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Panoramic view of cognitive impairment: Interdisciplinary cognitive research

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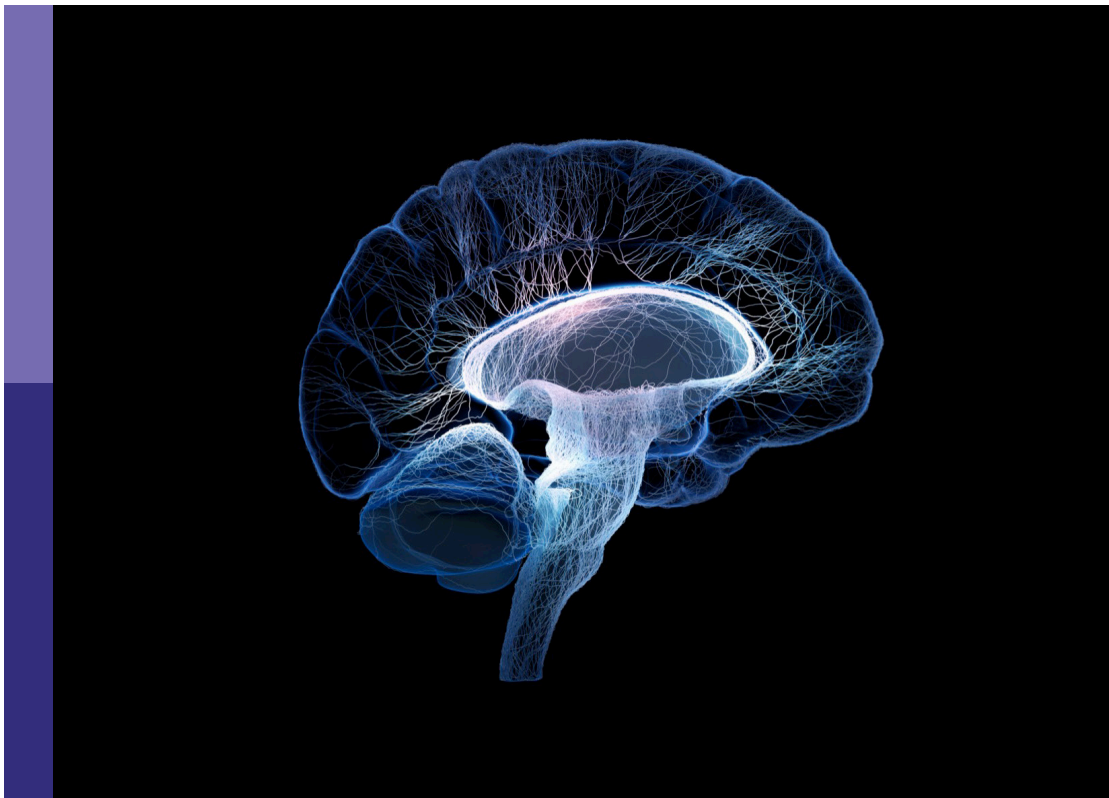
Published in
Frontiers in Neuroscience
Frontiers in Aging Neuroscience



ISSN 1664-8714
ISBN 978-2-8325-5251-3
DOI 10.3389/978-2-8325-5251-3

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Panoramic view of cognitive impairment: Interdisciplinary cognitive research

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Citation

Tian, C., Ge, S., Ma, L., Xiao, Y., Xu, F., eds. (2024). *Panoramic view of cognitive impairment: Interdisciplinary cognitive research*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-5251-3

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frontiers | Frontiers in Neuroscience

TYPE Editorial
PUBLISHED 22 July 2024
DOI 10.3389/fnins.2024.1453945

OPEN ACCESS

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RECEIVED 24 June 2024
ACCEPTED 11 July 2024
PUBLISHED 22 July 2024

CITATION
Tian C, Ge S, Ma L, Xiao Y and Xu F (2024) Editorial: Panoramic view of cognitive impairment: interdisciplinary cognitive research. *Front. Neurosci.* 18:1453945. doi: 10.3389/fnins.2024.1453945

Editorial: Panoramic view of cognitive impairment: interdisciplinary cognitive research

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KEYWORDS

cognition, interdisciplinary research, phenomenological description, risk factors, diagnosis

Editorial on the Research Topic
Panoramic view of cognitive impairment: interdisciplinary cognitive research

Cognition, information processing activities for individuals to understand the objective world, is a reflection of the real world in the human brain. Cognitive impairment refers to a decline in cognitive functioning of varying degrees, from subjective cognitive impairment to severe dementia. With the accelerated global population aging, the number of people with cognitive impairment is increasing rapidly. Dementia has become a major contributor to the global burden of disease and loss of disability-adjusted life years. Cognitive impairment is a heterogeneous syndrome, the cause of which is still myriad. Although significant advancement in the understanding of the pathology of cognitive impairment has been made in recent decades, the tools and strategies at our disposal to deal with cognitive impairment are still very limited. Currently, no disease-modified treatment has been identified.

Interdisciplinary research refers to the methodology of comprehensive understanding or problem-solving through the intersection between natural science, social science, and other disciplines or the internal intersection between many disciplines within a certain category of science. It is conducive to the overall understanding of problems and identifying effective solutions to complex problems faced by human society. In recent years, studies in many fields other than neurology have inspired our understanding of cognitive impairment, putting forward new insights into its phenomenology and providing many effective prevention or alleviation strategies to delay cognitive decline or manage the symptoms. It is very likely that interdisciplinary research would shed light on our efforts to cope with the challenges brought by the growing epidemic of cognitive impairment.

This research initiative aims to publish cutting-edge, interdisciplinary studies that contribute to a deeper understanding of cognitive impairment. The primary objectives include identifying underlying contributing factors, developing tools for assessment, diagnosis, treatment, or rehabilitation of cognitive impairment, and enhancing daily

functioning and quality of life for affected individuals. The overarching goal is to address the escalating epidemic of cognitive impairment. The scope of Research Topics encompasses a wide range, including providing a phenomenological description of the prevalence, risk factors, manifestations, and prognosis of cognitive impairment from diverse disciplinary perspectives. The research also encourages the proposal of novel preventive strategies, the development of innovative assessment and diagnostic methods, and the implementation of multidisciplinary interventions to enhance cognitive functioning and alleviate associated symptoms. The emphasis extends to strategies that aim to preserve daily functioning and improve the overall quality of life for individuals grappling with cognitive impairment. The call welcomes various types of contributions, particularly Original Research Articles, Clinical Trials, Systematic Reviews, Meta-analyses, Reviews, and Mini Reviews. This comprehensive approach seeks to foster advancements in our ability to comprehend, address, and ultimately mitigate the impact of cognitive impairment on individuals and society.

At last, an array of studies addressing cognitive functioning in older adults from different angles were included. Each article presents unique insights, contributing to a nuanced understanding of the multifaceted factors influencing cognitive health. The gathered research spans various dimensions, shedding light on both traditional and emerging aspects of this critical Research Topic.

In exploring the multifaceted landscape of cognitive health in older adults, several studies have delved into diverse aspects of the issue. The study entitled "*Higher blood cotinine level is associated with worse cognitive functioning in non-smoking older adults*" by Fu et al. probed the relationship between secondhand smoke (SHS) exposure, quantified by serum cotinine level, and cognitive functioning in 2,703 non-smoking adults aged 60 and above. It revealed a concerning association, indicating that elevated cotinine levels correlated with diminished cognitive scores, affecting memory, fluency, and overall cognitive function negatively. This study underscores the imperative of reducing SHS exposure in older adults to safeguard cognitive health, advocating for targeted public health interventions. Moving beyond conventional factors, the article "*Sensory impairment and cognitive decline among older adults: An analysis of mediation and moderation effects of loneliness*" by Ge et al. unraveled intricate connections between sensory impairment, loneliness, and cognitive decline. Emphasizing the importance of addressing social and psychological wellbeing in older adults with sensory impairment, the study highlighted that visual impairment coupled with heightened loneliness may exert a more detrimental impact on cognitive function than visual impairment alone. This study shed light on the nuanced interplay between sensory impairment, loneliness, and cognitive decline in aging populations. In another study entitled "*Impact of hearing loss on cognitive function in community-dwelling older adults: serial mediation of self-rated health and depressive anxiety symptoms*," by Chen et al. it was found that hearing loss not only directly affected cognitive function negatively but also had an indirect impact through self-rated health and depressive anxiety symptoms. Serial mediation analysis indicated that the total indirect effect of self-rated health and depressive anxiety symptoms accounted for 52.04% of the total effect of the model. This underscores the importance of enhancing self-rated health and promoting good mental health to potentially delay the cognitive decline associated with hearing loss in older adults. Risk factors for agitation in home-cared older adults with dementia are dissected through evidence gleaned from a substantial elder population in East China. The article "*Risk factors for agitation in home-cared older adults with dementia: evidence from 640 elders in East China*" by Liu et al. revealed that 42.8% of the sample exhibits agitated behaviors. Risk factors include basic health issues such as activities of daily living (ADL), family support issues measured by the Zarit Burden Interview (ZBI) scale and Family APGAR Questionnaire (APGAR), and behavioral awareness issues like falls and scalds. Older adults with severe ADL disorders, a high ZBI score, severe APGAR disorders, and a history of falls or scalds are more likely to exhibit agitated behaviors.

The Research Topic unfolded the intricate association between serum biomarkers and cognitive health, touching upon lead levels, globulin, cystatin C, and cardiovascular risk markers. The study "*Concurrent serum lead levels and cognitive function in older adults*" by Deng et al. investigated the correlation between serum lead levels and cognitive function in older adults from the National Health and Nutrition Examination Survey (NHANES) 2011–2013, showed that serum lead concentration was not associated with cognitive performance in older adults. The study "*Association between serum globulin and cognitive impairment in older American adults*" by Huang et al. revealed a non-linear association between serum globulin levels and cognitive impairment, with inflection points identified for specific tests. Elevated serum globulin was linked to increased cognitive impairment, emphasizing a potential threshold effect. The findings highlighted the complex, non-linear nature of the association between serum globulin and cognitive function. The cross-sectional study entitled "*Association between serum cystatin C level and cognition in older adults: a cross-sectional analysis*" by Wang S. et al. investigated the relationship between serum Cystatin C levels and cognition in U.S. older adults. Revealing that higher serum Cystatin C levels were independently associated with lower scores in processing speed, sustained attention, and working memory. This research identified a potential link between kidney function, as indicated by Cystatin C levels, and specific cognitive domains.

