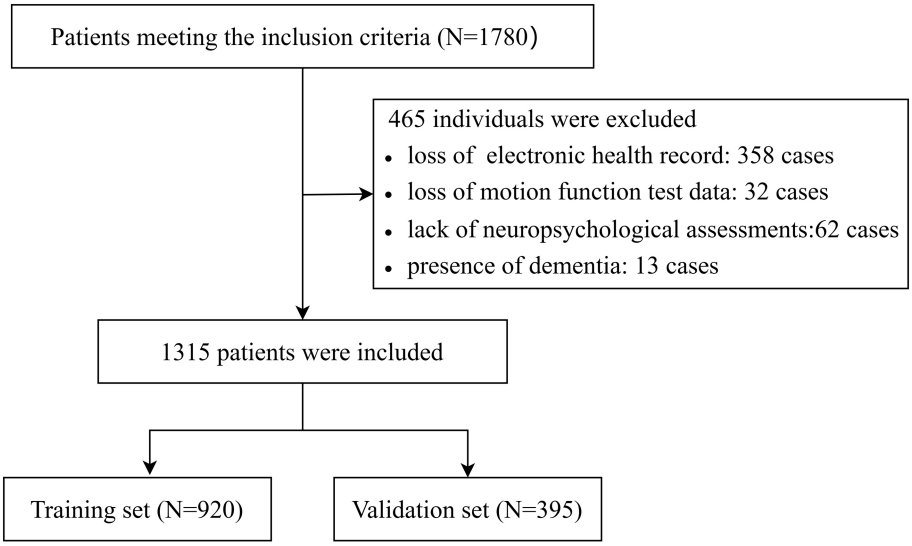

FIGURE 1
The flowchart of participant selection.

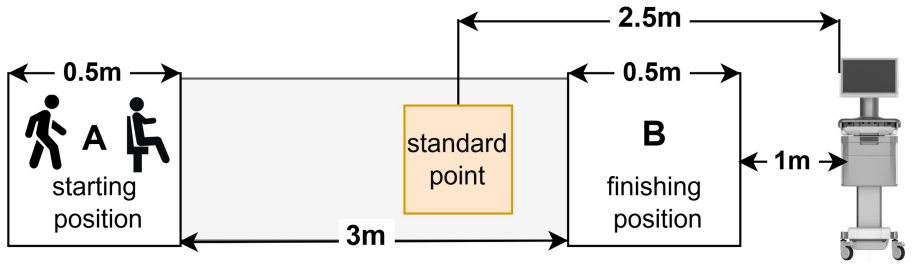

FIGURE 2
The process of motor function data collection.

old) were 0.857, 0.745, and 0.65 m/s in females and 0.812, 0.749, and 0.621 m/s in males.

2.4 Measurement of gait analysis test and the Time Up and Go test

In this study, we used the gait analysis test and the Time Up and Go (TUG) test to evaluate motor functions in older adults. Gait parameters and the TUG test were measured using a quantitative evaluation of the motor function system (ReadyGo, Beijing Zhongke Ruiyi Information Technology Co., Ltd.). The ReadyGo system, based on deep visual sensing and motion capture technology, accurately captures individuals' movement point cloud data, quantitatively assesses human kinematic characteristics and parameters using deep learning algorithms, and automatically generates reports directly. All tests were conducted in a bright indoor environment. After inputting the ID number, age, sex, and education level of the older adults into the equipment, a community doctor explained the process of the gait test and TUG test to the older adults and instructed them to complete it (Figure 2). For the gait analysis test, participants were asked to stand in the starting position A. When the community doctor gave the "start" instruction, they walked at their usual pace on a 3-meter walkway to the finishing position B without using any assistive devices, then turned around and walked back to the starting position A. The test is completed by walking three times without interruption. Upon completion of the test, the equipment autonomously computes the spatiotemporal gait parameters. These included stance phase (%GC), swing phase (%GC), double support phase (%GC), step width (m), step stride (m), step height (m), step cadence (steps/min), gait speed (m/s), stride speed (m/s), swing speed (m/s), turn time (s). For the TUG test, older adults were asked to stand up from a chair with trunk support and armrests in the starting position A, walk on a 3 m straight lane at their usual pace to the finishing position B, then turn around, walk back to the starting position A, and sit down. The whole test process only walked once, and the equipment automatically recorded and generated the TUG test data, which included test time (s), sit-to-stand time (s), stand-to-sit time (s), and turn time (s).

2.5 Neuropsychological assessments

Cognitive function was assessed using the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment

(MoCA). Community physicians trained by experienced clinical psychologists performed neurological assessments of older adults in a quiet environment. First, a community doctor used the MMSE to screen for dementia (20). Then, MoCA was used to evaluate global cognitive status with a total score ranging from 0 to 30. The MoCA evaluated a variety of cognitive areas, such as visuospatial and executive function, naming, memory, attention, language, abstraction, delayed recall, and orientation, and presented excellent sensitivity and specificity to detect cognitive impairment (21). To account for the influence of education, one point was added to the MoCA scores of participants with 12 years of education or less, and a total MoCA score of less than 26 was considered evidence of mild cognitive impairment (22).

2.6 Other measurements

Building on the previous findings (23), demographic characteristics, lifestyle factors, and chronic disease were selected from the residents' electronic health records and physical examination records as covariates to identify the risk factors in this study. Demographic characteristics included age, gender, education level (elementary school or below/middle/college or above), marital status (married/others), living condition (solitary/non-solitary). Lifestyle factors comprised sleep issues (no/yes), sleep duration (<6 h/≥6 h), smoking status (current smoker or former/non-smoker), drinking frequency (never/occasionally/often), physical exercise frequency (never/occasionally/often), body mass index (BMI; kg/m^2), and abdominal obesity (no/yes). Sleep issues typically include difficulty sleeping, insomnia, excessive dreams, night wakings, and early wake-up. BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2). Abdominal obesity was defined as waist circumference (WC) of >90 cm in men and > 85 cm in women. In addition, previously diagnosed chronic diseases by self-report or the history of the residents' electronic health records and physical examination records were investigated, including hypertension, diabetes mellitus, hyperlipoidemia, and osteoarthritis disease. Moreover, this study assessed the degree of depression among older adults using the Geriatric Depression Scale (GDS), which has good reliability and validity in screening depression among a large-scale survey of older adults (24). The GDS-15 scored 0–15, with higher scores indicating more severe depressive symptoms. We implemented a cut-off score of >6 to differentiate individuals with depression from those without depression (25).

2.7 Statistical methodology

Data analysis was applied using R software (version 3.3.4) and SPSS 25.0. Non-normally distributed continuous variables were expressed as medians with interquartile ranges, and the Mann–Whitney test was employed for inter-group comparison. Categorical variables were reported as number and percentage (%), and inter-group comparison was conducted using χ^2 tests or Fisher's test as appropriate. Subsequently, the variables that showed statistical significance in the univariate analysis in the training group were included in the multivariate logistic regression. Co-linearity among the variables was examined using the variance inflation factors (VIF) with a threshold of 5 (26). We excluded highly associated variables according to VIF before using multivariate logistic regression. The multivariate logistic regression was used to determine independent risk variables, and only those with a statistical significance level of p-values <0.05 were eventually chosen. Simultaneously, the 95% confidence interval (CI), odds ratio (OR), and p-value of independent risk factors were calculated. The regression coefficients' results were employed to construct a risk prediction model for MCR, which is represented by a nomogram. The discrimination capability of the model was evaluated using the area under the receiver operating characteristic (ROC) curve (AUC). The Hosmer-Lemeshow goodness-of-fit test and calibration curves were implemented to assess the concordance between predicted and observed probabilities in the nomogram. Additionally, the predictive nomogram's clinical validity was evaluated using decision curve analysis (DCA).

3 Results

3.1 Characteristics of study participants

Participant characteristics of the study are presented in Table 1. Overall, the study consisted of 1,315 participants with an average age of 69.59 ± 5.45, and the participation of males (56.5%) in the study was higher than the females (43.5%). Among the 1,315 participants, 123 older adults were diagnosed with MCR. The overall prevalence of MCR syndrome was 9.35%. As shown in Table 1, most of the study characteristics were significantly different (p <0.05) between older adults with and without MCR in the training set, including education, sleep duration, sleep issue, BMI, physical exercises, abdominal obesity status, hyperlipoidemia status, osteoarthritis status, depression status, and MoCA. However, some study characteristics were similar with no statistically significant difference (p >0.05), including age, gender, marital status, living condition, smoking status, drinking frequency, hypertension status, and diabetes status.

3.2 Comparison of motor function between the MCR and non-MCR groups

As shown in Table 2, during the gait analysis test, significant differences were seen between the MCR and non-MCR groups in all gait variables (p <0.05), including stance phase, swing phase, double support phase, step width, step stride, step height, step cadence, gait speed, stride speed, swing speed, and turn time. During the TUG test, there were significant differences (p <0.05) between the groups for the MCR and non-MCR groups for TUG test time, sit-to-stand time, stand-to-sit time, and turn time.

3.3 Multivariate logistic regression analysis

Taking community-dwelling older adults with MCR syndrome as the dependent variable (assignment: absence = 0, presence = 1), and the statistically significant factors in the univariate analysis as the independent variables, multivariate logistic regression analysis was performed. From the list of candidate variables, 11 gait variables (stance phase, swing phase, double support phase, step width, step

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TABLE 1 Baseline characteristics of participants.

Variables	Training set (n = 920)			Validation set (n = 395)		
	Non-MCR (n = 834)	MCR (n = 86)	p	Non-MCR (n = 358)	MCR (n = 37)	p
Age, mean ± SD	69.00 (66.00, 73.00)	69.00 (66.00, 72.00)	0.957	70.00 (66.00, 73.00)	71.00 (68.00, 74.00)	0.070
Gender, n (%)			0.626			0.899
Male	462 (55.40)	50 (58.14)		209 (58.38)	22 (59.46)	
Female	372 (44.60)	36 (41.86)		149 (41.62)	15 (40.54)	
Education, n (%)			<0.001			<0.001
Elementary or below	40 (4.80)	12 (13.95)		21 (5.87)	8 (21.62)	
Middle[a]	540 (64.75)	70 (81.40)		222 (62.01)	25 (67.57)	
College or above	254 (30.46)	4 (4.65)		115 (32.12)	4 (10.81)	
Marital status, n (%)			0.557			0.782
Married	747 (89.57)	75 (87.21)		322 (89.94)	33 (89.19)	
Others[b]	98 (10.43)	11 (12.79)		36 (10.06)	4 (11.8)	
Living condition, n (%)			0.548			0.475
Non-solitary	89 (10.67)	11 (12.79)		38 (10.61)	2 (5.41)	
Solitary	745 (89.33)	75 (87.21)		320 (89.39)	35 (94.59)	
Sleep issue, n (%)			0.005			0.662
No	453 (54.32)	33 (38.37)		180 (50.28)	20 (54.05)	
Yes	381 (45.68)	53 (61.63)		178 (49.72)	17 (45.95)	
Sleep duration, n (%)			<0.001			0.152
<6 h	455 (54.56)	64 (74.42)		198 (55.31)	25 (67.57)	
≥6 h	379 (45.44)	22 (25.58)		160 (44.69)	12 (32.43)	
BMI (kg/m^2), median (IQR)	25.06 (23.44, 27.03)	26.70 (24.23, 28.22)	0.002	24.80 (23.11, 26.92)	25.10 (24.03, 27.99)	0.199
Smoking, n (%)			0.337			0.436
No	653 (78.6)	66 (74.2)		289 (80.73)	28 (75.68)	
Yes	178 (21.4)	23 (25.8)		69 (19.27)	9 (24.32)	
Drinking, n (%)			0.346			0.708
Never	628 (75.6)	61 (68.5)		282 (78.77)	29 (78.38)	
Occasionally	125 (15.0)	17 (19.1)		46 (12.85)	5 (13.51)	
Often	78 (9.4)	11 (12.4)		30 (8.38)	3 (8.11)	
Physical exercise, n (%)			<0.001			<0.001
Never	84 (10.07)	25 (29.07)		38 (10.61)	10 (27.03)	
Occasionally	272 (32.61)	41 (46.67)		121 (33.80)	18 (48.65)	
Often	478 (57.31)	20 (23.26)		199 (55.59)	9 (24.32)	
Abdominal obesity, n (%)			0.001			0.024
No	502 (60.4)	38 (42.7)		223 (62.29)	16 (43.24)	
Yes	329 (39.6)	51 (57.3)		135 (37.71)	21 (56.76)	
Hypertension, n (%)			0.113			0.192
No	345 (41.37)	28 (32.56)		156 (43.58)	12 (32.43)	
Yes	489 (58.63)	58 (67.44)		202 (56.42)	25 (67.57)	
Diabetes mellitus, n (%)			0.152			0.013
No	586 (70.26)	54 (62.79)		255 (71.23)	19 (51.35)	
Yes	248 (29.74)	32 (37.21)		103 (28.77)	18 (48.65)	

(Continued)

TABLE 1 (Continued)

Variables	Training set (n = 920)			Validation set (n = 395)		
	Non-MCR (n = 834)	MCR (n = 86)	p	Non-MCR (n = 358)	MCR (n = 37)	p
Hyperlipoidemia, n (%)			<0.001			<0.001
No	615 (73.74)	39 (45.35)		289 (80.73)	17 (45.95)	
Yes	219 (26.26)	47 (54.65)		69 (19.27)	20 (54.05)	
Osteoarthritis, n (%)			<0.001			<0.001
No	805 (96.52)	71 (82.56)		351 (98.04)	29 (78.38)	
Yes	29 (3.48)	15 (17.44)		7 (1.96)	8 (21.62)	
Depression, n (%)			0.005			0.086
No	745 (89.33)	68 (79.07)		320 (89.39)	29 (78.38)	
Yes	89 (10.67)	18 (20.93)		38 (10.61)	8 (21.62)	
MoCA, median (IQR)	26.00 (24.00, 28.00)	25.00 (23.00, 27.00)	<0.001	26.00 (25.00, 28.00)	26.00 (24.00, 28.00)	0.165

[a]Middle: junior school, technical secondary school, high school.
[b]Others: such us divorced, widowed, or single.
BMI, Body mass index; MoCA, the Montreal Cognitive Assessment.

TABLE 2 Comparison of motor function between the MCR and non-MCR groups.