Similarly, the article titled "*Association of Life's Simple 7 with mild cognitive impairment in community-dwelling older adults in China: a cross-sectional study*," by Yang et al. a cross-sectional study in Chinese community-dwelling older adults, investigated the association between Life's Simple 7 (LS7), a cardiovascular health metric, and mild cognitive impairment (MCI). The study found a significant association between MCI and both the overall LS7 score and the biological score, even after adjusting for demographic and cardiovascular factors, suggesting that adhering to LS7 guidelines may have a positive impact on preventing MCI in the community, implementing LS7 guidelines could serve as a valuable strategy for community-based interventions to safeguard cognitive health in older adults. This research highlighted the potential link between

cardiovascular health and cognitive wellbeing. These studies underscored the importance of holistic approaches for cognitive wellbeing in older individuals. A population-based cross-sectional study entitled "*The neutrophil-to-lymphocyte ratio is associated with mild cognitive impairment in community-dwelling older women aged over 70 years: a population-based cross-sectional study*" by Li et al. revealed that a higher NLR was an independent risk factor for MCI in women older than 70, with an odds ratio of 1.28. The review "*The role of pyroptosis in cognitive impairment*" by Yang and Tang explored the role of pyroptosis, a pro-inflammatory form of programmed cell death, in the occurrence and progression of cognitive impairment. The exploration of potential therapeutic implications of targeting pyroptosis offers valuable insights for future cognitive impairment research. Understanding the link between pyroptosis and cognitive decline may open new avenues for developing effective therapeutic interventions in the field.

The complex interplay between exercise, sleep, and cognitive health in older populations was studied in several studies. The study "*Threshold effects of the relationship between physical exercise and cognitive function in the short-sleep elder population*" by You et al. indicated a positive association between exercise volume and cognitive scores in the Animal Fluency and Digit Symbol Substitution tests. However, a two-piecewise linear regression model revealed a threshold effect, suggesting that cognitive benefits did not consistently increase with higher exercise volumes for short-sleep elders. The study challenges existing knowledge by proposing that cognitive performance in the short-sleep elderly group can be maintained with no more than 800 MET-min/week of physical exercise. The article "*Association between sedentary behavior and risk of cognitive decline or mild cognitive impairment among the elderly: a systematic review and meta-analysis*" by Cai et al. investigated the association between sedentary behavior (SB) and the risk of cognitive decline (CD) or mild cognitive impairment (MCI) in the elderly, revealing a significant positive association between SB and the increased risk of CD (OR = 1.69) or MCI (OR = 1.34) in the elderly. Subgroup analyses considering comorbidity, lifestyle, family structure, publication year, and region demonstrated statistical differences between groups, contributing to the understanding of heterogeneity sources. The findings support the notion that reducing sedentary behavior may contribute to maintaining cognitive health in the elderly and provide valuable evidence for clinicians and policymakers to promote healthy behaviors in the elderly population.

Several studies contribute valuable insights into the prevalence, diagnosis, and perception of cognitive health and prevention. The article "*Evidence from a meta-analysis and systematic review reveals the global prevalence of mild cognitive impairment*" by Song W-x. et al. aimed to determine the global prevalence of mild cognitive impairment (MCI). Analyzing 233 studies with 676,974 individuals aged above 50, the study found an overall global MCI prevalence of 19.7% and an increasing trend in global MCI prevalence, particularly after 2019, with a significant rise to 32.1%. Additionally, MCI prevalence was higher in hospitals (34.0%) compared to nursing homes (22.6%) and communities (17.9%), emphasizing the need for further attention and resource allocation to address MCI in at-risk populations. The study "*Perception and knowledge of dementia prevention and its associated socio-demographic factors in China: a community-based cross-sectional study*" by Song D. et al. extends to the realm of societal perceptions and knowledge surrounding dementia prevention. The authors found that only 32.4% of Chinese adults aged over 40 believed dementia was preventable. The findings underscore significant disparities in public knowledge and highlight the need for comprehensive educational programs targeting all age groups. The exploration offered a glimpse into the socio-demographic factors shaping these perspectives in China and emphasized that specific attention should be given to individuals with lower income and education levels to enhance their access to dementia prevention and management resources. Practical diagnostic tools are discussed. The authors of the article "*A dual-task gait test detects mild cognitive impairment with a specificity of 91.2%*" by Wang Y. et al. aimed to develop a convenient method for detecting mild cognitive impairment (MCI) in the community. Utilizing a novel dual-task gait test, in which participants went through a gait test while identifying animals in pictures (AniP-DT gait test), participants with MCI could be identified through the gait performance with a specificity of 91.2%, highlighting its potential as an easy and reliable screening tool for older adults in the community setting. The study emphasizes the significance of integrating dual-task gait assessments for community-based cognitive screening, offering a practical approach to detecting cognitive decline in aging populations. The article "*Machine vision-based gait scan method for identifying cognitive impairment in older adults*" by Qin et al. introduced a machine vision-based gait scan method, DO-GaitPart, for identifying cognitive impairment in older adults. Employing a dataset labeled with cognitive performance scores, DO-GaitPart outperforms other methods in gait recognition tasks and achieved a promising ROCAUC of 0.876 in cognitive state classification, offering a valuable tool for early detection and management of age-related cognitive impairments.

Exploring therapeutic interventions for mild cognitive impairment (MCI), two comprehensive reviews offer valuable insights into potential avenues for enhancing cognitive wellbeing. The systematic review and meta-analysis "*Donepezil combined with traditional Chinese medicine has promising efficacy on mild cognitive impairment: a systematic review and meta-analysis*" by Yu et al. evaluated the efficacy and safety of combining donepezil and traditional Chinese medicine (TCM) for treating mild cognitive impairment (MCI), revealing that the combination significantly improved cognitive function [Montreal Cognitive Assessment [MoCA] score] and activities of daily living (Barthel Index score) compared to donepezil alone. However, subgroup analysis suggested that MoCA scores did not significantly increase in MCI patients resulting from cerebrovascular diseases. This research provided insights into potential therapeutic approaches for MCI by combining Western medication with traditional Chinese medicine, although further high-quality studies are still needed to confirm these promising findings. In a parallel exploration, the review "*Effects of exercise therapy on patients with poststroke cognitive impairment: a systematic review and meta-analysis*" by Zhang et al. revealed that exercise therapy significantly improved cognitive function, motor function, and activities of daily living in individuals with poststroke cognitive impairment. The findings underscore the therapeutic benefits of exercise in enhancing

patients' both cognitive and physical performance, emphasizing the importance of medical practitioners prioritizing the active use of exercise therapy to enhance the cognitive function, motor skills, and daily living activities in stroke survivors. Together, these reviews contribute to a broader understanding of therapeutic strategies for cognitive impairment, emphasizing the potential of combined interventions and the pivotal role of exercise in promoting cognitive and physical wellbeing.

Collectively, this Research Topic offers a panoramic view of cognitive functioning in aging population, presenting a synthesis of evidence and insights from diverse angles. Bringing together these studies serves as a valuable resource for researchers, healthcare professionals, and policymakers seeking a comprehensive understanding of factors influencing cognitive health in older adults.

Author contributions

CT: Writing – review & editing, Writing – original draft, Funding acquisition, Conceptualization. SG: Writing – review & editing, Resources. LM: Writing – review & editing. YX: Writing – review & editing. FX: Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by the Humanities and Social Sciences Foundation of Ministry of Education of China (22YJC630126).

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

frontiers | Frontiers in Neuroscience

TYPE Original Research
PUBLISHED 24 November 2022
DOI 10.3389/fnins.2022.1080066

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Translational Neuroscience, a section of the journal Frontiers in Neuroscience

RECEIVED 25 October 2022
ACCEPTED 08 November 2022
PUBLISHED 24 November 2022

CITATION
Fu Z, Qi G, Qu Z, Lin X, Xu L, Shen B, Dong F and Ge S (2022) Higher blood cotinine level is associated with worse cognitive functioning in non-smoking older adults.
Front. Neurosci. 16:1080066.
doi: 10.3389/fnins.2022.1080066

Higher blood cotinine level is associated with worse cognitive functioning in non-smoking older adults

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Introduction: Secondhand smoke (SHS) is common in older adults; however, its cognitive effect is unclear. We aimed to examine the association between serum cotinine level and cognitive functioning among non-smoking older adults.

Materials and methods: A total of 2,703 older adults aged 60 and above from the National Health and Nutrition Examination (NHANES) Survey 2011–2014 were included. Serum cotinine level was analyzed in the laboratory. A level ≤10 ng/ml and a response of "no" to the question "Do you currently smoke?" were used to select non-smokers. Cognitive functioning was measured using the Consortium to Establish a Registry for Alzheimer's disease Word Learning subtest (CERAD-WL) immediate and delayed recall tests, the Animal Fluency test (AFT), and the Digit Symbol Substitution test (DSST). Multivariable linear regression models were constructed to examine the association between serum cotinine level quartile and test-specific and global cognition *z* scores adjusting for age, race/ethnicity, education, depressive symptoms, body mass index, alcohol use, smoking history, prevalent coronary heart disease (CHD), stroke, and systolic blood pressure.

Results: About half of the participants (mean age 70.5 years) were female (53.6%), non-Hispanic White (48.3%), and completed some college and above (50.2%). Multivariate linear regressions with a reference group being those in the 1st quantile (lowest) showed that participants in the 4th quartile (highest) of serum cotinine level had lower immediate recall [β = −0.16, 95% confidence interval (CI) = −0.29, −0.03], AFT (β = −0.19, 95% CI = −0.33, −0.05), DSST (β = −0.27, 95% CI = −0.39, −0.15), and global cognition (β = −0.26,

95% CI = −0.39, −0.14) *z* scores. Participants in the 3rd quartile had lower immediate recall (β = −0.16, 95% CI = −0.30, −0.02) and global cognition (β = −0.16, 95% CI = −0.29, −0.02) *z* scores. Participants in the 2nd quartile had lower delayed recall *z* scores (β = −0.16, 95% CI = −0.29, −0.02).

Conclusion: Higher serum cotinine level was associated with worse cognitive functioning in non-smoking older adults. Prevention and reduction of SHS in older adults may help protect their cognitive functioning.