Variables	Training set (n = 920)			Validation set (n = 395)		
	Non-MCR (n = 834)	MCR (n = 86)	p	Non-MCR (n = 358)	MCR (n = 37)	p
Gait analysis, median (IQR)						
Stance phase (%GC)	67.47 (66.10, 68.76)	68.97 (67.86, 70.53)	<0.001	67.25 (66.13, 68.52)	69.06 (68.02, 70.01)	<0.001
Swing phase (%GC)	32.52 (31.23, 33.89)	31.02 (29.47, 32.14)	<0.001	32.73 (31.47, 33.86)	30.93 (29.98, 31.98)	<0.001
Double support phase (%GC)	35.14 (32.91, 37.38)	38.19 (36.75, 40.57)	<0.001	35.27 (33.03, 37.53)	38.52 (36.76, 40.01)	<0.001
Step width (m)	0.14 (0.12, 0.15)	0.15 (0.13, 0.16)	<0.001	0.13 (0.12, 0.15)	0.14 (0.13, 0.17)	0.001
Step stride (m)	1.11 (1.01, 1.20)	0.92 (0.80, 0.97)	<0.001	1.11 (1.03, 1.20)	0.89 (0.74, 0.95)	<0.001
Step height (m)	0.12 (0.10, 0.13)	0.10 (0.09, 0.11)	<0.001	0.12 (0.10, 0.13)	0.10 (0.09, 0.11)	<0.001
Step cadence (steps/min)	109.19 (102.94, 116.25)	100.00 (92.85, 104.41)	<0.001	109.19 (102.94, 116.25)	102.94 (95.00, 109.19)	<0.001
Gait speed (m/s)	0.97 (0.87, 1.07)	0.71 (0.64, 0.79)	<0.001	0.99 (0.90, 1.09)	0.69 (0.64, 0.79)	<0.001
Stride speed (m/s)	1.00 (0.91, 1.11)	0.74 (0.66, 0.81)	<0.001	1.01 (0.93, 1.11)	0.74 (0.67, 0.80)	<0.001
Swing speed (m/s)	2.41 (2.19, 2.62)	1.86 (1.68, 2.04)	<0.001	2.45 (2.23, 2.65)	1.86 (1.72, 2.03)	<0.001
Turn time (s)	1.30 (1.10, 1.53)	1.66 (1.43, 2.06)	<0.001	1.30 (1.13, 1.50)	1.66 (1.40, 2.16)	<0.001
TUG test, median (IQR)						
Test time (s)	10.45 (9.21, 11.97)	14.15 (12.44, 15.84)	<0.001	10.37 (9.28, 11.77)	13.86 (12.56, 15.13)	<0.001
Sit-to-stand time (s)	0.56 (0.46, 0.70)	0.66 (0.53, 0.83)	<0.001	0.56 (0.46, 0.70)	0.56 (0.50, 0.73)	0.630
Stand-to-sit time (s)	0.53 (0.46, 0.66)	0.60 (0.51, 0.80)	<0.001	0.53 (0.46, 0.66)	0.60 (0.50, 0.73)	0.071
Turnaround time (s)	1.23 (0.93, 1.56)	1.56 (1.26, 1.95)	<0.001	1.16 (0.90, 1.46)	1.56 (1.36, 2.03)	<0.001

TUG test: Time Up and Go test; %GC: Percent of gait cycle.

stride, step height, step cadence, gait speed, stride speed, swing speed, turn time) were excluded from multivariate logistic regression analysis due to their high multicollinearity (threshold VIF > 5) with outcome variables. As shown in Table 3, multivariate logistic regression analysis showed that education, physical exercise, hyperlipoidemia, osteoarthritis disease, depression, and TUG test time were independent factors for MCR syndrome.

3.4 Nomogram development and validation

Based on the results of multivariable logistic regression, a nomogram was developed to predict the probability of MCR in community-dwelling older adults was constructed, as shown in Figure 3. The predictors included education, physical exercise, hyperlipoidemia, osteoarthritis, depression, and TUG test time. Each

TABLE 3 Multivariable logistic regression analysis of independent risk factors affecting the occurrence of MCR.

Variables	B	SE	Z	p-value	OR (95%CI)
Intercept	−8.76	0.89	−9.79	<0.001	0.00 (0.00 ~ 0.00)
Education (college and above)					
Elementary or below	1.87	0.55	3.42	<0.001	6.47 (2.22 ~ 18.88)
Middle	2.74	0.68	4.02	<0.001	15.54 (4.09 ~ 59.14)
Physical exercise (never)					
Occasionally	−0.53	0.37	−1.43	0.153	0.59 (0.29 ~ 1.22)
Often	−1.74	0.40	−4.31	<0.001	0.18 (0.08 ~ 0.39)
Hypertension	1.01	0.29	3.53	<0.001	2.74 (1.56 ~ 4.80)
Osteoarthritis	1.26	0.44	2.86	0.004	3.52 (1.49 ~ 8.36)
Depression	1.27	0.36	3.56	<0.001	3.55 (1.77 ~ 7.13)
TUG test time	0.40	0.05	8.10	<0.001	1.50 (1.36 ~ 1.65)

OR, Odds Ratio; CI, Confidence Interval.

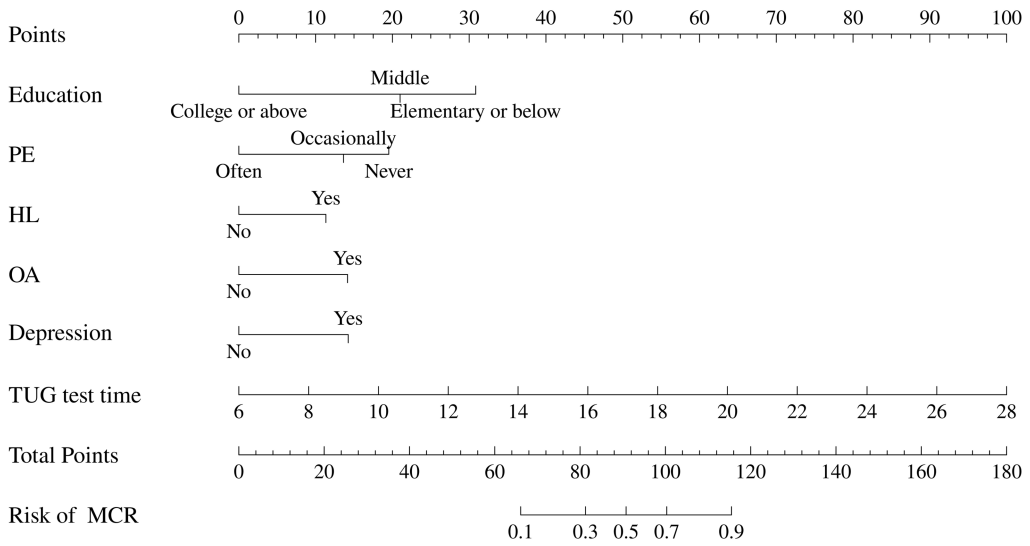

FIGURE 3
Nomogram for predicting the risk of MCR. The nomogram is employed by identifying the position of each variable on the corresponding axis and drawing a line to the points axis for the number of points. Then, the risk of motoric cognitive risk syndrome at the lower line of the nomogram is calculated by summing the values of all the variables. PE, physical exercise; HL, hyperlipoidemia; OA, osteoarthritis; TUG, Time Up and Go.

factor has a corresponding score, and the cumulative sum of the corresponding scores for all factors was the total score, which correlates with the probability of MCR.

The area under the ROC curve (AUC) of the nomogram was 0.909 (95% CI: 0.880–0.939), and 0.908 (95% CI: 0.863–0.953), respectively in the training and validation set, indicating that the model had good discrimination, as shown in Figures 4A,B. The calibration curves align well with the ideal line of the model in both the training set (Figure 5A) and the validation set (Figure 5B), demonstrating that the prediction probability of the model was consistent with the actual probability. Furthermore, the results of the Hosmer-Lemeshow goodness of fit test indicated that good fitting was obtained in both training ($\chi^2 = 2.47$, $p = 0.96$) and validation ($\chi^2 = 6.86$, $p = 0.55$) set. In the training group, the sensitivity and specificity of the model were 88.8 and 79.9%, positive-predictive value (PPV) was 97.5%, and negative-predictive value (NPV) was 33.5%, indicating that the model had good accuracy. For the validation set, the nomogram showed a sensitivity of 92.2% and a specificity of 70.3%, PPV of 96.8% and an NPV of 48.1%, further evidencing its robustness.

3.5 Clinical practice

The DCA for the nomogram was conducted to proved clinical usefulness of the nomogram model. As shown in Figure 6A, the net benefit of the training model is higher in the threshold probability interval of 5–75%. Meanwhile, as shown in Figure 6B, the net benefit of the validation model is higher in the threshold probability interval of 5–90%. According to the decision curve, the nomogram model had superior net benefit and predictive accuracy.

4 Discussion

In this study, education, physical exercise, hyperlipoidemia, osteoarthritis, depression, and TUG test time were selected as predictor factors to develop a nomogram for predicting the risk of MCR in community-dwelling older adults. Our study showed a MCR syndrome incidence rate of 9.35%, which is lower than the previously reported rate of 12.7% in another Chinese cohort study (27). This

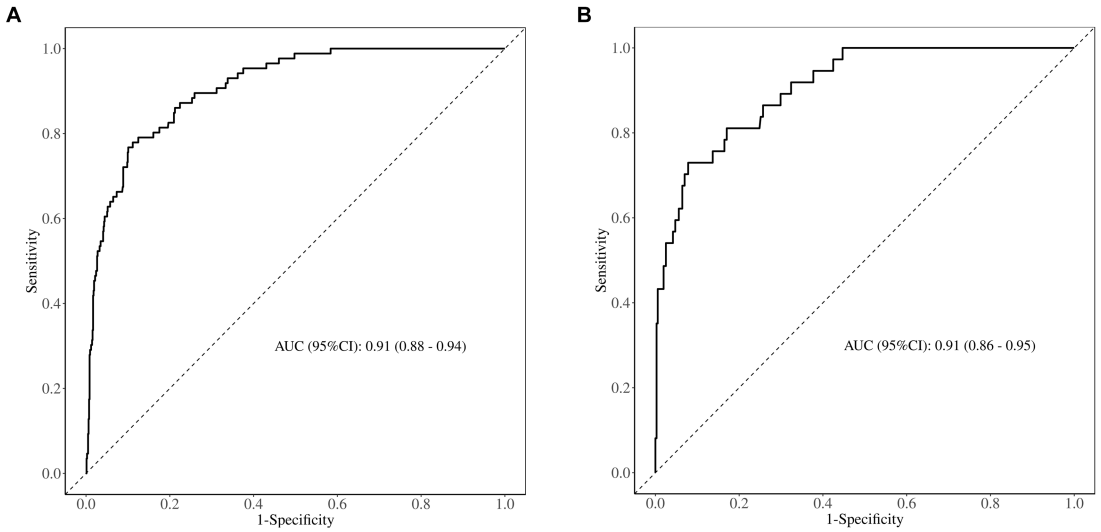

FIGURE 4
ROC curve of the predictive model for (A) the training set and (B) the validation set. AUC, area under the ROC curve.

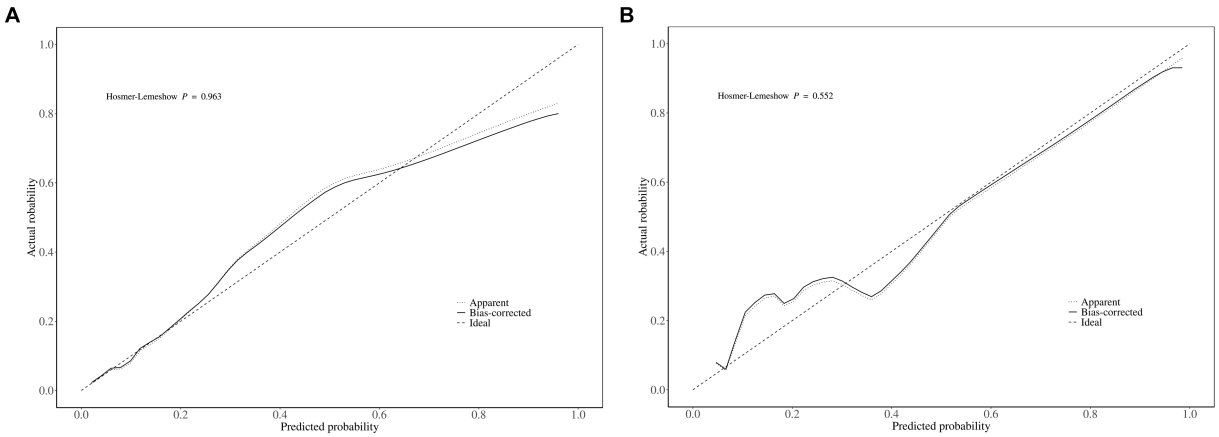

FIGURE 5
The calibration curves of the MCR nomogram model in (A) the training set and (B) the validation set. Notably, the calibration curve nearly overlays the ideal line, thereby indicating a high consistency between the predicted probabilities and the actual observed incidences of MCR.

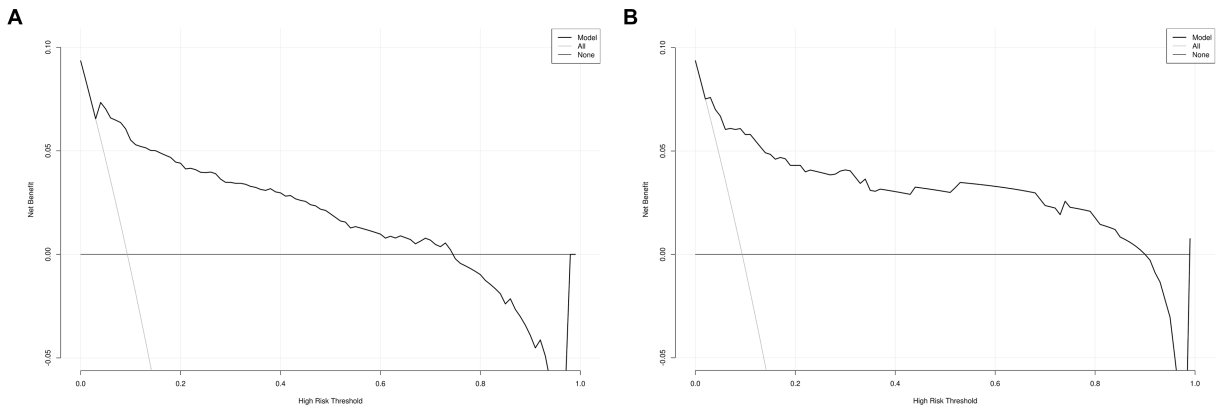

FIGURE 6
Decision curve for MCR nomogram model in the training (A) the training set and (B) the validation set.

might be due to the fact that our study sample was all recruited from communities located in a better-developed city. Most older adults lived a high quality of life with a high level of education, which maintained strong physical and mental capabilities, resulting in a lower prevalence of MCR in our study.

The study revealed that lower educational status was associated with MCR. Various studies have reported that lack of education is related to a higher prevalence of MCR. In a cross-sectional study involving 17,577 participants from Colombian reported that lack of education is related to a higher risk of MCR (28). Similarly, a prospective panel study done in Mexico older adults reported a lower educational status was associated with the presence of MCR (13). Cognitive reserve is recognized as a safeguard against cognitive decline, as it effectively slows down the advancement of neurodegenerative disorders by conserving brain metabolism and enhancing connection in the temporal and frontal regions (29). On the other hand, physical exercise also was associated with MCR. Building on previous relevant studies, the lack of physical activity increased the risk of MCR (9, 29, 30). Regular physical activity can effectively help older adults improve or delay the decline of physical function and mobility and reduce the risk of injury associated with falls (31). What is more, physical activity can enhance angiogenesis and neurogenesis, improve cognitive function, and effectively slow down the progression of neurodegenerative diseases (32–34). Therefore, community family doctors can regularly share exercise videos, providing scientific guidance and supervision to older adults based on their health status and exercise habits. In addition, community health service centers can cooperate with other community organizations to carry out regular group exercise activities, such as morning exercises and square dances, so as to stimulate their enthusiasm for physical exercise.

In addition, this study showed a higher prevalence of MCR among older adults with chronic diseases such as hyperlipidemia, osteoarthritis, and depression. Hyperlipidemia, as a prominent manifestation of the metabolic syndrome, has been identified as a major trigger of cognitive decline and may be affecting overall physical function as well (35, 36). Osteoarthritis, the most common joint disease in older adults, is a significant risk factor for falls and disability (37). Osteoarthritis causes damage and dysfunction of the joint nervous system, affects tissue blood supply, interferes with position sense and pain transmission, and prevents the body from correcting abnormal loads, which in turn leads to joint destruction, so that the brain morphology and physical activity will be altered (38). Our finding aligns with prior research, indicating a strong correlation between depressive symptoms and quantitative gait impairment (19). According to cross-sectional research, MCR was associated with almost 3-fold odds of cognitive impairment in middle-aged adults with depression (39). Additionally, Xu et al. (40) discovered that depression was significantly associated with MCR in both cross-sectional analysis and prospective analysis. Similar to MCI and dementia, several studies have also reported that depression usually occurs in conjunction with mild cognitive impairment, which also accelerates the progression of the spectrum of neurodegenerative diseases (41). Therefore, community health centers can establish health records and classify and manage older adults with chronic diseases through the family doctor team, regular health checkups and record assessments, give reasonable dietary guidance, and develop regular physical exercise programs.