KEYWORDS

cotinine, cognitive function, older adults, NHANES, secondhand smoke, tobacco

Introduction

Dementia primarily affects older adults, with an age-standardized prevalence ranging from 5 to 7% in older adults aged over 60 in most parts of the world (Prince et al., 2013). With 33.1 million disability-adjusted life years lost in 2019, Alzheimer's disease and related dementia (ADRD) has emerged as a major global cause of mortality and morbidity in older adults (Nandi et al., 2022). With the population aging, by 2060, 13.9 million Americans are expected to have ADRD, with the prevalence of ADRD reaching 3.3% in US adults aged ≥65 years (Matthews et al., 2019). Globally, 35.6 million people were estimated to have dementia in 2010, which is expected to nearly double in 20 years, reaching 65.7 million in 2030 and 115.4 million in 2050 (Prince et al., 2013). Thus, older adults, their caregivers, communities, and healthcare systems worldwide are seriously threatened by ADRD now and in the future. ADRD negatively affects a person's memory, thought processes, and functioning (Ge et al., 2018, 2020). People with ADRD and their families are subject to a significant financial burden as a result, which is primarily incurred by increased home healthcare costs (Deb et al., 2018). Since ADRD is currently incurable, one of the main strategies to reduce the burden of the disease is to spot and address modifiable risk factors before the clinical manifestation of ADRD.

Active smoking is considered a modifiable risk factor for ADRD (Peters et al., 2008; Rusanen et al., 2011). Even though cigarette smoking has declined in the US over the past few decades, it is still common among older adults, with 9% of those 65 and older reporting that they currently smoke (Cornelius et al., 2022). Many studies have examined the relationship between active tobacco smoking and cognitive functioning in older adults, with most studies supporting the harmful cognitive effects of tobacco smoking (Ott et al., 2004; Llewellyn et al., 2009; Orsitto et al., 2012; Vermeulen et al., 2018; Nadar et al., 2021) and a few having the opposite finding (Ge et al., 2020). Besides active smoking, secondhand smoke (SHS) exposes a lot of older adults to tobacco (Craciun et al., 2022). SHS, also called passive smoking, refers to a circumstance in which a non-smoker is exposed to either side-stream or mainstream smoke and therefore inhales another person's smoke (Ling and Heffernan, 2016). A limited number of studies have examined the effect of SHS on cognitive functioning in this population (Llewellyn et al., 2009). Among the existing studies, most used participants' self-report exposure to SHS (Friedrich, 2007; Barnes et al., 2010; Heffernan and O'Neill, 2013; Bai et al., 2020) and thus was unprecise and subject to recall and report bias. Thus, studies involving the use of biomarkers to objectively measure the extent of SHS are needed to clarify its relationship with cognitive functioning in this growing population.

In this study, we utilized the National Health and Nutrition Examination Study (NHANES) 2011–2014 waive of data (NHANES) to examine the relationship between serum cotinine level and cognitive functioning in a group of non-smoking older adults. The findings of this study will provide implications for clinical practice and policy development to protect cognitive functioning in the growing number of older adults in most countries of the world.

Materials and methods

The parent study design and recruitment

Every 2 years, the NHANES, a continuous cross-sectional survey of civilian, non-institutionalized adults and children in the United States, is conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention (CDC) (NHANES). A complex, multistage probability strategy involving a selection of census blocks or area segments within clusters of census blocks is used to recruit participants all over the US for each 2-year cycle (Johnson et al., 2013). The socio-demographic, health, and nutritional status of participants are evaluated using in-person interviews at participants' homes and medical exams at mobile

exam centers with specialized equipment. For this analysis, the NHANES 2011–2012 and the NHANES (2013/2014) were merged to increase power. People who were aged 60 and above, did not actively smoke at the time of the survey, and had available information on serum cotinine level and cognitive functioning were included. A total of 9,338 individuals took part in the NHANES 2011–2012 survey and 9,813 individuals in the NHANES (2013/2014) survey. We excluded those who aged < 60 (n = 15,679), had missing data on serum cotinine level (n = 228), self-reported "yes" to the question, "Do you currently smoke?" (n = 423), or had a serum cotinine level > 10 ng/ml (n = 118). People whose serum cotinine level > 10 ng/ml were excluded from the analysis because serum cotinine level greater than 10 ng/ml is almost universally present in every smoker (Hukkanen et al., 2005). Finally, a total of 2,703 non-smoking participants aged 60 and above were included in this study.

Ethical considerations

The National Center for Health Statistics Research Ethics Review Board gave its approval to NHANES. This study was granted an exemption by the University of Houston-Downtown Committee for the Protection of Human Subjects because we only used de-identified, publicly available data.

Measures

Independent variable: Quartile of serum cotinine level (ng/ml)

As the primary metabolite of nicotine with a half-life of about 15–20 h, cotinine levels in bodily fluids can serve as indicators of SHS as well as active smoking (Llewellyn et al., 2009). The Division of Laboratory Sciences, National Center for Environmental Health, and CDC collected participants' serum samples during physical exams, aliquoted them, and kept them frozen at −20°C until they could be analyzed. The isotope-dilution high-performance liquid chromatography/atmospheric pressure chemical ionization tandem mass spectrometric (ID HPLC-APCI MS/MS) technique was used to measure serum cotinine level. The detailed method has been published elsewhere (Jacob et al., 2011). A blank and two quality-control pools were used in each analytical run. Quality control/quality assurance program was conducted by the Division of Laboratory Sciences, National Center for Environmental Health, and CDC; therefore, precise and accurate results were reported (Caudill et al., 2008). Using the variance from the repeated analysis of a small, spiked serum sample (0.2 ml), this method for measuring serum cotinine has a lower detection limit of 0.015 ng/ml.

Dependent variable: Cognitive functioning

Several cognitive psychomotor tests, including the Consortium to Establish a Registry for Alzheimer's Disease Word Learning subtest (CERAD-WL), the Animal Fluency test (AFT), and the Digit Symbol Substitution test (DSST) were used to assess participants' cognitive functioning.

(1) The CERAD-WL assessed participants' immediate and delayed learning ability for new verbal information and included an immediate recall test and a delayed recall test after three successive immediate learning trials (Davis et al., 1992; Fillenbaum et al., 2008). In the immediate recall test, participants were required to read aloud ten random words displayed on a computer screen as large, bolded letters, one at a time, during each of the three learning trials. Participants were instructed to remember and recall as many of the 10 words as they could right away. Each time, these 10 words were presented in a different order. The maximum score for each trial is 10. Consequently, the participant's immediate recall score was represented by the sum of the three trials' scores, which ranged from 0 to 30. Participants were asked to recall as many words from the same 10-word list as they could after completing the DSST and AFT, the other two cognitive tests. This served as their delayed recall test. The number of accurate words that the participant could recall determined their delayed recall test score, which ranged from 0 to 10. It has been used in major epidemiologic studies of diverse racial and cultural communities (Morris et al., 1989; Prince et al., 2003; Gao et al., 2009).

(2) The AFT was used to measure participants' language fluency, a component of executive function (Strauss et al., 2006). The participants were given 60 s to name as many animals as they could. One point was awarded for each animal identified. The AFT has been shown to differentiate mild cognitive impairment and probable Alzheimer's disease in older people with a sensitivity of 98.8% (García-Herranz et al., 2020). The AFT has been used in large-scale screenings and epidemiologic studies (Clark et al., 2009).

(3) Participants' processing speed, sustained attention, and working memory was evaluated by the DSST, which was a performance module from the Wechsler Adult Intelligence Scale (WAIS-III) (Ryan and Schnakenberg-Ott, 2003). This test was given using a paper form with a top-mounted key that had nine numbers and paired symbols. The 133 boxes next to the 133 numbers containing the corresponding symbols had to have the symptoms copied to them within the allotted 2 min. The total number of right matches determined the DSST score, ranging between 0 and 133. The DSST has been used in large screening, epidemiological, and clinical studies (Plassman et al., 2007; Proust-Lima et al., 2007).

Covariates

To control for potential confounding between serum cotinine level and cognitive functioning, after reviewing several related studies (Peters et al., 2008; Pan et al., 2018; Ge et al., 2020; Yang et al., 2022), we included the following

covariates in the analysis- age (years), sex (male or female), race/ethnicity (Mexican Americans, other Hispanics, non-Hispanic White, or non-Hispanic Black), education (below high school, high school graduate, or some college or above), depressive symptoms, body mass index (<18.5, 18.5–24.9, 25–29.9, or ≥30 kg/m^2), alcohol use (0–1 drink per day, 2 drinks per day, or 3 and more drinks per day), smoking history (former smokers or never smokers), prevalent coronary heart disease (CHD) (yes or no), stroke (yes or no), and systolic blood pressure (mmHg). All the above information was collected from face-to-face interviews or assessed during health exams. The Patient Health Questionnaire (PHQ-9) total score (range 0–27) was used to represent depressive symptoms (Kroenke et al., 2001). Regarding smoking history, if participants responded "no" to the question, "Have you smoked at least 100 cigarettes in your entire life?," they were categorized as never smokers; otherwise, they were categorized as former smokers.

Statistical analysis

Standardized *z* scores of the CERAD-WL immediate recall, the CERAD-WL delayed recall, the AFT, and the DSST were calculated using means and standard deviations of the cognitive test scores. Then, global cognition *z*-scores were calculated using the means and standard deviations of all test-specific *z*-scores. Multivariable regression models were used to examine the independent relationship between quartiles of serum cotinine level (reference: 4th quartile, the lowest quantile) and test-specific and global cognition *z*-scores, controlling the covariates mentioned above. Prior to constructing the regression models, we examined whether there was multicollinearity among the covariates. The variance inflation factor (VIF) was less than 10, indicating no multicollinearity (Miles, 2014). A 95% confidence interval (CI) excluding zero was considered as statistical significance. All analyses were performed using SPSS 25.0.

Results

The characteristics of the excluded participants due to missing values and being current smokers (n = 769) were summarized in the Supplementary Appendix. Compared with the included participants, the excluded participants were younger, more likely to be male, non-Hispanic Blacks, and completed less education. They were also more likely to have higher systolic blood pressure, more depressive symptoms, normal body mass index, more alcohol use, lower CERAD W-L delayed recall, lower AFT, and lower DSST scores.

The characteristics of the study population were presented in **Table 1**. The 2,703 participants had a mean age of 70.5 years [standard deviation (SD) = 7.0]. About half of them were female (53.6%), non-Hispanic White (48.3%), completed some college or above (50.2%), had a BMI ≥ 30 kg/m^2 (38.1%), drank 0–1 drink of alcohol use per day (29.3%), and were never smokers (58.2%). The participants had a mean of 2.4 h of physical activity every week, a mean of 190.4 mg/dl total cholesterol, and a mean of 124.5 mmHg systolic blood pressure. Their mean serum cotinine level (ng/ml) was 0.13 (SD = 0.60), ranging from 0.01 to 9.90. Their mean CERAD-WL immediate recall, CERAD-WL delayed recall, AFT, and DSST score was 18.6 (SD = 5.1), 5.8 (SD = 2.4), 16.5 (SD = 5.5), and 46.5 (SD = 17.5), respectively.

The means and 95% CI of the cognitive test-specific *z* scores by serum cotinine level quartiles were presented in **Table 2**. For participants in 1st quartile (lowest) of serum cotinine level, their mean *z* score of CERAD W-L immediate recall, CERAD W-L delayed recall, AFT, and DSST was 0.09 (95% CI = −1.85, 2.03), 0.10 (95% CI = −1.85, 2.05), 0.13 (95% CI = −1.81, 2.08), and 0.21 (95% CI = −1.75, 2.17), respectively. For participants in 2nd quartile of serum cotinine level, their mean *z* score of CERAD W-L immediate recall, CERAD W-L delayed recall, AFT, and DSST was −0.03 (95% CI = −2.07, 2.01), −0.08 (95% CI = −2.20, 2.04), 0.04 (95% CI = −2.08, 2.16), and 0.03 (95% CI = −1.94, 1.99), respectively. Among participants in the 3rd quartile, their mean *z* score of CERAD W-L immediate recall, CERAD W-L delayed recall, AFT, and DSST was 0.00 (95% CI = −1.92, 1.91), 0.03 (95% CI = −1.92, 1.97), −0.01 (95% CI = −1.81, 1.79), and 0.02 (95% CI = −2.02, 2.06), respectively. The mean *z* score of CERAD W-L immediate recall, CERAD W-L delayed recall, AFT, and DSST was −0.09 (95% CI = −2.10,1.92), −0.05 (95% CI = −1.98, 1.88), −0.18 (95% CI = −2.07,1.71), −0.19 (95% CI = −2.07, 1.65), respectively among participants in the 4th quartile (highest). The mean global cognition *z* score of quartiles 1–4 was 0.13 (95% CI = −1.82, 2.07), −0.04 (95% CI = −2.12, 2.04), −0.03 (95% CI = −1.93, 1.88), −0.21 (95% CI = −2.07, 1.65), respectively.

Multivariate linear regressions results (**Table 3**) showed that participants in the 4th quartile (highest) of serum cotinine level, compared with those in the 1st quantile (lowest), had lower immediate recall (β = −0.16, 95% CI = −0.29, −0.03), AFT (β = −0.19, 95% CI = −0.33, −0.05), DSST (β = −0.27, 95% CI = −0.39, −0.15), and global cognition (β = −0.26, 95% CI = −0.39, −0.14) *z* scores. Participants in the 3rd quartile, compared with those in the 1st quartile, had lower immediate recall (β = −0.16, 95% CI = −0.30, −0.02) and global cognition (β = −0.16, 95% CI = −0.29, −0.02) *z* scores. Participants in the 2nd quartile, compared with those in the 1st quartile, had lower delayed recall *z* scores (β = −0.16, 95% CI = −0.29, −0.02). All results were controlled for age, race/ethnicity, education, depressive symptoms, body mass index, alcohol use, smoking history, prevalent CHD, stroke, and systolic blood pressure.

TABLE 1 Characteristics of the participants by quartile of serum cotinine level[a].

Variables	Quartile 1 ≤0.01 ng/ml (*n* = 1,205)	Quartile 2 0.01 < cotinine ≤ 0.02 ng/ml (*n* = 451)	Quartile 3 0.02 < cotinine ≤ 0.04 ng/ml (*n* = 398)	Quartile 4 >0.04 ng/ml (*n* = 649)	Total (*n* = 2,703)
Age (years)	71.4 (6.9)	69.9 (7.0)	69.5 (6.8)	69.7 (7.0)	70.5 (7.0)
Sex [*n* (%)]					
Male	517 (42.9%)	216 (47.9%)	189 (47.5%)	331 (51.0%)	1,253 (46.4%)
Female	688 (57.1%)	235 (52.1%)	209 (52.5%)	318 (49.0%)	1,450 (53.6%)
Race/ethnicity [*n* (%)]					
Mexican Americans	123 (10.2%)	49 (10.9%)	28 (7.0%)	49 (7.6%)	249 (9.2%)
Other Hispanics	123 (10.2%)	55 (12.2%)	50 (12.6%)	43 (6.6%)	271 (10.0%)
Non-Hispanic Whites	717 (59.5%)	182 (40.4%)	163 (41.0%)	243 (37.4%)	1,305 (48.3%)
Non-Hispanic Blacks	150 (12.4%)	98 (21.7%)	87 (21.9%)	223 (34.4%)	558 (20.6%)
Other	92 (7.6%)	67 (14.9%)	70 (17.6%)	91 (14.0%)	320 (11.8%)
Education [*n* (%)]					
Below high school	256 (21.3%)	133 (29.5%)	112 (28.1%)	222 (34.2%)	723 (26.7%)
High school graduate	249 (20.7%)	96 (21.3%)	106 (26.6%)	170 (26.2%)	621 (23.0%)
Some college or above	699 (58.0%)	222 (49.2%)	179 (45.0%)	255 (39.3%)	1,355 (50.2%)
Body mass index [*n* (%)]					
<18.5 kg/m^2	12 (1.0%)	5 (1.1%)	3 (0.8%)	11 (1.7%)	31 (1.1%)
18.5–24.9 kg/m^2	300 (24.9%)	104 (23.1%)	96 (24.1%)	137 (21.1%)	637 (23.6%)
25.0–29.9 kg/m^2	429 (35.6%)	167 (37.0%)	146 (36.7%)	214 (33.0%)	956 (35.4%)
≥30 kg/m^2	445 (36.9%)	167 (37.0%)	143 (35.9%)	274 (42.2%)	1,029 (38.1%)
Smoking					
Never	745 (61.8%)	277 (61.4%)	233 (58.5%)	318 (49.0%)	1,573 (58.2%)
Former	460 (38.2%)	173 (38.4%)	165 (41.5%)	329 (50.7%)	1,127 (41.7%)
Alcoholic drinks/day					
0–1 drink	393 (32.6%)	144 (31.9%)	116 (29.1%)	140 (21.6%)	793 (29.3%)
2 drinks	165 (13.7%)	47 (10.4%)	45 (11.3%)	82 (12.6%)	339 (12.5%)
3 or more drinks	59 (4.9%)	30 (6.7%)	32 (8.0%)	79 (12.2%)	200 (7.4%)
Depressive symptoms	3.3 (4.8)	3.3 (5.5)	3.9 (5.4)	3.7 (5.2)	3.5 (5.1)
Physical activity (hours/week)	2.0 (5.9)	2.4 (7.6)	3.8 (33.8)	2.3 (9.2)	2.4 (14.6)
Total cholesterol (mg/dl)	192.2 (42.6)	188.0 (44.2)	190.6 (43.6)	188.5 (42.5)	190.4 (43.0)
Systolic blood pressure (mmHg)	123.9 (19.4)	125.4 (20.6)	123.5 (19.8)	125.7 (20.3)	124.5 (19.9)
CERAD W-L immediate recall	19.0 (5.0)	18.3 (5.2)	18.4 (4.9)	18.0 (5.1)	18.6 (5.1)
CERAD W-L delayed recall	6.0 (2.4)	5.6 (2.6)	5.8 (2.4)	5.6 (2.3)	5.8 (2.4)
Animal fluency test	17.1 (5.5)	16.6 (6.0)	16.3 (5.1)	15.3 (5.4)	16.5 (5.5)
Digit symbol substitution test	49.2 (17.4)	45.9 (17.5)	45.8 (18.2)	42.2 (16.4)	46.5 (17.5)

[a]Data was presented as mean (standard deviation) for continuous variables and *n* (%) for categorical variables.

TABLE 2 Cognitive *z*-scores and 95% confidence intervals (CIs) by quartile of serum cotinine level.

	Quartile 1 ≤0.01 ng/ml	Quartile 2 0.01 < cotinine ≤ 0.02 ng/ml	Quartile 3 0.02 < cotinine ≤ 0.04 ng/ml	Quartile 4 >0.04 ng/ml
CERAD W-L immediate recall	0.09 (−1.85, 2.03)	−0.03 (−2.07, 2.01)	0.00 (−1.92, 1.91)	−0.09 (−2.10, 1.92)
CERAD W-L delayed recall	0.10 (−1.85, 2.05)	−0.08 (−2.20, 2.04)	0.03 (−1.92, 1.97)	−0.05 (−1.98, 1.88)
Animal fluency test	0.13 (−1.81, 2.08)	0.04 (−2.08, 2.16)	−0.01 (−1.81, 1.79)	−0.18 (−2.07, 1.71)
Digit symbol substitution test	0.21 (−1.75, 2.17)	0.03 (−1.94, 1.99)	0.02 (−2.02, 2.06)	−0.19 (−2.03, 1.66)
Global cognition	0.13 (−1.82, 2.07)	−0.04 (−2.12, 2.04)	−0.03 (−1.93, 1.88)	−0.21 (−2.07, 1.65)

TABLE 3 The associations of quartile of serum cotinine level (Reference: ≤0.01 ng/ml) with test specific and global cognition *z* scores[a].