Moreover, this study found that community-dwelling older adults with MCR took longer time to complete the TUG test. The TUG test, as a measure of functional activity with a wide range of clinical utility, has demonstrated excellent reliability and validity in identifying older adults prone to falls (42). Previous studies have also investigated patients with MCR who require more time to complete the TUG test compared to patients with mild cognitive impairment (43). In addition, previous studies have shown that the total time required to complete the TUG test was correlated with cognitive performance, and there was a strong correlation between prefrontal cognitive functioning and changes in TUG subtasks, especially those tasks that require transitions (sit-to-stand, turn-to-walk, and turn-to-sit) (44).

There are numerous advantages to our study. First of all, this study was the first large-scale screening of MCR among community-dwelling older adults in China. Based on the residents' electronic health records, this study included demographic characteristics, lifestyle factors, and self-reported chronic disease as covariates, which greatly shortens the time of large-scale screening in the community environment. Second, the quantitative evaluation of a motor function system used in our study allowed researchers to obtain more accurate and complex gait data compared to manual assessment. Furthermore, the gait analysis techniques significantly enhanced the efficiency and feasibility of large-scale screening by eliminating the need for wear and calibration. Moreover, nomogram prediction models have been extensively used in clinical research, particularly for prognosticating disease outcomes. Previous studies had mostly emerged to explore the prevalence risk factors of MCR (10, 11, 27, 45), only a few studies have focused on constructing the prediction model of MCR (14). This study developed a low-cost and user-friendly nomogram model of MCR based on six easily obtained variables, with higher accuracy and robust predictive capability than previous research.

Our study also has several limitations. Firstly, this investigation was cross-sectional design, so no causal relationships could be demonstrated. In order to further validate the model, future research should concentrate on longitudinal studies. Second, because this study only included participants from a single community health center, there may be selection bias, which could limit the applicability of the findings to other settings or populations. Future research could continue to recruit more older adults or cooperate with other centers to bolster the reliability and generalizability of the results. Finally, this study relied solely on self-reported subjective cognitive complaints that introduce a potential for recall bias and subjective interpretation, impacting the reliability of MCR diagnosis. Hence, it is warranted that objective cognitive complaint assessments be incorporated into future research in order to substantially enhance the study.

5 Conclusion

This study constructed a nomogram model for predicting the MCR risk of the older adults in the community by using six critical preoperative predictors. The ROC curve, calibration curve, and goodness-of-fit test results, which have been verified in both the training and validation databases, demonstrate that it has both good prediction ability and accuracy. Furthermore, the DCA curve demonstrates that it is clinically feasible and can be employed as a valuable instrument for the early detection and

intervention of MCR in older adults, particularly in primary healthcare institutions.

Data availability statement

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

Ethics statement

The studies involving humans were approved by the Beijing Rectum Hospital (Beijing Er Long Lu Hospital). 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. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

HY: Conceptualization, Data curation, Investigation, Methodology, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. YJ: Investigation, Methodology, Validation, Visualization, Writing – original draft. YL: Data curation, Investigation, Writing – original draft. LB: Data curation, Investigation, Writing – original draft. SZ: Data curation, Funding acquisition, 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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The mitochondrial function of peripheral blood cells in cognitive frailty patients

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Background: Cognitive frailty (*CF*), characterized by the coexistence of physical frailty and cognitive impairment, is linked to increased morbidity and mortality in older adults. While *CF* has been linked to multiple physiological and lifestyle factors, the underlying biological mechanisms remain poorly understood. This study investigated the risk factors for *CF* and explored the relationship between mitochondrial function and *CF* in hospitalized patients.

Methods: A total of 279 hospitalized individuals were recruited from December 2020 to August 2022, conducted comprehensive clinical assessments, and collected peripheral blood samples. *CF* was evaluated using the Physical Frailty Phenotype and Montreal Cognitive Assessment scales. Nutritional status was assessed with the Mini Nutritional Assessment, and depression was measured using the Geriatric Depression Scale. DNA was obtained from the peripheral blood and interrogated for mitochondrial DNA copy number (mtDNAcn). Peripheral blood mononuclear cells isolated from peripheral blood were examined for respiratory function and reactive oxygen species (ROS) levels. Additionally, plasma samples were analyzed for inflammatory markers and Carnitine Palmitoyltransferase II (CPT2).

Results: Among the participants, 90 were classified as *CF* and 46 as non-*CF*. Logistic regression analysis revealed that increased age (OR 1.156, 95% CI 1.064–1.255), lower educational attainment (OR 0.115, 95% CI 0.024–0.550), malnutrition (OR 0.713, 95% CI 0.522–0.973), and higher depression scores (OR 1.345, 95% CI 1.065–1.699) were significantly associated with *CF*. The independent t tests and Mann–Whitney U tests showed the *CF* group exhibited impaired mitochondrial function, characterized by reduced mtDNAcn and respiratory activity, coupled with elevated ROS, interleukin-6, and CPT2 levels compared with the non-*CF* group. After adjusted for age, sex, and BMI, compared with non-*CF* group, the OR values for the *CF* group of mtDNAcn and ROS were 0.234 (95% CI = 0.065–0.849) (p = 0.027) and 1.203 (95% CI = 1.075–1.347) (p = 0.001), respectively. The Sensitive analysis showed that the area under curve values for mtDNAcn and ROS were 0.653 and 0.925.

Conclusion: Age, lower educational attainment, malnutrition, and depression are significant risk factors for CF. Moreover, mitochondrial dysfunction, characterized by decreased mtDNAcn, impaired respiratory function and increased ROS levels appears to be a critical phenotype of *CF*.

KEYWORDS

aging, cognitive frailty, mitochondrial function, peripheral blood cells, risk factors

1 Introduction

Since the early 21st century, the world has transitioned into an aging society, prioritizing healthy aging (Clegg et al., 2013; United Nations Department of Economic and Social Affairs, Population Division, 2024). And preserving cognitive function plays a crucial role in maintain health throughout the aging process (Davies et al., 2018). Generally, cognitive impairment is commonly recognized as a hallmark symptom in individuals with dementia, such as Alzheimer's disease and vascular dementia. However, recent advancements in geriatric medicine have increasingly recognized cognitive frailty (*CF*), as a hidden yet pervasive syndrome, posing a significant threat to the cognitive health of many older adults. *CF*, introduced as a new concept in 2013, is characterized by the simultaneous presence of both physical frailty and mild cognitive impairment (MCI) (Panza et al., 2018; Kelaiditi et al., 2013; Sugimoto et al., 2022). While both *CF* and dementia in older adults involve cognitive impairment, they exhibit significant differences in clinical characteristics and pathological features. *CF* is defined as stable MCI that does not progress to dementia, whereas typical dementia is marked by a progressive decline in cognitive functions (Nader et al., 2023). Additionally, *CF* encompasses physical frailty, while dementia-related cognitive impairments tend to advance rapidly and are irreversible, with imaging studies revealing distinct changes such as brain atrophy and amyloid deposits (Kocagoncu et al., 2022).

Previous studies have shown that *CF* significantly increases risks for older adults, including falls, depression, malnutrition, disability, and higher hospitalization rates, positioning it as a predictor of adverse outcomes in this demographic (Guo X. et al., 2023; Zou et al., 2023; Tang et al., 2023; Qiu et al., 2023). Individuals with *CF* have a higher mortality rate compared with healthy older adults, those with MCI, and frail subjects, which places a substantial burden on society (Rivan et al., 2021; Vargas-Torres-Young et al., 2022). However, due to its potential reversibility, identifying risk factors and biomarkers for *CF*, coupled with targeted interventions, can facilitate healthier aging.

CF is reversible and may be mitigated through several interventions (Ibrahim et al., 2024; Hou et al., 2024; Tam et al., 2022; Li et al., 2022; Murukesu et al., 2020). Numbers of studies demonstrated that physical activity can ameliorate *CF*. A 24-month randomized controlled trial study reported that an organized moderate-intensity exercise can reduce *CF* (Liu et al., 2018). And another randomized controlled trial revealed that practicing mindfulness-based Tai Chi Chuan can boost both cognitive and physical functions in older adults (Jiayuan et al., 2022). Gutiérrez-Reguero et al. (2024) found that physical exercise can markedly enhance cognitive function, while dietary intervention alone cannot significantly improve cognitive frailty. Recently, Ibrahim et al. explored a multidimensional intervention for the reversal of *CF*, which consisted of vascular management, diet, exercise, cognitive and psychosocial stimulation (Ibrahim et al., 2024). Therefore, *CF* is not permanent and can potentially be alleviated through appropriate interventions, contributing to improved quality of life and independent living capabilities for older adults. And this feature of reversibility emphasizes the necessity for early detection and diagnosis of *CF*.

While *CF* has been linked to multiple physiological and lifestyle factors, the underlying biological mechanisms remain poorly understood. Mitochondria, known as the "energy factories" of the cells, are essential for supplying energy to neurons and regulating critical neuronal processes such as survival, regeneration, and the plasticity of axons and dendrites (Rangaraju et al., 2019). Impaired mitochondrial function in nerve cells is associated with cognitive decline, highlighting the close connection between mitochondrial health and cognitive abilities (Devine and Kittler, 2018; Apaijai et al., 2020). Restoration of mitochondrial function is critical for the management of cognitive dysfunction (Su et al., 2019). Previous studies reported that there was a negative correlation between mitochondrial DNA (mtDNA) levels in human peripheral blood mononuclear cells (PBMCs) and frailty, as well as cognitive decline (Ashar et al., 2015; Zhang et al., 2023a; Filograna et al., 2021; Tian et al., 2024). However, the relationship between mitochondrial function and *CF* remains unclear (Holland et al., 2024; Nader et al., 2023). Therefore, we hypothesize that mitochondrial dysfunction might be associated with *CF* and be a feature of *CF* in older adults.

This study aims to address this gap by investigating the risk factors associated with *CF* and exploring the relationship between mitochondrial function in peripheral blood and *CF* in hospitalized patients, offering insights into potential biomarkers and intervention strategies.

2 Methods

2.1 Participants, data collection and assessment scales

This study analyzed clinical data from 279 patients admitted to Jiangsu Province Hospital between October 2020 and August 2022 (Figure 1). Inclusion criteria were: (1) aged 50 years or older, (2) able to undergo all required examinations, and (3) stable underlying disease controlled by medication (for example, hypertension, coronary

Abbreviations: A/G, Android-to-Gynoid; ALB, Albumin; ASMI, Appendicular Skeletal Muscle Mass Index; ATP, Adenosine Triphosphate; AUC, Area Under Curve; BMI, Body Mass Index; CF, Cognitive Frailty; CHD, Coronary Atherosclerotic Heart Disease; CI, Confidence Intervals; CIRS-CI, Cumulative Illness Rating Scale - Comorbidity Index; CPT2, Carnitine Palmitoyltransferase II; DCFH-DA, 2′,7′-Dichlorofluorescin diacetate; DMEM, Dulbecco's Modified Eagle Medium; DXA, Dual-energy X-ray absorptiometry; ELISA, Enzyme-Linked Immunosorbent Assay; FCCP, Carbonyl cyanide-4 (trifluoromethoxy) phenylhydrazone; FMI, Fat Mass Index; FT3, Free Triiodothyronine; FT4, Free Thyroxine; GDS, Geriatric Depression Scale; GLU, Glucose; HbA1c, Glycosylated Hemoglobin; HDL, High-density Lipoprotein; HGB, Hemoglobin; IL-1β, Interleukin-1beta; IL-6, Interleukin-6; INS, Insulin; LDL, Low-density lipoprotein; LOS, Length of Stay; MCI, Mild Cognitive Impairment; MFS, Morse Fall Scale; μM, Micromole; mM, Millimole; MNA, Mini Nutritional Assessment; MoCA, Montreal Cognitive Assessment; mtDNA, Mitochondrial DNA; mtDNAcn, Mitochondrial DNA Copy Number; OCR, Oxygen Consumption Rate; OR, Odds Ratio; PA, Prealbumin; PBMCs, Peripheral Blood Mononuclear Cells; PBS, Phosphate-Buffered Saline; PFP, Physical Frailty Phenotype; Q-Q, Quantile-Quantile; qRT-PCR, Quantitative Real-Time Polymerase Chain Reactions; RBP, Retinal Binding Protein; ROC, Receiver Operating Characteristic; ROS, Reactive Oxygen Species; CIRS-CI, Cumulative Illness Rating Scale - Comorbidity Index; SARC-calf, strength, assistance walking, rise from a chair, climb stairs, and falls combined with calf circumference; SAS, Self-Rating Anxiety Scale; SD, Standard Deviation; SEM, Standard Error of the Mean; SPPB, Short Physical Performance Battery; TC, Total Cholesterol; TG, Triglyceride; TNF-α, Tumor Necrosis Factor-alpha; TP, Total Protein; TRF, Transferrin; TSH, Thyrotrophin; TUG, Timed Up and Go test; VIT-D, 25-Hydroxyvitamin D; WHR, Waist-to-Hip Ratio.

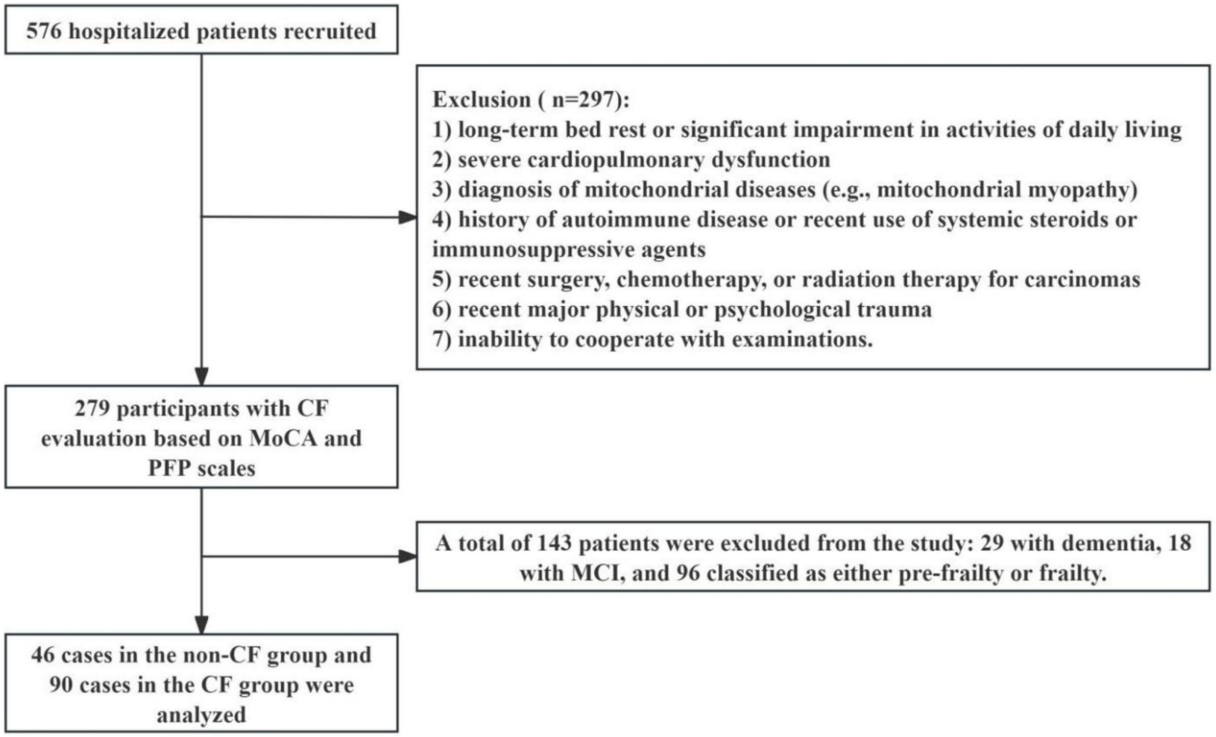

FIGURE 1
Flow chart of participants selection. *CF*: cognitive frailty, MCI, mild cognitive impairment; MoCA, the Montreal cognitive assessment; PFP, the physical frailty phenotype.

heart disease, diabetes, thyroid disease, etc.). Exclusion criteria included: (1) under 50 years of age, (2) long-term bed rest or significant impairment in activities of daily living, (3) severe cardiopulmonary dysfunction, (4) diagnosis of mitochondrial diseases (e.g., mitochondrial myopathy), (5) history of autoimmune disease or use of systemic steroids or immunosuppressive agents within the past 3 months, (6) recent (within 3 months) infection, surgery, chemotherapy, or radiation therapy for carcinomas, (7) recent (within 3 months) major physical trauma or diagnosed with depression, which means psychological impact of distressing events, major including accidents and natural disasters within last 3 months; and (8) inability to cooperate with examinations. The Ethical Committee of Jiangsu Province Hospital approved the study (2019-NT-48, 2024-SR-087), and all participants provided signed informed consent.