	Quartile 1 ≤0.01 ng/ml	Quartile 2 0.01 < cotinine ≤ 0.02 ng/ml	Quartile 3 0.02 < cotinine ≤ 0.04 ng/ml	Quartile 4 >0.04 ng/ml
CERAD W-L immediate recall	Reference	−0.07 (−0.20, 0.07)	**−0.16 (−0.30, −0.02)**	**−0.16 (−0.29, −0.03)**
CERAD W-L delayed recall	Reference	**−0.16 (−0.29, −0.02)**	−0.14 (−0.28, 0.01)	−0.12 (−0.25, 0.01)
Animal fluency test	Reference	0.04 (−0.11, 0.19)	−0.02 (−0.18, 0.13)	**−0.19 (−0.33, −0.05)**
Digit symbol substitution test	Reference	−0.10 (−0.23, 0.02)	−0.10 (−0.23, 0.03)	**−0.27 (−0.39, −0.15)**
Global cognition	Reference	−0.10 (−0.22, 0.04)	**−0.16 (−0.29, −0.02)**	**−0.26 (−0.39, −0.14)**

[a]All models were adjusted for age (years), sex (male or female), race/ethnicity (Mexican Americans, other Hispanics, non-Hispanic Whites, or non-Hispanic Blacks), education (below high school, high school graduate, or some college or above), BMI (<18.5, 18.5–24.9, 25.0–29.9, or ≥30 kg/m^2), alcohol use (0–1, 2, 3, or more drinks per day), smoking history (never or former), depressive symptoms, physical activity (hours/week), total cholesterol (mg/dl), and systolic blood pressure (mmHg). Bolded values mean statistically significant results (95% confidence interval excluding zero).

Discussion

In this group of 2,703 US non-smoking older adults, higher serum cotinine level is independently associated with worse new verbal information learning ability, language proficiency, executive functioning, processing speed, sustained attention, working memory, as well as global cognition. Although our results still need to be validated by longitudinal studies, they indicate that prevention and reduction of SHS in older adults may help protect their cognitive functioning.

Controversy exists on the association between SHS and cognitive functioning in older adults, although a limited number of studies have examined the relationship between the two and found a negative cognitive effect of SHS. In a longitudinal study of 6,875 middle-aged and older Chinese women, women who had lived with a smoking husband experienced a significantly faster decline in global cognitive function, visuospatial ability, and episodic memory function than those who had not (Bai et al., 2020). However, in that study, researchers failed to adjust important covariates such as body mass index, exercise, and alcohol use. In addition, SHS was assessed by self-report. Based on findings of another longitudinal study of 970 participants, in comparison to participants with 0–15 years' SHS exposure and ≤25% carotid artery stenosis, those with >25 years of SHS exposure and >25% carotid artery stenosis had a threefold increased dementia risk (Barnes et al., 2010). In that study, SHS was also assessed by self-report. In another study of college students (n = 68), daily prospective memory and executive function deficits were linked to SHS (Heffernan and O'Neill, 2013). However, the sample size of that study is small, and the researchers did not control any covariates. In another cohort study of Chinese middle-aged women, researchers found a significant decline in cognitive abilities, including memory, among Chinese women who are exposed to SHS, and this decline can last for up to 2 years (Pan et al., 2018). However, in that study, SHS was assessed by self-report, and the participants were not exclusively older adults. SHS was also assessed by self-report in another two relevant studies targeting older adults (Orsitto et al., 2012; He et al., 2020). In a cross-sectional study of 2,542 non-smoking older adults, each unit increase in log-transformed blood cotinine level resulted in a decrease in cognitive performance score of 2.03 points (Akhtar et al., 2013). However, the data of that study were collected two decades ago (between 1999 and 2002), and only one cognitive-specific test (the DSST) was analyzed. Thus, although many studies have examined this relationship, few used biomarkers to assess SHS and exclusively target a large sample of older adults.

The possible mechanisms that account for the negative association between SHS exposure and cognitive performance are complicated. One popular hypothesis is that the carbon monoxide in tobacco smoke obstructs blood's delivery of oxygen to the brain (Levy, 2015). Another possible explanation comes from animal studies. Studies have shown that animals exposed to various concentrations of harmful chemicals contained in tobacco smoke experienced a decline in neuronal mass in regions of the brain related to learning and memory (Bai et al., 2020). SHS exposure may also increase the risk of cardiovascular disease (Penn et al., 1994; Teo et al., 2006), which in turn elevates the risk of cognitive impairment and dementia (Otsuka et al., 2001; Newman et al., 2005). Even short-term SHS exposure has been shown to have detrimental effects on endothelial function and instantly impairs the cardiovascular system (Hachinski, 2007). Dysfunctional endothelial cells may lead to vasoconstriction, atherogenesis, and thrombosis, which may restrict blood supply to the brain. Additionally, SHS exposure is a risk factor for stroke (Bernal-Pacheco and Román, 2007), and the discrepancies in subclinical cerebrovascular disease may account for the different cognitive functions in late adulthood (Allwright et al., 2005). Despite these proposed mechanisms, the exact reasons underlying the differential effects of SHS on specific

cognitive domains are still unclear and need to be further studied.

There are many strengths of this study. To our knowledge, there are few studies that examined the relationship between SHS using serum cotinine level and cognitive functioning, exclusively targeting a large sample of non-smoking older adults. Therefore, our study makes a unique contribution to the literature and adds strong evidence of the negative cognitive effect of SHS in older adults. With our sample size being relatively large and representative, our study has good generalizability. Active smokers were removed using two criteria to make sure that the participants of this study were not current smokers. Additionally, global cognition was calculated to evaluate an older adult's overall cognition. Moreover, to lessen the possibility of residual confounding, a wide range of socio-demographic, lifestyle, mental health, and physical health covariates were adjusted. Studies have shown that with long-term cumulative damage, the consequence of smoking disproportionately affects older adults. Compared to non-smokers, older adults who are exposed to tobacco are more likely to suffer from common age-related diseases like diabetes, osteoporosis, cardiovascular disease, chronic kidney disease, and respiratory issues with worse management and outcomes (Burns, 2000). Thus, our study targeted a vulnerable population and an overlooked issue.

This study is subject to several limitations. First, this study is a cross-sectional design which prevents us from assessing the temporal relationship between SHS and cognitive functioning. Moreover, since cotinine has a short half-life (15–20 h), it only measures a person's recent exposure to tobacco and does not reflect his/her long-term exposure to tobacco. In addition, the excluded people due to missing data and being current smokers (n = 769) and the included participants (n = 2,703) had several ethnic, mental health, and lifestyle differences. Therefore, selection bias is likely (Lu et al., 2022). Finally, using three cognitive performance tests, we may not have assessed all cognitive domains. Future students are expected to use longitudinal designs to examine the temporal relationship between serum cotinine level and other biomarkers of tobacco exposure with a longer half-life, such as 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) (Goniewicz et al., 2011) and the full cognitive domains in non-smoking older adults, especially those from non-western countries.

The clinical implications of this study are as follows: In this study, we found an independent and negative relationship between serum cotinine level, a biomarker of tobacco exposure, and various domains of as well as global cognitive functioning in non-smoking older adults. Given the negative effects of SHS on cognitive functioning in older adults, policymakers should continually promote smoking-free policies and use social media and other educational approaches to inform the public of the negative effect of SHS. Clinicians and health educators should encourage older adults to prevent and reduce SHS exposure in clinical and community settings (Hovell and Hughes, 2009). For example, if an older adult has a partner who is a smoker, he should be given instructions on specific measures to reduce SHS. These joint efforts may help protect older adults' cognitive functioning.

In conclusion, higher serum cotinine level is independently associated with worse cognitive functioning in non-smoking older adults. Prevention and reduction of SHS in older adults may help protect their cognitive functioning.

Data availability statement

The data that support the findings of this study are openly available on the NHANES website and can be accessed at https://wwwn.cdc.gov/nchs/nhanes/Default.aspx.

Ethics statement

The NHANES were ethically reviewed and approved by the National Center for Health Statistics Research Ethics Review Board. The patients/participants provided their written informed consent to participate in this study.

Author contributions

GQ, ZF, SG, and XL drafted the initial manuscript, designed the study, and searched for literature. ZQ and LX conducted statistical analysis. BS, LX, and FD critically revised the manuscript. All authors contributed to the article and approved the submitted version.

Acknowledgments

We thank all participants in the NHANES Study. We also thank the NHANES research team for collecting and sharing the data.

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/fnins.2022.1080066/full#supplementary-material

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frontiers | Frontiers in Neuroscience

TYPE Original Research
PUBLISHED 05 December 2022
DOI 10.3389/fnins.2022.1093169

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Translational Neuroscience, a section of the journal Frontiers in Neuroscience

RECEIVED 08 November 2022
ACCEPTED 21 November 2022
PUBLISHED 05 December 2022

CITATION
Song D, Yu D and Sun Q (2022) Perception and knowledge of dementia prevention and its associated socio-demographic factors in China: A community-based cross-sectional study. *Front. Neurosci.* 16:1093169. doi: 10.3389/fnins.2022.1093169

Perception and knowledge of dementia prevention and its associated socio-demographic factors in China: A community-based cross-sectional study

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Background: Although considerable progress has been made on the risk factors of dementia, less is known about the extent of the gaps between the general public's understanding of dementia prevention and contemporary scientific evidence. This study aimed to determine the beliefs and knowledge of dementia prevention among the Chinese general public and examine the socio-demographic factors of the belief and knowledge of dementia prevention.

Methods: The study adopted a cross-sectional design. A total of 358 Chinese adults aged over 40 years were recruited from four healthcare centers. We designed questionnaires that include items on the belief of dementia prevention, risk factors for dementia, and health education needs regarding dementia prevention based on previous literature. Descriptive statistics and multivariate regression analyses were conducted.

Results: Only 32.4% of the respondents agreed that dementia is preventable. Less participants were able to correctly identify cardiovascular risk factors (i.e., obesity, diabetes, dyslipidemia, hypertension, unhealthy diet, smoking, and alcohol) as part of dementia risk factors. Younger age, higher education, and having contact with patients with dementia are associated with stronger belief that dementia is preventable. Older age, higher income, higher education, having memory complaint, and having contact with patients with dementia are associated with a better understanding of dementia risk factors. A total of 88.9% respondents thought that they are not well informed of dementia from public education, and most respondents (65%) prefer receiving dementia-related health advice from primary care providers.

Conclusion: The present study reveals the great gaps between the Chinese general public's knowledge of dementia prevention and the latest research evidence. Public health educational programs for all age groups are

encouraged to close this knowledge gap. More attention and resources should be paid to individuals with low income and low education level as they have limited access to dementia prevention information. Researchers should work in partnership with primary care providers to help translate evidence into community practice with a special focus on the link between cardiovascular risk factors and dementia.

KEYWORDS

dementia, risk factors, prevention, belief, knowledge

Introduction

The rapid aging of the global population entails an increase in the prevalence of cognitive impairment among older adults (Bettio et al., 2017). Dementia is one of the principal causes of disability and decreased quality of life amongst the elderly. In 2020, over 50 million people worldwide are living with Dementia (World Health Organization [WHO], 2022). This number is expected to increase to 63 million in 2030 and 114 million in 2050 (Wu et al., 2017). By 2030, the annual cost for dementia globally is projected to be 2 trillion dollars (Prince et al., 2016). Dementia has reached the forefront of the public health agenda because of its tremendous physical, emotional, and economic burden.

Dementia has no cure, but has a wide range of potentially modifiable risk factors. In 2019, the World Health Organization (WHO) published the latest guideline on the risk reduction of cognitive decline and dementia (World Health Organization [WHO], 2019). This guideline reviewed existing evidence on the 12 most substantial modifiable risk factors for dementia, including cardiovascular risk factors (i.e., hypertension, diabetes, dyslipidemia, and obesity), psycho-social factors (i.e., depression and social isolation), and lifestyle factors (i.e., low level of physical or mental activity, unbalanced diet, alcohol abuse and smoking, and hearing loss). Roughly one third of all dementia cases could be potentially prevented through the management of the modifiable risk factors (Livingston et al., 2017). These evidences highlight the opportunity for dementia prevention.

A good understanding of the modifiable risk factors for dementia may encourage preventative health behaviors, which ultimately reduce the incidence of dementia. In 2017, WHO released the global action plan on dementia, which urges all countries to implement campaigns to raise public awareness about dementia (World Health Organization [WHO], 2017). One of the major priorities to inform this action is to determine the knowledge gaps about cognitive health and related risk factors among the general public such that education programs can be most effectively targeted.

Although researchers have made considerable progress on the risk and preventive factors of dementia, less is known about the extent of the gaps between the general public's understanding of dementia prevention and contemporary scientific evidence. Yeo et al. (2007) surveyed older adults in the UK and found a poor overall knowledge of the risk and protective factors for dementia. Connell et al. (2007) surveyed the general public in the USA and found that nearly half of the respondents see dementia as unpreventable. Low and Anstey examined the patterns of beliefs underlying the behaviors and beliefs of the Australian public on what can reduce dementia risk (Low and Anstey, 2009); they concluded that the public perceptions of what might reduce dementia risk are not influenced by scientific evidence. The beliefs and knowledge about dementia prevention of those living in low- and middle-income countries are still largely unknown. China has the largest aging population and faces tremendous burden on dementia care. The general public's knowledge of dementia prevention is necessary to understand first to inform dementia risk reduction public health campaigns.

Therefore, the aim of this study was to compare the Chinese general public's understanding of dementia prevention and contemporary scientific evidence and to identify the socio-demographic factors related to the beliefs and level of knowledge regarding dementia prevention. Such an assessment can provide important insights for the design of dementia risk reduction strategies.

Materials and methods

Design and sample

A cross-sectional study design was used. This study was conducted in four community healthcare centers (CHCs) in Hangzhou City, southeast China, including Tianshui CHC, Wulin CHC, Huanbei CHC, and Huanxi CHC. In China, CHCs are set up by the government in communities to provide basic medical and public health services for the communities residents. The main work of medical treatment service in CHCs is to consult, diagnose, and treat residents for the common and frequently occurring chronic diseases. A consecutive sample of 358 adults aged over 40 years who visited the CHCs for

general medical service from September 2019 to December 2019 was recruited. Participants were excluded if they had a diagnosis of dementia or cognitive impairment or had impaired hearing or vision, which may inhibit them from giving consent and answering the questionnaires. This study was approved by the Zhejiang Chinese Medical University (No. SBREC-20181231). Written consent was obtained from each participant. All information was kept strictly confidential.

Measures

The questionnaire was designed by the research team in partnership with a neurological physician based on the most current evidence. Standardized tests, such as the Alzheimer's Disease Knowledge Scale (Carpenter et al., 2009), were not appropriate for this study, as they include few questions on dementia risk factors and do not have dementia prevention sub-scales according to the latest evidence. The self-designed questionnaire (**Supplementary material**) includes items on beliefs of dementia prevention, risk factors for dementia, and health education needs regarding dementia.

Attitude toward dementia prevention

The first section of the questionnaire contains two questions. The respondents were asked to circle 1 of 3 options: "yes," "no," and "no idea." The questions include (1) "Do you think that dementia is caused by normal aging?" (2) "Do you think that the risk of dementia can be reduced?"

Risk factors for dementia

The second section of the questionnaire has 12 items on dementia risk factors, which were chosen based on the latest evidence reported by the 2019 WHO guidelines on risk reduction of cognitive decline and dementia (World Health Organization [WHO], 2019). The dementia risk factors include hearing loss, smoking, alcohol abuse, unbalanced and unhealthy diet, hypertension, diabetes, dyslipidemia, obesity, physical inactivity, cognitive inactivity, depression, and social isolation. Participants were asked to identify risk factors and circle 1 of 3 options: "yes," "no," and "no idea."

Health education needs regarding dementia prevention

The last section of the questionnaire includes one item that asks the respondents whether they are well informed of dementia prevention from public education and five items regarding their preferred health education delivery format. The education delivery format includes community bulletin board, health talks by experts, advice from family physicians and community nurses, education booklets, and regular peer sharing. Participants were asked to tick their preferred education content and delivery format in the questionnaire.

Socio-demographic information

The key socio-demographic factors include age, gender, education, and income. In addition, the respondents were also asked to indicate whether they had memory complaint and whether they were in contact with anyone who had dementia.

Statistical analyses

Statistical analysis was performed with SPSS version 22. Continuous data are summarized in means with standard deviation (SD), and categorical data are presented as count and percentage. We calculated the percentage of participants who correctly answered each item on the questionnaire to assess the dementia prevention beliefs and knowledge. Multiple logistic regression was conducted with each item regressed on the socio-demographic factors. Adjusted odds ratios (AORs) and 95% confidence intervals (CIs) are presented. A Bonferroni multiple comparison correction was applied to the results of the logistic regression.

Results

Sample characteristics

A total of 358 adults were surveyed. The characteristics of the respondents are shown in **Table 1**. The mean age was 64.03 years (SD = 12.8), and most were aged 40–59 years (43.6%). A higher proportion of respondents were women (55.9%). Only 31.8% participants had an education level above high school. A higher proportion of the respondents had a monthly income less than the average city level (54.2%). Around half of the participants (45.5%) reported having contact with someone who had dementia, and around 80% of the participants had memory complaint.

Prevalence of beliefs and knowledge about dementia prevention

Approximately 41.9% of the respondents agreed that dementia is caused by normal aging. Less than one third of the respondents (32.4%) agreed that

TABLE 1 The characteristics of the respondents (N = 358).

Variables	N = 358
Age (mean ± SD)	64.0 ± 12.8
Age groups	
40–59	43.6%
60–69	24.0%
≥ 70	32.4%
Gender	
Male	158 (44.1%)
Female	200 (55.9%)
Marital status	
Married	262 (73.2%)
Single	96 (26.8%)
Education level	
Below high school	244 (68.2%)
High school and above	114 (31.8%)
Monthly income[a]	
Less than 4,000 CNY	194 (54.2%)
Above 4,000 CNY	164 (45.8%)
Having a close relative with dementia	
Yes	163 (45.5%)
No	195 (54.5%)
Having memory complaint	
Yes	286 (79.9%)
No	72 (20.1%)

[a]1 US dollar = 7 CNY.

dementia could be preventable. The proportions of each item identified by the participants as a risk factor for dementia are presented in Figure 1. Most of the participants (99.2%) correctly identified at least one risk factor, but only 12.3% of the respondents identified all the risk factors correctly. Among the risk factors, "stress and depression" was endorsed by the most respondents (78.2%). The percentage of participants who accurately identified the risk factors of dementia was 62.6% for social isolation, 58.1% for cognitive inactivity, 55.9% for physical inactivity, 44.7% for hypertension, 44.1% for hearing loss, 36.3% for obesity, 35.8% for diabetes, 34.1% for dyslipidemia, 33.2% for unhealthy diet, 30.7% for smoking, and 30.2% for alcohol.

Multivariable analysis of factors associated with dementia prevention beliefs

Table 2 presents the results for the significant correlates of dementia prevention beliefs. Compared with middle-aged adults (aged 40–59 years), older adults aged over 70 were more likely to believe that dementia is caused by normal aging (AOR = 1.99, 95% CI = 1.19–3.34) but were less likely to believe that dementia can be preventable (AOR = 0.47, 95% CI = 0.26–0.86). The participants with higher education level (high school and above) were more likely to believe that dementia can be preventable (AOR = 2.24, 95% CI = 1.34–2.75) than those with lower education level (below high school). Compared with the participants who were in contact with someone with dementia, the participants who were never in contact with patients with dementia were less likely to believe that dementia can be preventable (AOR = 0.48, 95% CI = 0.31–0.75). The beliefs of dementia prevention were not influenced by gender, income, marital status, or the presence of memory complaint.

Multivariable analysis of factors associated with knowledge on dementia risk factors

Table 3 present the results for the significant correlates of knowledge on dementia risk factors. Compared with middle-aged adults (aged 40–59 years), older adults were more aware that cognitive inactivity (aged ≥ 70 years: AOR = 3.84, 95% CI = 2.10–7.03), alcohol abuse (aged 60–69 years: AOR = 2.64, 95% CI = 1.49–4.66), dyslipidemia (aged ≥ 70 years: AOR = 2.48, 95% CI = 1.33–4.64), and unhealthy diet (aged ≥ 70 years: AOR = 2.73, 95% CI = 1.45–5.13) are dementia risk factors. Compared with the participants with lower education level (below high school), the participants with higher education level (high school and above) had a better understanding that obesity (AOR = 3.21, 95% CI = 1.79–5.75), smoking (AOR = 3.37, 95% CI = 1.79–6.34), and unhealthy diet (AOR = 3.57, 95% CI = 1.85–6.89) are risk factors for dementia. Compared with the participants who were in contact with someone with dementia, the participants who were never in contact with patients with dementia had lesser knowledge that diabetes (AOR = 0.41, 95% CI = 0.26–0.66) is a dementia risk factor. Gender, income, marital status, and the existence of memory complaint did not influence the awareness of dementia risk factors.