Patients underwent assessments across various health dimensions: (1) *CF* status measured with the Montreal Cognitive Assessment (MoCA) and the Physical Frailty Phenotype (PFP). Frailty status was assessed based on PFP including five components (Fried et al., 2001): PFP score < 1 = non-frail, $1 \leq$ PFP score < 3 = pre-frail, $3 \leq$ PFP score ≤ 5 = frail; Cognitive function was evaluated based on MoCA (Nasreddine et al., 2005): $26 \leq$ MoCA score = normal cognitive function, $15 \leq$ MoCA score < 26 = mild cognitive impairment (MCI), MoCA score ≤ 15 = dementia. Subjects were classified into the non-*CF* group if they had a PFP score = 0 and a MoCA score ≥ 26. In contrast, subjects with a PFP score of ≥ 1 and a MoCA score between 16 and 25 were classified into the *CF* group; (2) Mental Health, measured with the Self-Rating Anxiety Scale (SAS) and the Geriatric Depression Scale (GDS). SAS: total score ranges from 20 to 80, and higher scores correspond to a more pronounced tendency toward anxiety. GDS: total score ranges from 0 to 30, and higher scores indicate greater severity of depressive symptoms. (3) Physical Function, assessed with the Timed Up and Go test (TUG), the Short Physical Performance Battery (SPPB), and the strength, assistance walking, rise from a chair, climb stairs, and falls combined with calf circumference (SARC-Calf); (4) Nutritional Status, determined via the Mini Nutritional Assessment (MNA); (5) Fall Risk, evaluated using the Morse Fall Scale (MFS); (6) Comorbidity, assessed using the Cumulative Illness Rating Scale - Comorbidity Index (CIRS-CI).

2.2 Body composition

Dual-energy X-ray absorptiometry (DXA) (HOLOGIC, US) scans provided detailed assessments of body composition, including total fat mass, android and gynoid fat mass, and appendicular skeletal muscle mass. These measurements facilitated the calculation of the Fat Mass Index (FMI, defined as total fat mass divided by height squared), the Android-to-Gynoid (A/G) ratio, and the Appendicular Skeletal Muscle Mass Index (ASMI, calculated as appendicular skeletal muscle mass divided by height squared).

2.3 Total DNA extracted from peripheral blood

A total of 200 μL of fresh human venous blood was collected from participants using Vacutainer tubes containing sodium heparin as an anticoagulant. Total DNA was extracted from this peripheral blood,

yielding a final volume of 75 μL, utilizing the FastPure® Blood DNA Isolation Mini Kit V2 (Vazyme, China), according to the manufacturer's instructions.

2.4 Quantitative real-time polymerase chain reactions (qRT-PCR)

Mitochondrial DNA copy number (mtDNAcn) was assessed using Quantitative Real-Time Polymerase Chain Reactions (qRT-PCR) Instrument (Thermo Fisher, US). The reactions were conducted in a 10 μL volume, consisting of 2 μL of mtDNA template and 5 μL of ChamQ Universal SYBR qPCR Master Mix (Vazyme, China). qRT-PCR data were analyzed using the $2 - \Delta\Delta CT$ method. The forward primer sequence for β-actin: ATTGGCAATGAGCGGT TCCGC, reverse primer: CTCCTGCTTGCTGATCCACATC; Forward primer sequence for MT-ND-1: CACTCACATCAC AGCGCTAA; reverse primer: GGATTATGGATGCGGTTGCT.

2.5 Isolation of peripheral blood mononuclear cells (PBMCs)

All blood samples were obtained after overnight fasting. Two milliliters of freshly collected whole blood, anticoagulated with heparin, were obtained from participants for the isolation of PBMCs (T cells, B cells, dendritic cells, monocyte, phagocyte, natural killer cells, and a few other cell types) and plasma via Ficoll gradient centrifugation (TBD, China), in accordance with the manufacturer's guidelines. The isolated PBMCs were subsequently used to evaluate oxygen consumption rate (OCR) and reactive oxygen species (ROS), while the plasma was stored at −80°C Refrigerator (Sanyo, Japan) for later analysis.

2.6 Oxygen consumption rate measurements (OCR) in mitochondria of PBMCs

OCR measurements in PBMCs were conducted using a Seahorse XFe24 extracellular flux analyzer (Agilent, US), following the manufacturer's instructions. Briefly, 2×10^5 PBMCs were seeded onto Cell-Tak-coated XF24 V7 PS cell culture microplates in XF assay medium and incubated at 37°C for 1 h in a non-CO2 incubator. The XF assay medium was comprised of XF DMEM medium supplemented with 1 mM pyruvate, 1 mM glutamine, and 1 mM glucose. Subsequently, OCR was monitored at baseline and during sequential injections of oligomycin (1.5 μM), Carbonyl cyanide-4 (trifluoromethoxy) phenylhydrazone (FCCP, 0.5 μM), and a mix of rotenone and antimycin A (Rot/AA, 0.5 μM for each), using the XFe24 system. Data were collected and analyzed with Wave software and Microsoft Excel. The following mitochondrial respiration parameters were calculated: Basal Respiration = (baseline OCR) - (OCR after rotenone/antimycin A treatment), ATP-Linked Respiration = (Basal Respiration) - (OCR after Oligomycin treatment), Proton leak = (OCR after Oligomycin treatment) - (OCR after rotenone/antimycin A treatment), Maximal Respiration = (OCR after FCCP treatment) - (OCR after rotenone/antimycin A treatment), Spare Respiratory Capacity = (Maximal Respiration) - (Basal Respiration).

2.7 Reactive oxygen species (ROS) detection in PBMCs and flow Cytometric analysis

ROS levels in PBMCs were assessed using a Reactive Oxygen Species Assay Kit (Beyotime, China), according to the manufacturer's instructions. Notably, 2′,7′-Dichlorofluorescin diacetate (DCFH-DA) is a non-fluorescent probe that can be oxidized by reactive oxygen species (ROS), resulting in the formation of the highly fluorescent dichlorofluorescein (DCF). Freshly isolated PBMCs were incubated with 10 μmol/L DCFH-DA probes at 37°C for 20 min, with mixing every 3 min. PBMCs were then washed three times with phosphate-buffered saline (PBS). Sample analysis was performed using flow cytometer (BD, USA).

2.8 Enzyme-linked immunosorbent assay (ELISA)

Concentrations of inflammatory markers (IL-1β, IL-6, TNF-α) (Multi Sciences, China) and metabolites (CPT2, L-Carnitine) (Maisha, China) in plasma were measured using ELISA kits, following the manufacturers' protocols (Niu et al., 2024; Xuekelati et al., 2024). Optical density was measured at wavelengths of 570 nm and 630 nm using a microplate reader.

2.9 Statistical analysis

Data were analyzed using IBM SPSS Statistics Version 25. Normality was assessed using measures of Skewness and Kurtosis, the Shapiro–Wilk test, histograms, and Q-Q plots. Continuous variables were expressed as mean ± standard deviation (SD). We first examined differences in participants' characteristics by *CF* status. We used independent t tests or Mann–Whitney U tests for used independent t tests for continuous variables, and chi-square for categorical variables, as appropriate. To investigate the risk factors of *CF*, we used the binary logistic regression models, including the univariate and multivariate analyses, which adjusted for age, sex, BMI, education level, (MNA) scores, and (GDS) scores. We then examined the association between the level of mtDNAcn, mitochondrial respiration, ROS, CPT2, L-Carnitine, IL-1β, IL-6, or TNF-α and *CF* using the independent t tests or Mann–Whitney U tests, as appropriate. To adjust for age, sex, and BMI, we also used logistic regression analysis to investigate the relationship between mtDNAcn or ROS and *CF*. Furthermore, to evaluate whether mtDNAcn or ROS may be a predictor of *CF*, we used the sensitivity analysis to analyze the sensitivity of data. Differences in mitochondrial function between groups were illustrated through columnar scatter plots generated using GraphPad Prism software, and ROS levels were analyzed with FlowJo software. The sensitivity analysis was conducted by

IBM SPSS Statistics Version 25 and GraphPad Prism software. Statistical significance was defined at $p < 0.05$.

3 Results

3.1 Demographics and group distribution

This study involved 279 participants, with a mean age of 73.63 (± 10.19 years) and a Body Mass Index (BMI) of 23.95 (± 3.21 kg/m^2), including 185 males (66.31%) and 94 females (33.69%). Participants were categorized based on the PFP and the MoCA scales. The non-*CF* group ($n = 46$) exhibited no signs of frailty and maintained normal cognitive function, while the *CF* group ($n = 90$) showed indicators of pre-frailty or frailty combined with MCI. An additional 143 participants were identified as having conditions such as frailty, MCI, or dementia.

Comorbidities included hypertension (47.83% in the non-*CF* group, 22 cases; 32.72% in the *CF* group, 53 cases), diabetes (39.13% in the non-*CF* group, 18 cases; 25.17% in the *CF* group, 37 cases), coronary heart disease (10.87% in the non-*CF* group, 5 cases; 35.94% in the *CF* group, 23 cases), malnutrition (4.35% in the non-*CF* group, 2 cases; 44.83% in the *CF* group, 26 cases), and dyslipidemia (43.48% in the non-*CF* group, 20 cases; 31.25% in the *CF* group, 35 cases). The hospital length of stay was 8.98 ± 1.20 days for the non-*CF* group and 12.90 ± 0.94 days for the *CF* group. There were notable differences in malnutrition and the hospital length of stay between the two groups (Table 1). Additionally, in the assessment of *CF* using the MoCA and PFP scales in 279 participants, 143 individuals were excluded, including 29 diagnosed with dementia, 18 with MCI without frailty, and 96 classified as pre-frail or frail without MCI.

3.2 Clinical factors and group comparisons

Baseline characteristics are summarized in Table 1. The *CF* group was significantly older and had higher scores on the MFS, TUG, GDS, SAS, and CIRS-CI. Conversely, the *CF* group exhibited significantly lower educational attainment, BMI, ASMI, A/G ratios, SPPB scores, handgrip strength, 4-meter gait speed, and MNA scores, and various biochemical markers, including insulin, triglycerides, albumin, retinol-binding protein, prealbumin, hemoglobin, and free triiodothyronine. No significant differences were found in gender distribution, waist-to-hip ratio (WHR), smoking or drinking history, FMI, Glycosylated Hemoglobin, total cholesterol, glucose, low-density lipoprotein, high-density lipoprotein, total protein, transferrin, free thyroxine, thyroid-stimulating hormone, and vitamin D between the groups.

The binary logistic regression model included sex, age, BMI, education, MNA scores, and GDS scores (Figure 2). Results showed that older age was associated with increased of *CF* risk (OR 1.156, 95% CI 1.064–1.255), lower educational levels linked to higher *CF* risk (OR 0.115, 95% CI 0.024–0.550), declining MNA scores indicated greater *CF* risk (OR 0.713, 95% CI 0.522–0.973), and higher GDS scores correlated with increased *CF* risk (OR 1.345, 95% CI 1.065–1.699).

3.3 Correlation between mitochondrial function and *CF*

Our results indicated that the *CF* group had lower mtDNAcn expression levels compared with the non-*CF* group (Figure 3A). Additionally, key mitochondrial respiratory function parameters—such as basal respiration, ATP-linked respiration, maximal respiration, and spare respiratory capacity—were significantly reduced in the *CF* group, while proton leak did not show significant differences between the groups (Figure 3B). ROS levels were higher in the *CF* group relative to the non-*CF* group (Figure 3C). Notably, although plasma levels of Carnitine Palmitoyltransferase II (CPT2) were elevated in the *CF* group, circulating levels of L-carnitine did not differ statistically (Figure 3D).

After adjustment for age, sex, and BMI, compared with non-*CF* group, the OR values for the *CF* group of mtDNAcn and ROS were 0.234 (95% CI = 0.065–0.849) ($p = 0.027$) and 1.203 (95% CI = 1.075–1.347) ($p = 0.001$), respectively. Similar results were obtained in both the unadjusted and the age-sex-adjusted model (Table 2).

3.4 Correlation between inflammatory cytokines levels and *CF*

In addition, plasma IL-6 levels were elevated in the *CF* group compared with the non-*CF* group, while no significant differences were found for IL-1β or TNF-α levels between the groups (Figure 3E).

3.5 The diagnostic value of mtDNAcn and ROS for *CF*

The *CF* group was designated as the positive cohort, while the non-*CF* group served as the negative cohort for plotting the ROC curve. The analysis revealed that the area under curve (AUC) values for mtDNAcn and ROS in predicting *CF* were 0.653 and 0.925, respectively, as shown in Table 3 and Figure 4.

4 Discussion

This study identified a 32.26% prevalence of *CF* among inpatients. Our results showed that the *CF* group had a longer hospital length of stay compared with the non-*CF* group. The independent t tests, Mann–Whitney U tests and binary logistic regression suggested that notable risk factors of *CF* included advancing age, lower educational attainment, malnutrition, and depressive states. The study included 9 females (19%) in the non-*CF* group and 27 females (30%) in the *CF* group. While women were generally more frail, they appeared less susceptible to mortality than men (Arosio et al., 2023; Bai et al., 2023). To assess potential gender differences between the two groups, we performed a chi-square test ($\chi^2 = 1.703$, $p = 0.192$) and a multivariate logistic regression analysis (95% CI: 0.289–5.497, $p = 0.758$), both of which indicated no significant effect of gender on *CF*. We found that lower levels of insulin, triglycerides, albumin, retinol-binding protein, prealbumin, hemoglobin, and free triiodothyronine in the *CF* group. Sugimoto et al. also reported the

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TABLE 1 The overall characteristics of participants.