Health education needs of dementia

Most respondents (88.9%) thought that they were not well informed of dementia from public education by the government, media, or medical institution. When asked about their preferred health education delivery format, most respondents would like to receive advice from family physicians and community nurses (65%),

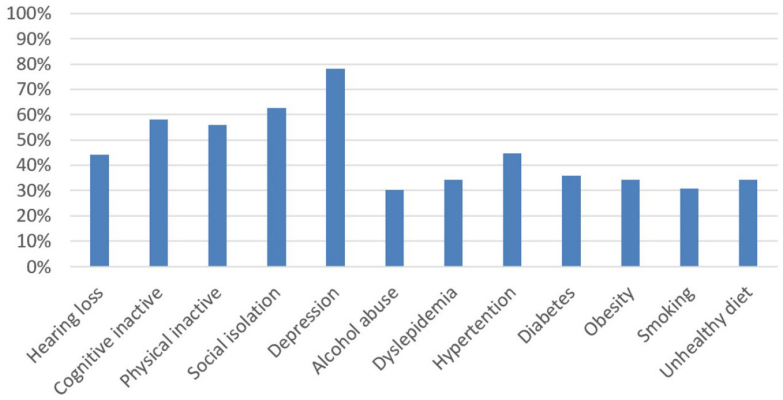

FIGURE 1
Proportion of participants who identified each dementia risk factor.

TABLE 2 Socio-demographic factors associated with dementia prevention beliefs.

	Dementia is caused by normal aging		Dementia can be preventable	
	AOR	95% CI	AOR	95% CI
Age group				
40–59 (Ref)				
60–69	0.87	0.49–1.54	1.73	0.98–3.04
≥ 70	1.99*	1.19–3.34	0.47*	0.26–0.86
Gender				
Men (Ref)				
Women	0.99	0.63–1.57	1.35	0.83–2.20
Income				
< 4,000 CNY[a] (Ref)				
≥ 4,000	1.08	0.67–1.74	1.03	0.62–1.72
Education				
Below high school (Ref)				
High school and above	0.56	0.34–0.93	2.24*	1.34–2.75
Marriage				
Single (Ref)				
Married	0.88	0.50–1.55	1.05	0.56–1.97
Memory complaint				
Yes (Ref)				
No	0.71	0.38–1.34	0.55	0.29–1.05
Contact with dementia				
Yes (Ref)				
No	1.22	0.76–1.99	0.48*	0.31–0.75

[a]1 US dollar = 6.5 CNY. *Significant results after Bonferroni correction for two measurements per subject ($P < 0.05/2 = 0.025$).
AOR, adjusted odds ratio; Ref, reference.

followed by education booklets (60.9%), community bulletin (53.4%), health talks by experts (45.5%), and regular peer sharing (36.6%).

Discussion

Latest evidence on the modifiable risk factors of dementia provides a strong rationale for focusing on dementia prevention by reducing dementia risk factors. The success of such efforts relies on the public's understanding of dementia. The results of the survey revealed that, although huge scientific progress has been made on understanding the risk factors of dementia, a great gap still exists between the Chinese general public's understanding of dementia prevention and contemporary scientific evidence. Additionally, beliefs on dementia prevention and an understanding of dementia risk factors are remarkably associated with socio-demographic variables, such as age, education level, and having contact with patients with dementia. These findings strongly suggest an urgent need to promote dementia prevention knowledge among the Chinese general public and develop different education strategies for people with different socio-demographic backgrounds.

Existing surveys of the general population on dementia prevention were predominantly conducted in Europe, the USA, and Australia. The results of the present study showed that 42.5% of our sample believed in the misconception that dementia is caused by normal aging and only 32.4% of them believed that dementia could be preventable. These proportions are even higher compared with those found in high-income countries, in which the survey results showed that 14–40% of the general public agreed that dementia is a part of normal aging (McParland et al., 2012; Tan et al., 2012; Seo et al., 2015) and 45–59% believed that dementia is not preventable (Connell et al., 2007; Smith et al., 2014; Seo et al., 2015). This misconception may delay seeking professional help and taking health behaviors to reduce dementia risk factors. Overall, the knowledge level of the risk factors of dementia among the Chinese general public is poor. Among all the dementia risk factors, social and psychological risk factors were endorsed more by the respondents, and cardiovascular risk factors were less

TABLE 3 Socio-demographic factors associated with knowledge of dementia risk factors.

	Hearing loss	Cognitive inactive	Physical inactive	Social isolation	Depression	Alcohol	Dyslipidemia	Hypertension	Diabetes	Obesity	Smoking	Unhealthy diet
	AOR	AOR	AOR	AOR	AOR	AOR	AOR	AOR	AOR	AOR	AOR	AOR
Age group												
40–59 (Ref)												
60–69	2.79	1.18	0.96	2.46	0.88	2.63*	1.04	1.06	1.05	0.83	2.48	1.13
≥ 70	1.96	3.84*	1.37	1.95	0.68	1.04	2.48*	1.59	1.25	2.32	0.96	2.73*
Gender												
Men (Ref)												
Women	1.23	1.01	1.30	1.26	1.59	0.97	0.97	1.29	1.08	1.09	0.82	1.14
Income												
< 4,000 CNY (Ref)												
≥ 4,000 CNY	1.94	0.93	1.66	0.80	1.51	1.58	1.58	1.16	1.35	1.33	1.79	1.51
Education												
Below high school (Ref)												
High school and above	1.76	2.02	0.77	0.70	0.67	1.09	1.09	2.10	1.35	3.21*	3.37*	3.67*
Marriage												
Single (Ref)												
Married	1.23	1.03	1.45	1.02	1.03	1.34	1.35	0.90	1.05	0.63	1.36	1.33
Memory complaint												
Yes (Ref)												
No	0.44	1.58	1.58	0.64	1.42	1.55	0.55	0.88	0.97	0.40	0.52	1.20
Contact with dementia												
Yes (Ref)												
No	0.98	1.18	1.05	0.66	0.46	1.04	1.04	0.65	0.41*	0.63	1.03	0.51

[a]1 US dollar = 6.5 CNY. *Significant results after Bonferroni correction for 12 measurements per subject ($P < 0.05/12 = 0.004$).
AOR, adjusted odds ratio; Ref, reference.

10.3389/fnins.2022.1093169

endorsed as dementia risk factors. Previous studies also found that people have less awareness of the role of cardiovascular disease management in the development of dementia (Smith et al., 2014; Heger et al., 2019). This may be due the fact that dementia is predominantly regarded as a mental illness by the public, and there is lack of health education for the public to connect cardiovascular diseases with dementia. This finding highlights the need to design health education programs that emphasize the important link between cardiovascular risk factors and dementia.

The findings of this study regarding the factors associated with the beliefs of dementia prevention are consistent with previous studies (Smith et al., 2014; Seo et al., 2015). People with older age, a low level of education, and no contact with dementia were less likely to believe that dementia can be preventable. This study identified that participants with younger age are less knowledgeable about dementia risk factors. This finding is the opposite of another web-based study conducted in Asia (Zheng et al., 2020) but is consistent with the population-based survey conducted in Australia (Garvey et al., 2011). The inconsistency may be due to the different sampling methods across studies. The web-based study included young and highly educated participants, which may limit the representatives of the samples. The finding that younger participants are positive about dementia prevention but know less about dementia risk factors may be due to the fact that the younger generation is less concerned about the onset of dementia compared with older adults. Many of the dementia risk factors, such as cardiovascular and lifestyle risk factors, are likely different at all life stages; thus, public health programs on dementia prevention education should be provided across all age groups. The effects of dementia prevention strategies can be maximized this way. Lower education level was also identified to be associated with a lower understanding of dementia risk factors. This finding is in agreement with several previous studies (Low and Anstey, 2009; Roberts et al., 2014). This may because this disadvantaged group has limited access to the dementia prevention information, which highlights that more attention and resources should be invested in this group. Participants who have contact with patients with dementia were more knowledgeable of dementia risk factors probably because the situation renders oneself to pay more attention to the knowledge of dementia.

The majority of the respondents thought that they were not well informed of dementia from public education. Thus, the government, media, and medical institutions, as well as the communities, to make efforts to better popularize knowledge of dementia. In addition, receiving advice from family physicians and health education from community nurses is the preferred health education delivery format of the participants. This finding highlights the important role of primary care providers in dementia prevention. Ongoing education on dementia prevention for primary care providers is needed to transfer the latest scientific evidence to primary care practice.

Our study has several limitations that may influence the interpretation of the results. First, the conclusion of causality cannot be drawn because of the limitations of the cross-sectional study design. A repeated measures design would be ideal to track the trends in dementia prevention knowledge and its predictors. Second, in this study, only a limited number of communities were approached in a non-random manner for participants recruitment, thus selection bias may exist. Future studies should include a representative sample to increase the generalizability of the findings. Lastly, this study only adopted a quantitative survey study to investigate the research questions. Future studies are recommended to use in-depth qualitative approaches as a supplement to enrich our understanding on the public's attitudes toward dementia prevention and its related factors.

Conclusion

The present study reveals the great gaps between the Chinese general public's knowledge of dementia prevention and the latest research evidence. The findings highlight the need for greater public awareness of dementia prevention and enable the promotion of culturally appropriate strategies to increase public awareness. Specifically, cardiovascular factors are the least endorsed by the public; hence, health education programs should emphasize the important link between cardiovascular risk factors and dementia. Special attention should be paid to the population with low income and low education, because they are associated with a low level of dementia prevention knowledge. We suggest this health advice could be delivered by primary care providers during routine chronic disease management, as we identified that the Chinese general public prefer receiving dementia-related health advice from family physicians and community nurses. The partnership between researchers and practitioners can help translate evidence into community practice in a timely manner.

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 human participants were reviewed and approved by the Zhejiang Chinese Medical University

(No. SBREC-20181231). The patients/participants provided their written informed consent to participate in this study.

Author contributions

DS: conception and design of the work, acquisition, analysis, interpretation of the data, and drafted the work. DY and QHS: design of the work, acquisition, analysis, and interpretation of the data, and revised the work. All authors read and approved the final manuscript.

Funding

This research received external funding from the Humanities and Social Sciences Grants from the Ministry of Education of the People's Republic of China (No. 20YJCZH132).

Acknowledgments

Our thanks go to all participating adults for their good collaboration.