Variables	non-CF group (n = 46)	CF group (n = 90)	p value
Age (year)	66.15 ± 0.92	78.51 ± 1.03	<0.0001
Sex (F), n (%)	9 (19.57)	27 (30.00)	0.19
Education, n (%)			
Illiterate	0 (0)	2 (2.22)	0.0001
Primary	0 (0)	10 (11.11)	
Secondary	4 (8.70)	32 (35.56)	
College	42 (91.30)	46 (51.11)	
Smoking (yes)	12 (26.09)	58 (64.44)	0.32
Drinking (yes)	22 (47.83)	29 (32.22)	0.06
Hypertension, n (%)	22 (47.83)	53 (32.72)	0.27
Diabetes, n (%)	18 (39.13)	37 (25.17)	0.82
CHD, n (%)	5 (10.87)	23 (35.94)	0.05
Malnutrition, n (%)	2 (4.35)	26 (44.83)	0.001
Dyslipidemias, n (%)	20 (43.48)	35 (31.25)	0.61
LOS (day)	8.98 ± 1.20	12.90 ± 0.94	0.001
BMI (kg/m^2)	25.37 ± 0.47	23.46 ± 0.31	0.001
WHR	0.96 ± 0.01	0.94 ± 0.01	0.27
FMI (kg/m^2)	8.18 ± 0.37	8.11 ± 0.32	0.89
ASMI (kg/m^2)	6.51 ± 0. 19	5.62 ± 0.14	<0.0001
A/G	0.72 ± 0.03	0.65 ± 0.02	0.02
PFP scores	0	2.22 ± 0.12	<0.0001
MoCA scores	28.31 ± 0.21	21.53 ± 0.33	<0.0001
MFS scores	17.80 ± 1.24	30.75 ± 2.00	<0.0001
SPPB scores	11.62 ± 0.13	9.01 ± 0.76	<0.0001
Strength grip (kg)	34.74 ± 1.17	25.44 ± 0.95	<0.0001
4 meters gait speed (m/s)	1.39 ± 0.05	1.02 ± 0.04	<0.0001
TUG-single(s)	6.64 ± 0.18	9.38 ± 0.30	<0.0001
TUG-man(s)	9.34 ± 0.25	13.18 ± 0.43	<0.0001
TUG-cog(s)	9.24 ± 0.34	13.53 ± 0.51	<0.0001
SARC-calf	2.95 ± 1.00	6.73 ± 0.89	0.003
MNA scores	27.42 ± 0.37	24.66 ± 0.47	<0.0001
GDS scores	2.95 ± 0.35	8.47 ± 0.59	<0.0001
SAS scores	23.72 ± 0.78	27.55 ± 0.76	0.002
CIRS-CI scores	1.72 ± 0.23	3.09 ± 0.21	<0.0001
HbA1c (%)	6.23 ± 0.16	6.33 ± 0.11	0.32
GLU (mmol/L)	5.28 ± 0.22	5.36 ± 0.13	0.41
INS (pmol/L)	84.15 ± 10.66	48.44 ± 4.42	0.002
TC (mmol/L)	4.26 ± 0.15	4.18 ± 0.11	0.69
TG (mmol/L)	1.40 ± 0.09	1.23 ± 0.06	0.01
HDL (mmol/L)	1.10 ± 0.04	1.13 ± 0.03	0.63
LDL (mmol/L)	2.56 ± 0.11	2.49 ± 0.08	0.60
TP (g/L)	64.08 ± 0.86	63.47 ± 0.55	0.55
ALB (g/L)	39.05 ± 0.45	37.57 ± 0.38	0.02
RBP (mg/L)	41.06 ± 1.50	37.16 ± 1.07	0.04
PA (g/L)	0.28 ± 0.01	0.23 ± 0.01	<0.0001

(Continued)

TABLE 1 (Continued)

Variables	non-CF group (*n* = 46)	CF group (*n* = 90)	*p* value
TRF (g/L)	2.14 ± 0.06	2.01 ± 0.05	0.12
HGB (g/L)	138.10 ± 2.19	117.29 ± 3.66	0.001
VIT-D (nmol/L)	65.05 ± 3.05	61.97 ± 4.89	0.79
FT3 (pmol/L)	4.54 ± 0.083	4.15 ± 0.080	0.003
FT4 (pmol/L)	16.39 ± 0.38	16.27 ± 0.26	0.80
TSH (mIU/L)	2.93 ± 0.28	2.39 ± 0.16	0.32

Categorical data were presented as frequencies and percentages, and continuous variables were expressed as mean ± standard deviation (SD). Differences between groups were evaluated using Chi-square test, Student's *t*-tests, or Mann–Whitney U tests, as appropriate. Statistical significance was defined at $P < 0.05$. CF, cognitive frailty; CHD, coronary atherosclerotic heart disease; LOS, length of stay; BMI, body mass index; WHR, waist-to-hip ratio; FMI, fat mass index; ASMI, appendicular skeletal Muscle Mass Index; A/G, Android-to-Gynoid ratio; PFP, physical frailty phenotype; MoCA, Montreal cognitive assessment; MFS, Morse fall scale; SPPB, short physical performance battery; TUG, timed up and go test; SARC-calf, strength, assistance walking, rise from a chair, climb stairs, and falls combined with calf circumference; MNA, mini nutritional assessment; GDS, geriatric depression scale; SAS, self-rating anxiety scale; CIRS-CI, cumulative illness rating scale - comorbidity index; HbA1c, Glycosylated Hemoglobin; GLU, glucose; INS, insulin; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TP, total protein; ALB, albumin; RBP, retinal binding protein; PA, prealbumin; TRF, transferrin; HGB, hemoglobin; VIT-D, 25-hydroxyvitamin D; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyrotrophin.

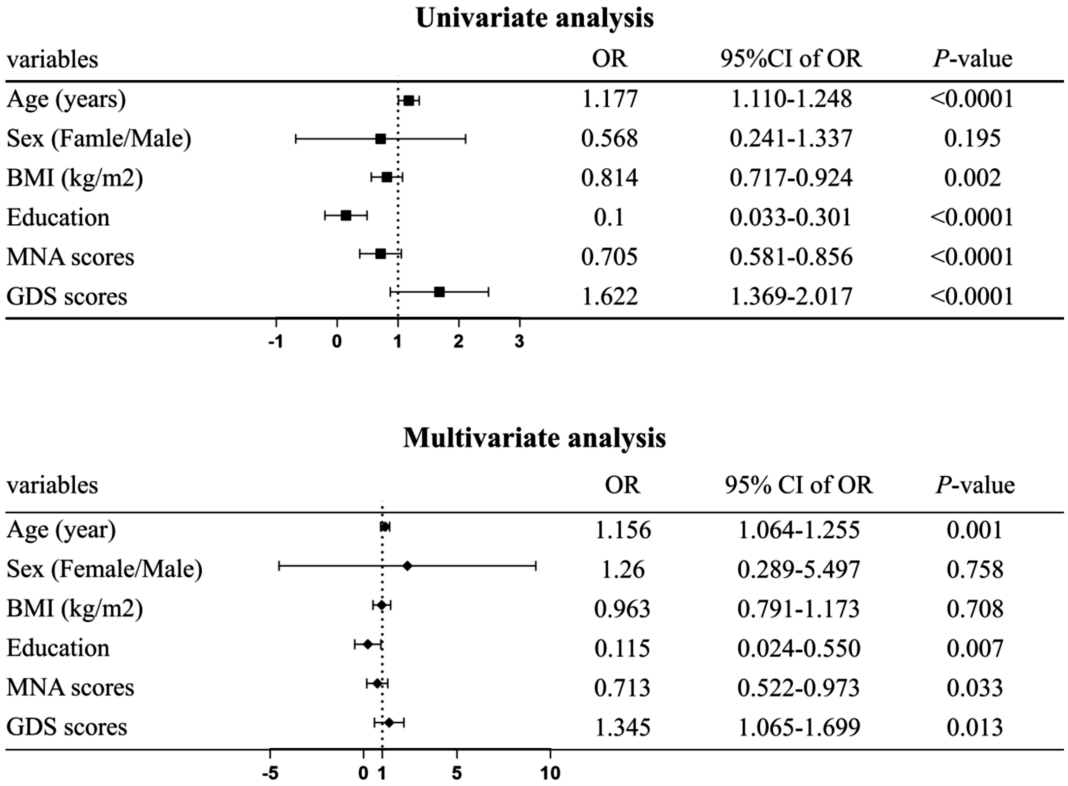

FIGURE 2
Forest plot factors significantly associated with cognitive frailty (*CF*). Data were analyzed using binary logistic regression. Adjusted for age, sex, body mass index (BMI), education level, mini nutritional assessment (MNA) scores, and geriatric depression scale (GDS) scores. Statistical significance was defined at $p < 0.05$.

risk factors of *CF* included sex, age, education level, socioeconomic status, malnutrition, and depressive states (Sugimoto et al., 2022). Moreover, multidomain lifestyle interventions for the older people, which incorporating exercise, nutritional support, and cognitive training, have proven effective in enhancing both physical frailty and cognitive function (Murukesu et al., 2020; Zhang et al., 2023b). Therefore, early detection, diagnosis, and intervention are essential for managing the onset and progression of *CF*.

Previous studies have utilized human peripheral blood samples as biomarkers for diagnosing various conditions, including heart failure, cognitive impairments, frailty, and dementia (Alexovič et al., 2022; Mahapatra et al., 2023; Lee et al., 2022). Furthermore, human PBMCs are widely recognized as critical targets for assessing mitochondrial function (Silaidos et al., 2018). *CF*, characterized as a geriatric syndrome affecting both physical and cognitive functions, is linked not only to mitochondrial dysfunction in specific tissues but also to systemic aging of tissues and organs (Robinson et al., 2022; Ruan et al., 2017; Zhang X. M. et al., 2022; Arosio et al., 2023; Ma and Chan, 2020). Consequently, to analyze the correlation between *CF* and

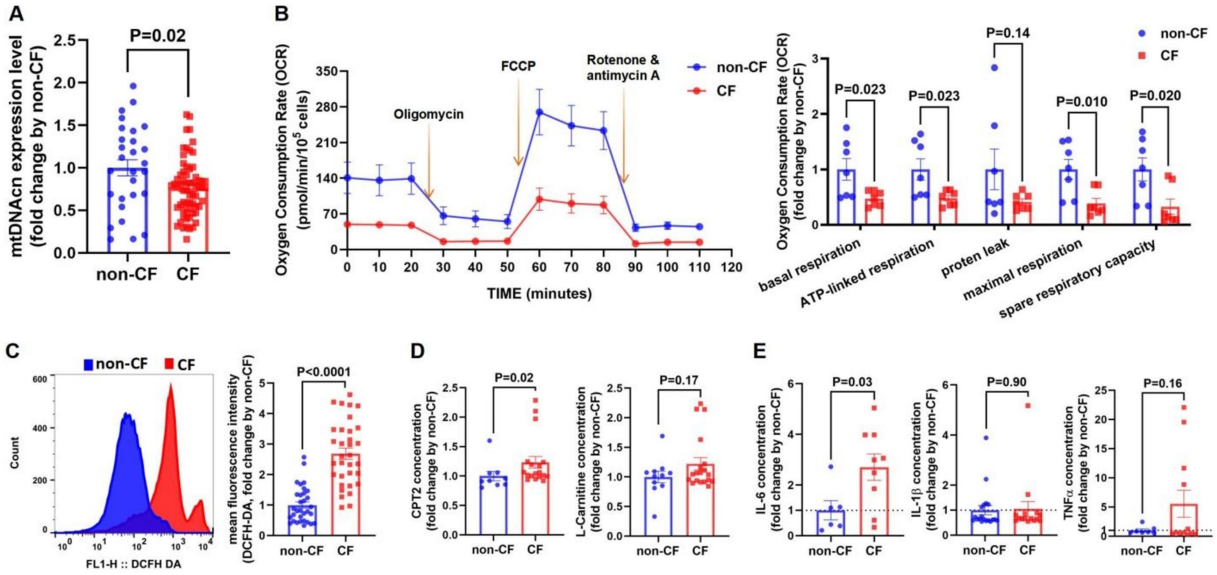

FIGURE 3
Mitochondrial dysfunction and inflammatory cytokines levels are increased in the cognitive frailty (*CF*) group. **(A)** qPCR was used to validate mitochondrial DNA copy number (mtDNAcn) levels in peripheral blood n (non-*CF*) = 28, n (*CF*) = 64. **(B)** Peripheral blood mononuclear cells (PBMCs) PBMCs underwent a mitochondrial stress test to measure oxygen consumption rate (OCR). Arrows indicate the addition of oligomycin, carbonyl cyanide-4 (trifluoromethoxy) phenylhydrazone (FCCP), and rotenone/antimycin A (left). Parameters analyzed included basal espiration, ATP-linked respiration, proten leak, maximal respiration, and spare respiratory capacity (right). n (non-*CF*) = 7, n (*CF*) = 7. **(C)** Flow cytometry analysis of DCFH-DA expression in PBMCs (left). Quantitative fluorescence analysis of DCFH-DA (right). n (non-*CF*) = 32, n (*CF*) = 33. **(D)** Secretion levels carnitine palmitoyltransferase 2 (CPT2) [n (non-*CF*) = 9, n (*CF*) = 18], and L-carnitine [n (non-*CF*) = 11, n (*CF*) = 19]. **(E)** Cytokines levels of interleukin-6 (IL-6) [n (non-*CF*) = 6, n (*CF*) = 9], interleukin-1 beta (IL-1β) [n (non-*CF*) = 7, n (*CF*) = 12] and tumor necrosis factor-α (TNF-α) [n (non-*CF*) = 19, n (*CF*) = 15] in plasma determined by ELISA. Notes: Differences in mitochondrial function between the two groups were illustrated using columnar scatter plots generated with GraphPad Prism software, while ROS levels were analyzed with FlowJo. Statistical comparisons were evaluated using Mann–Whitney U tests or Student's *t*-tests, as appropriate. Data are presented as means ± standard error of the mean (SEM). Statistical significance was defined at $p < 0.05$.

TABLE 2 Binary logistic regression model.

Variables	OR (95% CI)	*p*-value	OR (95% CI)	*P*-value
	Model 1		Model 2	
mtDNAcn	0.299 (0.116–0.773)	0.013	0.310 (0.098–0.983)	0.047
ROS	1.156 (1.078–1.240)	<0.0001	1.281 (1.087–1.365)	0.001
	Model 3		Model 4	
mtDNAcn	0.248 (0.069–0.891)	0.033	0.234 (0.065–0.849)	0.027
ROS	1.205 (1.080–1.344)	0.001	1.203 (1.075–1.347)	0.001

Data were analyzed using binary logistic regression. Model 1: Crude model; Model 2: adjust for age; Model 3: adjust for age, sex; Model 4: adjust for age, sex, BMI. Statistical significance was defined at $P < 0.05$. mtDNAcn: Mitochondrial DNA copy number; ROS: Reactive Oxygen Species; OR: odds ratio; CI: confidence interval.

mitochondrial function, we chose to assess mitochondrial function in peripheral blood cells rather than focusing on specific tissues such as skeletal muscle.

MtDNAcn quantifies mitochondrial content, influenced by various factors. Previous studies have linked elevated mtDNAcn levels in whole blood to an increased risk of glioma carcinogenesis, while lower mtDNAcn has been associated with greater susceptibility to aging and age-related diseases, such as coronary heart disease, cognitive impairments, and frailty (Shen et al., 2016; Wachsmuth et al., 2016; Mengel-From et al., 2014; Ashar et al., 2015; Klein et al., 2021; Yang et al., 2021). A review on aging and mtDNA suggested that most studies reported a decrease in mtDNAcn with aging (Filograna et al., 2021). Tian et al. demonstrated that higher mtDNAcn in human blood is associated with lower cognitive decline and frailty risk (Tian et al., 2024). However, a study reported that mtDNAcn increased with aging in liver samples (Wachsmuth et al., 2016). And another study showed no correlation between age and mitochondrial health index in PBMC (Karan et al., 2020). The variability in the relationship between age and mtDNAcn may be attributed to the heterogeneous composition of leukocytes and platelet abundance, which fluctuate with time of day, aging, and disease (Picard, 2021). In this study, the results demonstrated that the mtDNAcn in the *CF* group was lower than that in the non-*CF* group. After adjusted for age, sex, and BMI, our results still suggested that reduced mtDNAcn remained positively correlated

TABLE 3 The diagnostic value of mtDNAcn and ROS for cognitive frailty.

Variables	AUC	95% CI	*P*	Cut-Off	Sensitivity	Specificity
mtDNAcn	0.653	0.515–0.792	0.019	< 0.953	0.781	0.607
ROS	0.925	0.866–0.985	<0.001	> 321	0.758	0.937

The sensitivity analysis was used to analyze the effective predictor of CF. Statistical significance was defined at $P < 0.05$. mtDNAcn, mitochondrial DNA copy number; ROS, reactive oxygen species. AUC, area under the curve; CI, confidence interval.

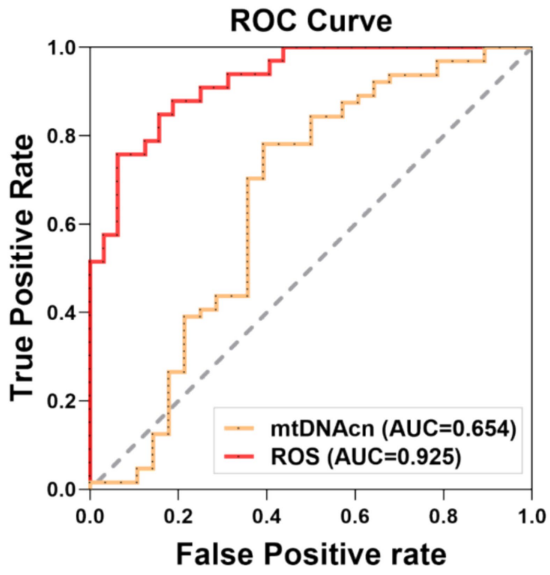

FIGURE 4
Receiver operating characteristic (ROC) curve for the prediction model. The sensitivity analysis was conducted by ROC curve, which was assessed the capacity of mtDNAcn and ROS to predictive *CF*, respectively. Statistical significance was defined at $p < 0.05$. AUC: area under the curve, mtDNAcn: mitochondrial DNA copy number, ROS: reactive oxygen species.

with *CF*. Moreover, the Sensitivity analysis suggested that mtDNAcn could be a key parameter for evaluating *CF*. Therefore, low mtDNAcn level in blood is associated with *CF* and may serve as a characteristic feature of *CF*.

Mitochondrial respiration is essential for maintaining normal cellular function. Mitochondrial health is particularly crucial in age-related disorders, including cardiovascular and neurodegenerative diseases, which often stem from imbalances in energy supply and demand (Amorim et al., 2022). The brain, being a high-energy-demand organ, is especially vulnerable to deficits in oxygen and energy. Mitochondrial dysfunction can trigger pathological responses in neural tissues, leading to cognitive decline (Yin et al., 2016; Cunnane et al., 2020). Moreover, Mahapatra et al., 2023 confirmed a positive association between mitochondrial respiratory capacity in human PBMCs and both cognitive ability and hippocampal volume. Additionally, aging-related impairments in object recognition and spatial memory have been linked to reduced synaptic mitochondrial ATP production in the hippocampus (Olesen et al., 2020). Ultimately, a decrease in neural energy availability may contribute to cognitive decline through impaired neural structure and function (Cheng et al., 2022; Rangaraju et al., 2019). Our study indicated that the *CF* group exhibited lower basal respiration, ATP-linked respiration, maximal respiration, and spare respiratory capacity compared with the non-*CF* group. These findings suggest that impaired mitochondrial respiration is associated with *CF*.

Mitochondria are the primary intracellular source of ROS; and previous reviews have suggested a potential link between *CF* and increased oxidative stress due to mitochondrial dysfunction (Bertero and Maack, 2018; Zhang B. et al., 2022). While ROS generated by the mitochondrial respiratory chain are critical signaling molecules in healthy cells, their excessive production during oxidative stress can lead to mtDNA damage, mitochondrial dysfunction, and cell death (Zarse and Ristow, 2021). In general, age-related mitochondrial abnormalities, such as accumulation of mtDNA mutations, diminished respiratory chain activity, and increased ROS generation, are implicated in the aging process. Some reviews proposed that the balance between ROS generation and clearance were disturbed in aging and neurodegenerative diseases (Guo Y. et al., 2023; Ionescu-Tucker and Cotman, 2021). And in aging animal models, ROS production in synaptic mitochondria disrupts essential neuronal proteins, contributing to cognitive decline (Kron et al., 2020; Olesen et al., 2020). Our results showed that ROS levels in PBMCs were significantly higher in the *CF* group compared with that in the non-*CF* group. After adjusted for age and sex, we observed that ROS levels in the *CF* group were significantly higher than that in the non-*CF* group. Furthermore, our results demonstrated that ROS levels might be an important parameter to assess *CF*. Therefore, high levels of ROS is correlated with *CF*, and may serve as a critical feature of *CF*.

Cellular stress can alter membrane permeability, and mitochondrial damage and its byproducts may exacerbate inflammation (Picca et al., 2021; Vringer and Tait, 2023). Recent studies suggested that mitochondria modulate inflammation through signaling pathways involving mtDNA and ROS, which trigger the release of TNF-α and IL-1β, disrupting the balance between pro-inflammatory and anti-inflammatory factors (Victorelli et al., 2023; Jiménez-Loygorri and Boya, 2024; Marchi et al., 2023). Previous research had highlighted the role of IL-6 and other pro-inflammatory markers in aging and cognitive decline, supporting their potential as disease predictors (Weaver et al., 2002; Leonardo and Fregni, 2023; Lyra et al., 2021; Parks et al., 2020). Given these reports, we assessed inflammatory cytokines levels in the bloodstream and the results revealed that elevated plasma IL-6 levels were associated with *CF*.

This study has several limitations. Firstly, while *CF* should be defined as excluding dementia, our use of the PFP and MoCA scales as diagnostic tools, may have inadvertently included participants with early-stage dementia. Future follow-up studies are planned to more rigorously exclude cases of rapidly progressing dementia (Nasreddine et al., 2005; Malek-Ahmadi and Nikkhahmanesh, 2024). Additionally, there was a significant age difference between the two groups in our study. Although we re-analyzed the relationship between mitochondrial function and *CF*, it would be more rigorous to compare subjects within the same age range in both the non-*CF* and *CF* group. Next, other techniques for broader

range of ROS assays is necessary to better understand the relationship between ROS and *CF*, such as spin trap compounds coupled with electron paramagnetic resonance spectroscopy, luminescence, mass spectrometry, and electrochemistry (Qu et al., 2020; Kornienko et al., 2018). Moreover, there was insufficient evidence to support the direct mechanistic roles of mitochondrial dysfunction, inflammation and *CF* in our study. Experimental studies should investigate mitochondria, metabolic and inflammatory alteration in the brain, such as metabolites levels in cerebrospinal fluid, PET brain glucose uptake, and magnetic resonance imaging. Additionally, the cross-sectional nature of this study limits our capacity to capture the temporal dynamics between mitochondrial function and *CF* progression. To address this, we will implement longitudinal follow-up assessments to better understand these relationships over time.

In summary, our findings highlight significant correlations between mitochondrial dysfunction and *CF*, suggesting that mitochondrial dysfunction in peripheral blood may serve as a potential phenotype of *CF*. These results underscore the need for further mechanistic studies to explore this relationship more comprehensively.

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 Ethical Committee of Jiangsu Province Hospital. 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

LQ: Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. TH: Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. DZ: Formal analysis, Investigation, Methodology, Writing – original draft. LW: Data curation, Writing – original draft. GL: Data curation, Writing – original draft. QZ: Data curation, Writing – original draft. QT: Data curation, Writing – original draft. GD: Conceptualization, Project administration, Supervision, Writing – review & editing. JL: Conceptualization, Funding acquisition, Project administration, Supervision, 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.

Generative AI statement

The authors declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

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Cross-sectional and longitudinal association between accelerometer-measured light-intensity physical activity and cognitive function in older adults

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Objectives: Regarding the methods of improving cognitive function in older adults, it is well-established that moderate-to-vigorous physical activity (MVPA) is beneficial. Considering the safety and mobility of older adults, recent research has focused on the benefits of light-intensity physical activity (LPA) on cognitive function. However, limited research has utilized the different domains of cognitive examination scales [such as the Mini-Mental State Examination (MMSE)] to analyze the relationship between LPA and different domains of cognitive function and compare the cross-sectional and longitudinal results. Thus, this study aimed to investigate the cross-sectional and longitudinal association between LPA and both overall and domain-specific cognitive function in older Taiwanese adults.

Methods: This longitudinal study recruited participants in an outpatient department of geriatrics and gerontology in a medical center in Taipei City, Taiwan. Data was collected from September 2020 to 2021; the follow-up data were collected until December 2022. Participants were community-dwelling older adults aged ≥ 65 years who could walk independently. Baseline physical activity (any bodily movement produced by skeletal muscles that requires energy expenditure) and sedentary behavior (any waking behavior while in a sitting, reclining or lying posture with low energy expenditure) were measured with a GT3X+ triaxial accelerometer, categorized as sedentary behavior (< 100 counts/min), LPA (100–2,019 counts/min) and MVPA (≥ 2,020 counts/min). Cognitive functions were measured using the Chinese version of MMSE for the baseline and follow-up data. Binary logistic regression analysis was used to examine the association between 3 h/day of LPA and cognitive functions. Baseline dependent variables were whether participants had overall cognitive impairment and whether scores of domain-specific MMSE were at the maximum level; in the follow-up analysis, the dependent variables were

whether overall and domain-specific scores of MMSE maintained or increased (obtained by subtracting the baseline from the follow-up overall and individual domain MMSE scores).

Results: A total of 167 participants were included (52.10% female; 76.11 ± 6.47 years). The cross-sectional analysis results indicated that in the adjusted model (adjusted for age, sex, educational degree, wear time, MVPA time, and sedentary behavior time), both overall and domain-specific cognitive functions were not significantly associated with ≥ 3 h/day of LPA. The longitudinal analysis results indicated that in the adjusted model, ≥ 3 h/day of LPA was significantly negatively associated with the maintenance or increase of language [odds ratio (OR): 0.88; 95% confidence interval (CI): 0.01–0.99; P = 0.049], and significantly positively associated with the maintenance or increase of orientation (OR: 3.83; 95% CI: 1.01–14.46; P = 0.048).

Conclusion: The cross-sectional and longitudinal impacts of engaging in ≥ 3 h/day of LPA on cognitive functions differed. While engaging in ≥ 3 h/day of LPA has no significant short-term benefits, performing ≥ 3 h/day of LPA is beneficial for maintaining or improving orientation cognitive function in long term. Further studies should explore the longitudinal relationship between LPA and orientation cognitive function to provide a more comprehensive understanding of their potential interactions.

KEYWORDS

light-intensity physical activity, older adults, cognitive function, accelerometer, MMSE

1 Introduction

Lead by the decline in fertility and increase in longevity, population aging has become a critical issue worldwide. It is anticipated that Taiwan will enter the status of a super-aged society by 2050 (National Development Council, 2022). Aging-related diseases include neurodegenerative, cardiovascular, and metabolic diseases; Alzheimer's disease (AD), the most prevalent form of dementia, is a progressive neurological disorder that commonly occurs in older adults (Guo et al., 2022). A major symptom of dementia is the loss of cognitive function, causing problems with language skills, visual perception, or paying attention in daily life (National Institutes of Health, 2020). In Taiwan, the prevalence rate of dementia among older adults aged ≥ 65 years is 7.99%, and it is projected that the number of people aged ≥ 65 years with dementia will become nearly 680,000 in < 20 years (Ministry of Health and Welfare, 2024). Based on previous research, dementia — especially among those with chronic diseases — inconveniences the daily lives of those affected and incurs large medical expenses and burdens on caregivers (Chang, 2016; Ku et al., 2016). Dementia is the last and the most severe stage of cognitive impairment (Alzheimer's Association, 2022). Specifically, the progression of cognitive impairment is categorized as normal cognition, prodromal dementia, and dementia (Golomb et al., 2004). While some individuals are diagnosed with Mild Cognitive Impairment (MCI), the majority tend to decline, with most of these declining patients eventually being diagnosed with AD (Golomb et al., 2004). Hence, the severity of cognitive impairment needs to be emphasized. To impede the trend of cognitive function deterioration, concerns regarding the cognitive function of older adults in Taiwan should be seriously considered.

Risk factors for cognitive function impairment can be classified as non-modifiable (including age, sex, and family medical history) or modifiable [including educational attainment, physical activity (PA), tobacco use, certain medical conditions, and social isolation] (World Health Organization, 2019). Among these risk factors, modifiable risk factors are targeted to delay the progression of cognitive impairment (World Health Organization, 2019). According to some cross-sectional and systematic reviews, physical activity (PA) is a crucial factor that has a positive impact on cognitive functions among older adults and can be incorporated into daily life (Coll-Padrós et al., 2019; de Frutos-Lucas et al., 2020; Feng et al., 2019; Kennedy et al., 2017; Kim et al., 2022; Livingston et al., 2020; Mc Ardle et al., 2023; Mellow et al., 2022; Pengpid and Peltzer, 2022; Veronese et al., 2023). Physical activity was defined as any bodily movement produced by skeletal muscles that requires energy expenditure (World Health Organization, 2024), categorized into different intensities referring to the rate of metabolic energy demand during exercise (MacIntosh et al., 2021). Measurements of physical activity can be divided into objective measurements and subjective measurements. Compared to subjective ones, objective measurements can avoid overestimating physical activity (Lee et al., 2011). It was previously reported that engaging in moderate-to-vigorous intensity PA (MVPA) had positive effects on cognitive function among older adults (Livingston et al., 2020); more specifically, it was demonstrated that engaging in 150 min of MVPA per week can enhance cognitive function among older adults (O'Brien et al., 2021). However, considering the difficulty of MVPA and the safety of older adults, light-intensity PA (LPA) — including casual walking, lifting lightweight objects, light household chores or yard

works, and stretching — is more realistically achievable and feasible to accomplish among older adults (Tse et al., 2015).

Although most relevant research has concentrated on the association between MVPA or total PA and cognitive function (Mellow et al., 2022; Sofi et al., 2011; Zhu et al., 2017), increasing research have proven that LPA is beneficial for cognitive function in older adults (Amagasa et al., 2018; Rojer et al., 2021). Additionally, previous research showed that LPA and overall cognitive function were positively related regardless of whether LPA was assessed by objective instruments or questionnaires (Hsiao et al., 2022; Lee et al., 2013; Stubbs et al., 2017; Wu et al., 2020), while cognitive function examination scales including the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA) and Ascertain Dementia 8-item Questionnaire (AD8) were used. Studies further proposed specific time threshold for engaging in LPA—engaging in $\geq$ 3 h/day LPA is associated with reduced risks of all-cause mortality (Ku et al., 2020) and engaging in $\geq$ 3 h of LPA is beneficial for cognitive function (Hsiao et al., 2022), providing clear time indicators for engaging in LPA. As for the domain-specific measurements of cognitive function, a scoping review reported that cognitive function testing could be categorized into memory (Verbal Digit Span-Forward test), attention and processing speed (Symbol Search task, Symbol Coding task and Trail Making test), executive function (Task-switching paradigm), and overall cognitive function (Telephonic assessment and interview) (Erlenbach et al., 2020). Adding to that, LPA was reported to be positively related to memory, attention, and executive function (Erlenbach et al., 2020).

In summary, most previous studies that used objective instruments and various cognitive examination scales and tests indicated a positive relationship between LPA and both overall and domain-specific cognitive functions (Amagasa et al., 2018; Erlenbach et al., 2020; Hsiao et al., 2022; Lee et al., 2013; Stubbs et al., 2017). However, limited research utilized the different domains of cognitive examination scales, such as MMSE, and accordingly focused on domain-specific cognitive functions to analyze the relationship between LPA and different domains of cognitive function. Furthermore, seldom has research explained the inconsistencies between cross-sectional and longitudinal results, analyzing the different effects of LPA on cognitive function in the short- and long-term.

This study aimed to investigate the cross-sectional and longitudinal associations between LPA and overall and different domains of cognitive function among community-dwelling older adults in Taiwan, and to compare the results of these two associations. Given that LPA is a possible protective factor for overall cognitive function, we hypothesized that engagement in 3 h/day of LPA was positively associated with older adults' overall and domain-specific cognitive functions (measured using MMSE) in the short-term and long-term.

2 Materials and methods

2.1 Participants and study design

This study collected data from community-dwelling older adults aged $\geq$ 65 years who were able to walk independently (individuals with assistive devices walking and use of wheelchair were excluded). Participants were recruited from an outpatient department of geriatrics and gerontology in a medical center in Taipei City, Taiwan. Using convenience sampling, the interval between baseline and follow-up was at least 1 year—the baseline data were collected between September 2020 and September 2021; the follow-up data were collected until December 2022. All participants provided written informed consent and were informed of the detailed study process and purpose after doctors from the outpatient department assessed whether the participants met the recruitment criteria and were willing to participate in the study. Baseline data collection included: (i) a self-reported questionnaire (sociodemographic variables, health status, lifestyles behaviors and depressive symptom); (ii) accelerometer-assessed PA [wearing a triaxial accelerometer (GT3X+; ActiGraph, Pensacola, FL, United States) on either left or right side of waists based on personal preference for seven consecutive days] (Aadland and Ylvisåker, 2015); and (iii) cognitive function (MMSE test). The cognitive function test was conducted again during the follow-up survey.

We conducted *a priori* analysis to estimate sample size via G*Power version 3.1.9.7 (Prajapati et al., 2010). The findings indicated that to achieve a statistical power of 0.80 in a binary logistic regression analysis examining the relationship between LPA and cognitive function, a minimum of 119 participants is required, assuming a significance level (α) of 0.05 (Prajapati et al., 2010). Initially, 301 participants were recruited. Participants with the following criteria were excluded: (1) did not meet the minimum criteria [wear $\geq$ 10 h per day, and at least four valid wear days (three weekdays and one weekend day)] for wearing the triaxial accelerometer ($n = 35$); (2) incompletely answered the self-reported questionnaires and Geriatric Depression Scale (GDS)-15 ($n = 9$); and (3) did not complete MMSE for both the baseline and follow-up survey ($n = 90$). After the data were screened by the exclusion criteria, 167 participants were enrolled in the final analysis. The recruitment procedure is shown in Figure 1. At the end of the study, participants were provided with an NTD 200 gift voucher, an incentive for study participation. This study was approved by the Research Ethics Committee of the National Taiwan University Hospital (202008046RINC).

2.2 Measures

2.2.1 Cognitive function

For the baseline and follow-up data, this study measured the cognitive function of participants using the Chinese version of MMSE, a 30-point questionnaire containing 11 questions that are used to assess six domains of cognitive impairment, including orientation (10 points), attention and calculation (eight points), delayed recall (three points), language (five points), executive function (three points), and visuoconstructional skills (one points) (Folstein et al., 1975; Jia et al., 2021; Lin et al., 2019). In the baseline analysis, the dependent variables were whether participants had overall cognitive impairment (adjusted for education level) and whether scores of domain-specific MMSE were at the maximum level; in the follow-up analysis, the dependent variables were whether scores of MMSE were maintained or increased (obtained by subtracting the baseline from the follow-up overall and individual domain MMSE scores). The Chinese

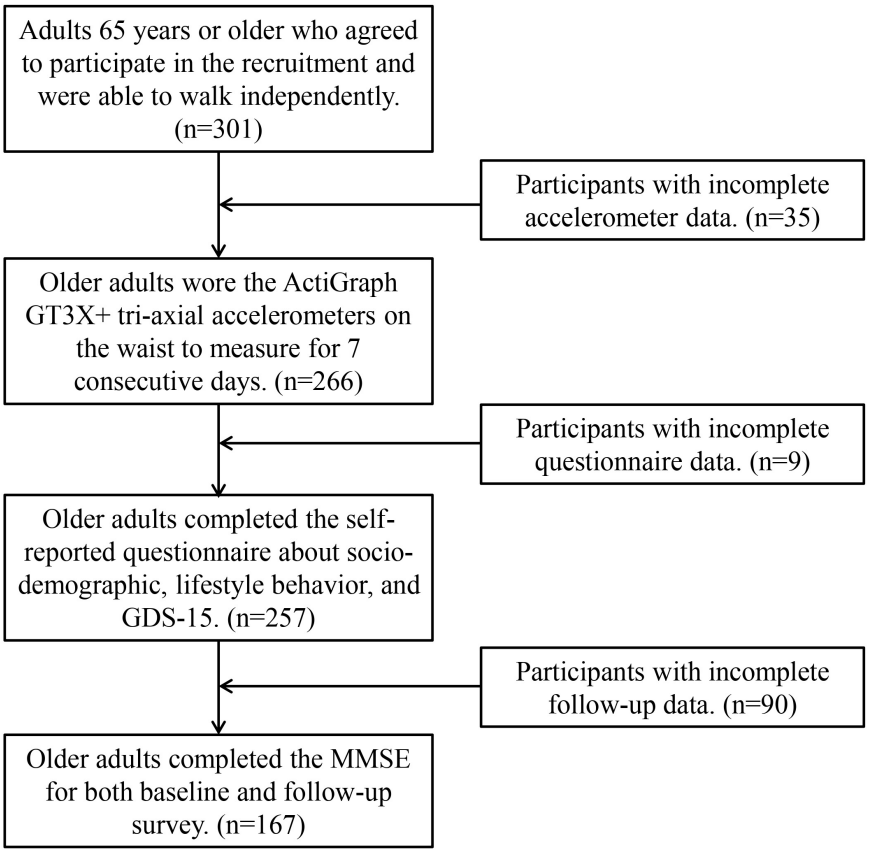

FIGURE 1
Flow chart of the research. GDS-15, 15-item geriatric depression scale; MMSE, Mini-Mental State Examination.

version of MMSE has a good sensitivity and specificity of 0.84 and 0.86, respectively (Tsai et al., 2016). Participants with higher total scores had more normal cognitive functions. The cognitive impairment of individuals with no formal schooling was defined with MMSE scores of $\leq$ 16; that of individuals with elementary school qualifications was defined with scores of $\leq$ 20; and that of individuals with junior high school qualifications or higher was defined with scores of $\leq$ 23 (Guo et al., 1988).

2.2.2 Physical activity levels and sedentary behavior

For the baseline data, participants were asked to wear a waist-worn triaxial accelerometer (GT3X+) to measure the times participants spent in sedentary behavior ($<$ 100 counts/min), LPA (100–2019 counts/min) and MVPA ($\geq$ 2020 counts/min) (Troiano et al., 2008). The accelerometer had to be worn for seven consecutive days, and removed during water-related activities, such as bathing or similar activities; in this case, participants were requested to record the non-wear time. The ActiGraph GT3X+ triaxial accelerometer was verified as having a high validity (Dobell et al., 2019; Hänggi et al., 2013; Kelly et al., 2013). Based on previous studies (Migueles et al., 2017), valid data for this study met the following criteria: (1) accelerometer was worn for at least four valid days, including three weekdays and one weekend day; (2) a valid day represents a day during which the participants wore the triaxial accelerometer for $\geq$ 600 min (10 h) in a single day. Non-wear time was defined as a zero count on the accelerometer for a continuous period $\geq$ 60 min. The cumulative time unit for triaxial accelerometer measurements (count) is called Epoch length. According to previous research (Migueles et al., 2017), older adults often use 60 s as the unit for cumulative time. Studies have demonstrated the benefits of 3 h/day of LPA for older adults (Hsiao et al., 2022; Ku et al., 2020). Therefore, this study adopted the 3 h/day cut-off points of LPA to examine whether there was the benefit to both overall and domain-specific cognitive functions. Valid data from accelerometers were transferred into ActiLife software (version 6.0; ActiGraph) for analysis.

2.3 Covariates

Self-reported questionnaires were used to assess potential covariates in this study, including sociodemographic characteristics, lifestyle behaviors, and depressive symptoms. Sociodemographic characteristics included sex (female or male), age, education level (no formal schooling, elementary school, and junior high school), living status (living alone or living with others), body mass index (BMI; the objectively measured weight in kilograms divided by the square of the objectively measured height in meters), and the number of chronic diseases ($<$ 4 or $\geq$ 4). We classified BMI into four groups such as underweight

(< 18.5 kg/m^2), normal (18.5–23.9 kg/m^2), overweight (24–26.9 kg/m^2), and obesity (≥ 27 kg/m^2) (Ministry of Health and Welfare, 2018). Lifestyle behaviors included smoking (yes or no) and use of alcohol (yes or no). According to a previous study (Rojer et al., 2021), independence from MPVA and sedentary behavior could ensure the benefits of LPA for cognitive function. Hence, objective accelerometer-measured MVPA and sedentary behavior were also considered as covariates. In line with the recommendations of the World Health Organization, older adults are recommended to engage in MVPA for ≥ 150 min/week. In this study, MVPA was divided into two groups: ≥ 150 min/week and < 150 min/week. Moreover, sedentary behavior was divided into two groups based on a previous study (Ku et al., 2019): ≤ 9 h/day and > 9 h/day. Depressive symptoms are also associated with cognitive impairment (Camacho-Conde and Galán-López, 2020); to assess depressive symptoms, we used the 15-item GDS. In accordance with previous research (Greenberg, 2012), this covariate was divided into two groups: non-depressive symptoms (< 5 points) and depressive symptoms (≥ 5 points). Additionally, the total wear time of the accelerometer was also collected and adjusted for this analysis.

2.4 Statistical analyses

In this study, IBM SPSS 23.0 (SPSS Inc., Chicago, IL, United States) was used to conduct statistical analyses. Descriptive analysis was used to present participants' characteristics. The Chi-squared test was used to identify associations between covariates and cognitive function, and the level of significance was set at $P < 0.05$. Next, using baseline data, binary logistic regression analysis was performed to examine the association between independent variable, whether participants engaged in ≥ 3 h/day of LPA and, and dependent variables, MMSE scores (whether the overall and individual domains— orientation, attention and calculation, delayed recall, language, executive function, and visuoconstructional skills— of MMSE scores were at the maximum level) in two models: Model 1 was unadjusted; Model 2 was adjusted for age, sex, educational degree, wear time, MVPA time, and sedentary behavior time (variables significantly associated with cognitive function as determined by chi-square test analysis). Additionally, using baseline and follow-up data, we also used adjusted binary logistic regression to determine the longitudinal association between independent variable, whether participants engaged in ≥ 3 h/day of LPA at baseline, and dependent variables, MMSE scores (whether the overall and individual domains of MMSE scores maintained or increased) in the two models. Based on previous studies, our research uses 3 h as the cutoff point for LPA engagement time. To determine whether the score was maintained or increased, we subtracted the baseline MMSE scores from the follow-up MMSE scores for each domain of cognitive function. Model 1 was unadjusted; Model 2 was adjusted for age, sex, educational degree, wear time, MVPA time, and sedentary behavior time. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for each variable. Further to that, an OR is the odds that an outcome will occur given a particular exposure, compared to the odds of the outcome occurring without that exposure. For instance, if the OR is 2.5 for participants who achieve 3 h/day of LPA, this means that those participants have 2.5 times the odds of maintaining or improving their cognitive function compared to participants who do not achieve 3 h/day of LPA.

3 Results

Table 1 presents characteristics of the participants and chi-square test results of covariates and cognitive functions. A total of 167 participants were included in this analysis. The means of participants were as follows: age, 76.11 ± 6.47 years; BMI, 24.40 ± 3.52 kg/m^2; wear time per day, 14.48 ± 1.34 min; MVPA per day, 16.11 ± 25.16 min; LPA per day, 4.10 ± 1.37 h; Sedentary Behavior per day, 10.11 ± 1.26 h; baseline MMSE total score, 26.84 ± 3.49 points (orientation score, 9.22 ± 1.41 points; attention and calculation, 7.05 ± 1.43 points; delayed recall, 1.96 ± 0.99 points; language, 4.81 ± 0.51 points; executive function, 2.93 ± 0.28 points; visuoconstructional skills, 0.88 ± 0.33 points); and follow-up MMSE total score, 26.81 ± 4.06 points (orientation score, 9.13 ± 1.74 points; attention and calculation, 6.85 ± 1.59 points; delayed recall, 2.13 ± 0.91 points; language, 4.77 ± 0.58 points; executive function, 2.98 ± 0.15 points; visuoconstructional skills, 0.93 ± 0.26 points). Additionally, most participants were female (52.1%), were aged ≥ 75 years (51.5%), had an educational level above university (49.1%), had a normal BMI (52.1%), were living with others (88.0%), had four or more chronic diseases (10.2%), did not smoke (92.2%), did not drink alcohol (89.2%), did not engage in 150 min/week of MVPA (74.3%), engaged in ≥ 9 h/day of sedentary behavior (83.2%), had no depressive symptoms (82.6%), and engaged in ≥ 3 h/day of LPA (80.8%). Moreover, at baseline, 91.6% were not at risk of cognitive function impairment, compared to 88.6% at follow-up.

In the Chi-squared test, a significance level of $P < 0.05$ and $P < 0.01$ were used; sex, age, and educational level were all significantly associated with cognitive function whether the other variable was pre-test overall cognitive function (impaired or not) or post-test overall cognitive function (impaired or not). We simultaneously adjusted for accelerometer wear time, MVPA time, and sedentary time per day (Ku et al., 2017) for analysis of PA. Therefore, we incorporated age, sex, educational level, wear time per day, MVPA time per day, and sedentary time per day as covariates for adjustment in the following analysis.

Table 2 presents the cross-sectional association between ≥ 3 h/day of LPA and cognitive function both overall cognitive function impairment and domain-specific cognitive function maximum levels using binary logistic regression models. In Model 1 (unadjusted), 3 h/day of LPA was significantly positively associated with overall cognitive function (OR: 3.66, 95% CI: 1.17–11.45; $P = 0.026$) and language (OR: 4.66; 95% CI: 1.80–12.10; $P = 0.002$), indicating that people who engage in 3 h/day of LPA are 3.66 times more likely to have better overall cognitive function compared to those who don't and that less than a 5% chance that the observed association is due to random chance; in Model 2 (adjusted for covariates), LPA was not significantly associated with any domain of cognitive function.

Table 3 presents the prospective association between 3 h/day of LPA and cognitive function using binary logistic regression models based on raw change score data obtained by subtracting

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TABLE 1 Characteristics of the participants and Chi-square test results of covariates and cognitive functions (n = 167).

Categorical variables	Content	Total	*N*%	*P*-value for χ2 test* (pre-test)	*P*-value for χ2 test*(post-test)
Sex	Female	87	52.1%	0.038*	0.045*
	Male	80	47.9%		
Age	65–74	81	48.5%	0.007**	< 0.001**
	≥ 75	86	51.5%		
Educational level	No formal schooling	6	3.6%	< 0.001**	< 0.001**
	Elementary school	32	19.2%		
	Junior high school or above	129	77.3%		
BMI (kg/m^2)	Underweight	2	1.2%	0.091	0.139
	Normal	83	49.7%		
	Overweight	50	29.9%		
	Obesity	32	19.2%		
Living alone	No	147	88.0%	0.149	0.836
	Yes	20	12.0%		
Having four or more chronic diseases	No	150	89.8%	0.596	0.452
	Yes	17	10.2%		
Smoking	No	154	92.2%	0.256	0.663
	Yes	13	7.8%		
Drinking alcohol	No	149	89.2%	0.174	0.410
	Yes	18	10.8%		
150 min MVPA per week	No	124	74.3%	0.105	0.119
	Yes	43	25.8%		
≥ 9 h/day of sedentary behavior	No	28	16.8%	0.795	0.154
	Yes	139	83.2%		
Depressive symptoms	No	138	82.6%	0.675	0.082
	Yes	29	17.4%		
≥ 3 h/day of LPA	No	32	19.2%	–	–
	Yes	135	80.8%		
Baseline cognitive function impairment	No	153	91.6%	–	–
	Yes	14	8.4%		
Follow-up cognitive function impairment	No	148	88.6%	–	–
	Yes	19	11.4%		
Continuous variables (independent variables)		Mean	SD	–	–
Age of baseline (years)		76.11	6.47	–	–
BMI (kg/m^2)		24.40	3.52	–	–
Wear time per day (hours)		14.48	1.34	–	–
MVPA per day (minutes)		16.11	25.16	–	–
LPA per day (hours)		4.10	1.37	–	–
SB per day (hours)		10.11	1.26	–	–

(Continued)

TABLE 1 (Continued)

Continuous variables (dependent variables in baseline)	Mean	Normal overall cognitive function and max scores of domain-specific cognitive functions (participants engaging in ≥ 3 h/day of LPA)	Normal overall cognitive function and max scores of domain-specific cognitive functions (participants engaging in < 3 h/day of LPA)
Baseline MMSE total score	26.84	*n* = 127 (94.1%)	*n* = 26 (81.3%)
Orientation	9.22	*n* = 92 (68.1%)	*n* = 17 (53.1%)
Attention and calculation	7.05	*n* = 78 (57.8%)	*n* = 19 (59.4%)
Delayed recall	1.96	*n* = 51 (37.8%)	*n* = 9 (28.1%)
Language	4.81	*n* = 123 (91.1%)	*n* = 22 (68.8%)
Executive function	2.93	*n* = 126 (93.3%)	*n* = 30 (93.8%)
Visuoconstructional skills	0.88	*n* = 122 (90.4%)	*n* = 25 (78.1%)
Continuous variables (dependent variables in follow-up)	**Mean**	**Maintenance or increase of overall and domain-specific cognitive functions (participants engaging in ≥ 3 h/day of LPA)**	**Maintenance or increase of overall and domain-specific cognitive functions (participants engaging in < 3 h/day of LPA)**
Follow-up MMSE total score	26.81	*n* = 94 (69.6%)	*n* = 18 (56.3%)
Orientation	9.13	*n* = 116 (85.9%)	*n* = 18 (56.3%)
Attention and calculation	6.85	*n* = 100 (74.1%)	*n* = 23 (71.9%)
Delayed recall	2.13	*n* = 108 (80.0%)	*n* = 26 (81.3%)
Language	4.77	*n* = 123 (91.1%)	*n* = 30 (93.8%)
Executive function	2.98	*n* = 131 (97.0%)	*n* = 32 (100%)
Visuoconstructional skills	0.93	*n* = 132 (97.8%)	*n* = 29 (90.6%)

*P-value for $\chi 2$ test < 0.05 represents a significant correlation; **P-value for $\chi 2$ test < 0.01 represents a significant correlation; BMI, body mass index; LPA, light-intensity physical activity; MVPA, moderate-to-vigorous physical activity; SB, sedentary behavior.

TABLE 2 Binary logistic regression models examine the cross-sectional association between light-intensity physical activity (LPA) and cognitive functions (*n* = 167).

Scores reach maximum or not	3 h/day of LPA	Model 1		Model 2	
		OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Baseline overall cognitive function impairment	No Yes	1.00 3.66 (1.17, 11.45)	0.026*	1.00 1.36 (0.17, 10.60)	0.770
Orientation	No Yes	1.00 1.89 (0.86, 4.13)	0.112	1.00 0.94 (0.30, 2.95)	0.913
Attention and calculation	No Yes	1.00 0.94 (0.43, 1.05)	0.869	1.00 0.41 (0.13, 1.26)	0.119
Delayed recall	No Yes	1.00 1.55 (0.67, 3.61)	0.309	1.00 0.71 (0.20, 2.45)	0.583
Language	No Yes	1.00 4.66 (1.80, 12.10)	0.002*	1.00 3.08 (0.33, 29.18)	0.327
Executive function	No Yes	1.00 0.93 (0.19, 4.55)	0.932	1.00 1.92 (0.23, 16.30)	0.549
Visuoconstructional skills	No Yes	1.00 2.63 (0.95, 7.25)	0.062	1.00 0.94 (0.19, 4.66)	0.938

Model 1: unadjusted; model 2: adjusted for age, sex, educational degree, wear time, MVPA time, and sedentary behavior time; LPA, light-intensity physical activity; MVPA, moderate-to-vigorous physical activity; OR, odds ratio; CI, confidence interval. *p < 0.05.

baseline data from follow-up data. In Model 1 (unadjusted), LPA was significantly positively associated with the maintenance or increase of the orientation function (OR: 4.75; 95% CI: 2.03–11.11; $P \leq 0.001$), indicating that people who engage in 3 h/day of LPA are 4.75 times more likely to maintain or improve their orientation function compared to those who don't and that less than a 5% chance that the observed association is due to random chance; in Model 2 (adjusted for covariates), LPA was also significantly positively associated with the maintenance or increase of the orientation function (OR: 3.83; 95% CI: 1.01–14.46; $P = 0.048$), indicating that people who engage in 3 h/day of LPA are 3.83 times more likely to maintain or improve their orientation function

TABLE 3 Follow-up survey: binary logistic regression models examine the prospective association between light-intensity physical activity (LPA) and cognitive functions (n = 167).

Scores maintain or increase	3 h/day of LPA	Model 1		Model 2	
		OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Overall cognitive function maintain or increase	No Yes	1.00 1.78 (0.81, 3.93)	0.151	1.00 0.89 (0.30, 2.68)	0.835
Orientation maintain or increase	No Yes	1.00 4.75 (2.03, 11.11)	< 0.001**	1.00 3.83 (1.01, 14.46)	0.048*
Attention and calculation maintain or increase	No Yes	1.00 1.12 (0.47, 2.65)	0.800	1.00 0.71 (0.22, 2.32)	0.576
Delayed recall maintain or increase	No Yes	1.00 0.87 (0.35, 2.47)	0.923	1.00 0.65 (0.18, 2.33)	0.507
Language maintain or increase	No Yes	1.00 0.68 (0.15, 3.22)	0.630	1.00 0.88 (0.01, 0.99)	0.049*
Executive function maintain or increase	No Yes	1.00 0.00 (0.00, –)	0.998	1.00 0.00 (0.00, –)	0.998
Visuoconstructional skills maintain or increase	No Yes	1.00 4.55 (0.87, 23.70)	0.072	1.00 0.02 (0.00, 2.60)	0.116

Model 1: unadjusted; model 2: adjusted for age, sex, educational degree, wear time, MVPA time, and sedentary behavior time; LPA, light-intensity physical activity; MVPA, moderate-to-vigorous physical activity; OR, odds ratio; CI, confidence interval. *$p < 0.05$. **$p < 0.001$.

compared to those who don't and that less than a 5% chance that the observed association is due to random chance; LPA was significantly negatively associated with the maintenance or increase of the language function (OR: 0.88; 95% CI: 1.01–0.99; $P = 0.049$), indicating that people who engage in LPA are 0.88 times as likely to maintain or improve their language function compared to those who don't and that less than a 5% chance that the observed association is due to random chance.

4 Discussion

To the best of our knowledge, this is the first study to examine the cross-sectional and longitudinal associations between accelerometer-measured LPA and both overall and the six domains of cognitive function measured using MMSE in a sample of older Taiwanese adults and adjusting for potential covariates. The main finding was that engaging in ≥ 3 h/day of LPA was beneficial to the maintenance or improvement of orientation in the long-term, regardless of the wear time of the accelerometer, time of sedentary behavior, and time of engagement in MVPA.

Our cross-sectional results revealed that LPA was not significantly associated with overall cognitive function, or all domains of cognitive function. This finding is consistent with previous research indicating an insignificant cross-sectional relationship between LPA and overall cognitive function measured using MMSE (Amagasa et al., 2020; Cavalcante et al., 2018; Fanning et al., 2017; Iso-Markku et al., 2018; Makizako et al., 2015; Marinac et al., 2015). It can be surmised that the effect of LPA on cognitive functions should be tracked over a long period of time; additionally, it can be explained that the risk factors for cognitive decline are multifactorial (World Health Organization, 2019), requiring in-depth research from multiple perspectives.

The main finding in this study corroborates previous findings that engaging in LPA is associated with reduced risks of cognitive function decline (Hsiao et al., 2022; Stubbs et al., 2017), and further indicates that engaging in ≥ 3 h/day of LPA could increase the chance of maintaining or improving the orientation function when compared with engaging in < 3 h/day of LPA. A possible explanation for the main finding of this study is that engaging in ≥ 3 h/day of LPA is associated with a lower white matter hyperintensity (WMH) volume (Spartano et al., 2019), which was very common findings on brain magnetic resonance imaging (MRI) or computed tomography (CT) scans in older adults and patients with stroke and dementia (Wardlaw et al., 2015); higher WMH volume exhibited significantly lower functional connectivity within the default-mode network (DMN) (Zhang et al., 2021), which mental orientation in space, time, and person is managed by Peer et al. (2015). Moreover, the result of a longitudinal study has indicated that physical activity was positively associated with the cortical connectivity within the DMN (Boraxbekk et al., 2016). Thus, lower white matter hyperintensity volume and higher connectivity within DMN may be factors influencing the orientation function of older adults that regularly engage in LPA. More specifically, the orientation function can be divided into two types in MMSE: time and spatial orientation. Time disorientation is related to global acute or chronic brain dysfunction, requiring bilateral lesions (Dumurgier et al., 2016). Spatial orientation can be categorized into several types — including landmark, egocentric, heading, and anterograde agnosia — related to the posterior parietal lobe of the brain, right hippocampus, and parahippocampal gyrus (Tseng and Fang, 2022). From the above, it is evident that to further investigate the physiological mechanisms linking LPA with specific domains of cognitive function, future research could focus on white matter and lateral ventricles. Also, future studies should further explore how LPA affects brain structures related to orientation.

The cross-sectional and longitudinal associations between engaging in ≥ 3 h/day of LPA and cognitive function are different. While engaging in ≥ 3 h of LPA was beneficial to language performance in the unadjusted model in the short-term, the longitudinal relationship became negatively significant between engagement in LPA and the maintenance or increase of the language score in the adjusted model. The reason may be first

that the number of individuals with maximum scores of language domain in MMSE was already high in the cross-sectional findings (145/167 participants); the number of participants whose language performance remained unchanged or improved increased slightly to 155, causing the negative longitudinal relationship. Additionally, a longitudinal study demonstrated that orientation was the better domain to predict the overall MMSE score compared with other domains (Guerrero-Berroa et al., 2009), meaning that the language domain may be less discriminating. Moreover, previous research has also indicated the negative relationship between physical activity and language function, demonstrating that the comprehension speed of language of older adults became slower after the exercise training intervention, which was inferred to be related to the cost of language processing (Fernandes et al., 2024).

This study featured several strengths; first, objective instruments (triaxial accelerometers) were used to evaluate PA levels, enhancing the robustness and validity of the study results. Second, a comprehensive range of potential covariates in the analysis were included. Adjusting for these covariates underscored the robustness of the findings, supporting a significant positive longitudinal association between LPA and the orientation function. Third, our findings demonstrated that LPA specifically benefits orientation cognitive function, providing a basis for institutions to recommend it for maintaining or enhancing orientation cognitive function in older adults in a long term.

This study also had some limitations; first, due to time constraints and limited accelerometers, our study's small sample size may cause wide confidence intervals, along with primarily urban participants with a low likelihood of cognitive impairment (from 8.4% at baseline to 11.4% at the follow-up) may affect the generalizability of the results to the overall population of older Taiwanese adults (Cassarino et al., 2016). Second, the sociodemographic, lifestyle behavior, and accelerometer-measured data were only collected at baseline, potentially overlooking changes over a year. Future research should control and analyze lifestyle changes (e.g., exercise participation). Third, using the same version of MMSE at baseline and follow-up may result in practice effects (Galasko et al., 1993). Also, the prognostic capability for cognitive impairment and dementia risk of MMSE is limited. Future research can use various other cognitive assessment tools, such as Trail Making Test, Digit Symbol Coding, Delayed Recall Tests, Rey Auditory Verbal Learning Test, and Repeatable Battery for the Assessment of Neuropsychological Status, to provide a more comprehensive understanding of participants' cognitive status and avoid the ceiling effect. Lastly, our study calculated cognitive function changes by subtracting raw pre-test from raw post-test MMSE scores, potentially causing interindividual variability issues. And the high percentage of participants achieved maximum scores of cognitive functions, got maintained or increased scores, and engaged in $\geq$ 3 h/day of LPA, which may have influenced the results. While we examined the association between LPA and cognitive functions, we did not investigate differences between MVPA, LPA, and sedentary behavior, which should be explored further. Our research used binary logistic regression; future studies could use linear regression to better understand cognitive function variations.

5 Conclusion

This study demonstrated that engaging in $\geq$ 3 h/day of LPA was associated with the maintenance or improvement of the orientation function in older adults over a period of 1 year. Maintaining or increasing orientation cognitive function in a long term could be achieved by engaging in LPA according to this finding, particularly for older adults who are unable to participate in higher-intensity PA. As preliminary research, our study uniquely contributes to the literature by highlighting the specific benefit of LPA on orientation function, laying the groundwork for future research to explore these associations further and to investigate the impact on other domains of cognitive function.

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 Research Ethics Committee of the National Taiwan University Hospital (202008046RINC). 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. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

J-HJ: Conceptualization, Formal Analysis, Writing – original draft. JC: Formal Analysis, Writing – review and editing. T-FL: Formal Analysis, Writing – review and editing. J-HP: Supervision, Funding acquisition, Writing – review and editing. YL: Conceptualization, Supervision, Writing – review and 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.

The reviewer G-MK declared a shared affiliation with the authors T-FL, J-HP to the handling editor at the time of review.

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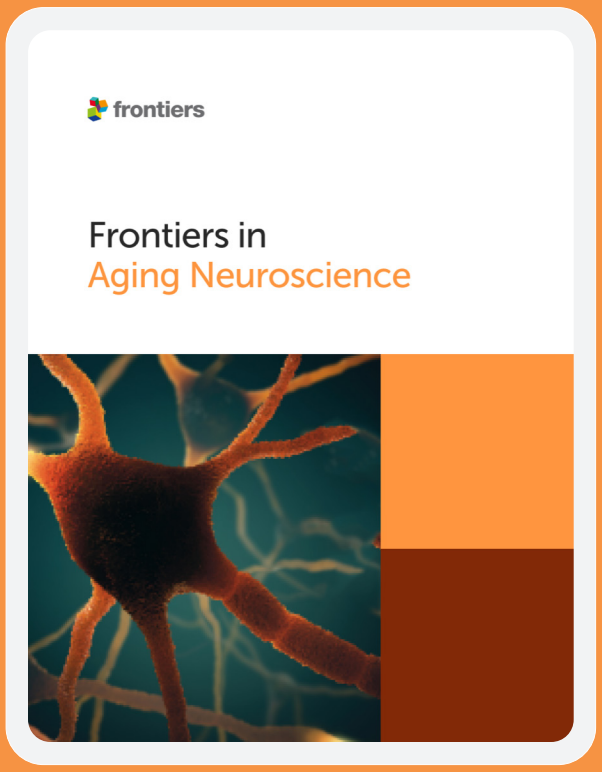

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