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/fnins.2022.1093169/full#supplementary-material

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frontiers | Frontiers in Neuroscience

TYPE Original Research
PUBLISHED 09 January 2023
DOI 10.3389/fnins.2022.1092297

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Translational Neuroscience, a section of the journal Frontiers in Neuroscience

RECEIVED 07 November 2022
ACCEPTED 12 December 2022
PUBLISHED 09 January 2023

CITATION
Ge S, Pan W, Wu B, Plassman BL, Dong X and McConnell ES (2023) Sensory impairment and cognitive decline among older adults: An analysis of mediation and moderation effects of loneliness.
Front. Neurosci. 16:1092297.
doi: 10.3389/fnins.2022.1092297

Sensory impairment and cognitive decline among older adults: An analysis of mediation and moderation effects of loneliness

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Background: Multiple studies have reported that hearing and vision impairment are linked to cognitive decline. Yet little is known about factors that may influence the association between sensory impairment and cognitive decline. This study examined if loneliness mediates or moderates the impact of sensory impairment on cognitive decline as individuals age.

Methods: This was a longitudinal study using data from the Health and Retirement Study (HRS) and The Aging, Demographics, and Memory Study (ADAMS) (N = 243). We used one timepoint of hearing and vision (ADAMS 2006–2008), one timepoint of loneliness (HRS 2006–2008), and five waves of cognition (HRS 2006–2014). Hearing impairment was defined by an inability to hear pure-tone stimuli of 25 dB at frequencies between 0.5 and 4.0 kHz in either ear. Visual impairment was defined as having corrected binocular vision worse than 20/40. Longitudinal parallel-process (LPP) analysis was conducted at a significance level of $\alpha = 0.05$ (one-tailed).

Results: Loneliness moderated but did not mediate the association between visual impairment and the rate of cognitive decline (standardized $\beta = -0.108$, $p < 0.05$). No moderation or mediation effect of loneliness was found for the association between hearing impairment and cognitive decline. Both vision and hearing impairment were significantly associated with increased severity of loneliness.

Conclusion: Visual impairment combined with an elevated level of loneliness may produce a more synergistic, deleterious impact on older adults' cognitive

function than visual impairment alone. This study highlights the importance of promoting a healthy social and psychological status for older adults with sensory impairment.

KEYWORDS

sensory impairment, cognitive aging, Alzheimer's disease, psychosocial, risk factors

Introduction

Hearing impairment and visual impairment are highly prevalent among older adults (Lin et al., 2011c; Varma et al., 2016) and have been found to be independently associated with cognitive decline (Reyes-Ortiz et al., 2005; Lin et al., 2011b, 2013; Deal et al., 2016; Zheng et al., 2018; Ge et al., 2021). Understanding the pathways connecting sensory impairment and cognitive function has been acknowledged as a priority for future research (Whitson et al., 2018). Loneliness, or perceived social isolation (Cacioppo et al., 2011), has been hypothesized to be both a potential moderator (Hämäläinen et al., 2019) and mediator (Lin et al., 2011a,b; Fulton et al., 2015) between sensory impairment and cognitive function. A better understanding of these relationships would support the development of targeted interventions to prevent cognitive decline among the growing population of older adults.

Theoretically, loneliness has been hypothesized to partially explain the association between sensory impairment and cognitive function (Fulton et al., 2015). However, empirical evidence for this mediational relationship is scarce and inconsistent; the prior studies are also methodologically limited by the use of self-reported hearing impairment (Maharani et al., 2019) or being cross-sectional (Hämäläinen et al., 2019). Longitudinal studies exploring the potential mediation effect of loneliness in the relationship of either hearing or vision impairment with cognitive decline using objectively measured sensory function are warranted.

In addition to the potential for loneliness to mediate the effects of sensory impairment on cognitive decline, prior studies have also suggested that loneliness may moderate this relationship (Hämäläinen et al., 2019). One might expect lonely individuals to demonstrate a stronger association between sensory impairment and cognitive decline given previous research showing that lonely individuals tend to view sensory impairment as more stressful (Hawkley and Cacioppo, 2003). Loneliness is an important psychosocial factor for older adults and has been found to moderate the relationship between life stressors and health outcomes (Norman et al., 2011; Doane and Thurston, 2014; Zeligman et al., 2017). However, whether loneliness moderates the association between sensory impairment and cognitive decline has not been explored. Previous studies have found older adults who have sensory impairment were more likely to feel lonely (Nachtegaal et al., 2009; Mick et al., 2018), and both sensory impairment and loneliness have been found to be risk factors for cognitive decline (Livingston et al., 2017). Therefore, sensory impairment and loneliness may reinforce each other and produce synergistic, deleterious effects on cognitive function.

The purpose of this study was to better understand the inter-relationships among sensory impairment, changes in cognitive function, and loneliness. Specifically, we aimed to examine (a) if loneliness mediates the association between sensory impairment (i.e., hearing or vision impairment) and cognitive decline over time; and (b) if loneliness moderates the association between sensory impairment (i.e., hearing or vision impairment) and cognitive decline over time. We hypothesized that sensory impairment is associated with cognitive decline via the pathway of an elevated level of loneliness (mediation). We also hypothesized that older adults with both sensory impairment and higher-level of loneliness have worse cognition or faster rates of cognitive decline than those with sensory impairment alone (moderation).

Methods

Parent study overview and data source

This was a longitudinal study using data from the Health and Retirement Study (HRS) and its supplement: The Aging, Demographics, and Memory Study (ADAMS) (Plassman et al., 2007). The ongoing Health and Retirement Study (HRS) is a population-based, nationally representative epidemiological survey of U.S. adults aged 51 years and older. Participants were interviewed every 2 years since 1992. The Aging, Demographics, and Memory Study (ADAMS) is an HRS substudy of dementia among older adults aged 70 or older (grant number NIA U01AG009740) (Plassman et al., 2007). Four waves of data collection (waves A, B, C, and D) occurred during Aug 2001–Dec 2003, Nov 2002–Mar 2005, Jun 2006–May 2008, and Jan 2008–Dec 2009. After Wave A, participants without dementia at any given wave were targeted for the next wave of data collection.

Data from the HRS and ADAMS were merged using household and participant IDs. Hearing and vision were objectively measured in ADAMS Wave C (N = 315). For this study, we used one wave of hearing and vision data from

ADAMS Wave C (Jun 2006–May 2008), one wave of loneliness data from HRS (collected between 2006 and 2008), and five waves of cognitive function data measured in HRS in 2006–2014. **Figure 1** demonstrates how we have derived the analytic sample in this study from ADAMS Wave C. Among the 315 older adults with measured sensory status in ADAMS Wave C, 243 had cognitive function and loneliness data from HRS, providing a sample of 243 for the current study. The study was approved by the Duke University IRB.

Measures

Cognitive function

Cognitive function was measured either via telephone or in-person for those aged 65 and older at every wave (every 2 years) of HRS using the HRS Telephone Interview for Cognitive Status (TICS) (Ofstedal et al., 2005). No items of the HRS TICS relied on visual presentation because the measure was designed to be administered over the telephone. Previous research has shown no measurable differences in cognitive performance based on the mode of the test administration in HRS (Herzog and Rodgers, 1999). The HRS TICS included immediate and delayed free-recall (range 0–20), serial 7 subtraction (range 0–5), counting backward tests (range 0–2), orientation to time (range 0–4), object naming (range 0–2), and president/vice president naming (range 0–2) (Brandt et al., 1988). A total cognitive function score was calculated by summing the score for all items (range: 0–35) with a higher score indicating better cognitive function.

Hearing impairment

Hearing impairment was measured by administering the Pure Tone Thresholds test (Sensitive Health Data, 2013). Pure tone stimuli were presented at 0.5, 1, 2, and 4 kHz at both 25 and 40 dB to the right and the left ear individually. The response was documented "yes" for the frequency and decibel-level combination if a participant reported being able to hear the 25 or 40 dB stimulus at a specific Hz level, otherwise was "no." Criteria for hearing impairment were defined based on the American Speech-Language-Hearing Association guidelines and other studies (Clark, 1981; Lin et al., 2011c). We categorized participants as (a) having normal hearing if the better ear could hear 25 dB for at least some of the frequencies, and (b) having hearing impairment if the better ear could not hear 25 dB at any frequencies.

Visual impairment

Visual impairment was measured by using a Snellen chart (Sensitive Health Data, 2013). Visual impairment was defined as the best-corrected binocular vision being worse than 20/40. This cut-point has been used in other studies of visual impairment, including large-scale population-based surveys (West et al., 1997; Lin et al., 2004; Reyes-Ortiz et al., 2005). This cut-point has also been used in screening for issuing driver's license (West et al., 1997).

Loneliness

Loneliness was measured by the 3-item UCLA Loneliness Scale in the HRS self-administered leave-behind psychosocial and lifestyle questionnaire (Smith et al., 2017). Participants were asked "How much of the time do you feel you lack companionship?", "How much of the time do you feel left out?", and "How much of the time do you feel isolated from others?" The response options ranged from 1 (often) to 3 (hardly ever or never). Loneliness was reverse coded and was calculated as the average score of the three items, with a higher score representing a higher level of loneliness. This measure has been used in large-scale population telephone surveys and has good reliability (Hughes et al., 2004). In our sample, the Cronbach's alpha for the measure was 0.80.

Covariates

Covariates included in our models were chosen based on the literature (Plassman et al., 2010). The covariates initially considered for selection included demographics (age, sex, and race), socioeconomic status (years of education, marital status, living arrangement, and annual household income), health status (number of reported health conditions and depression), lifestyle factors (smoking and exercise), and an Alzheimer's disease risk gene (APOE). The covariates retained in the final models were those that have demonstrated statistically significant associations with the outcome variable (i.e., cognitive function). These covariates included age (in years), education level (0 = "$\leq$ 12 years", 1 = " $>$ 12 years"), race (1 = white, 2 = black, 3 = other race), survey wave (time), household income (in quartiles), number of health conditions (range 0–8), and physical exercise (0 = no, 1 = yes). All of these variables were measured in HRS.

Statistical analysis

Descriptive statistics were computed for sample characteristics. We conducted Little's test for missing completely at random (MCAR) (Little, 1988) and found that data were missing completely at random in our sample. We implemented the expectation-maximization (EM) imputation to acquire robust estimates (Allison, 2009).

Both mediation and moderation effects of loneliness on the relationship between sensory impairment and cognitive decline were examined in the same model using the two-step longitudinal parallel-process (LPP) analysis (Hooke et al., 2018). In the first step, the intercept and slope of the longitudinal outcome, cognitive function, were estimated from multilevel modeling with SAS Proc Mixed. Age (centered at its mean of

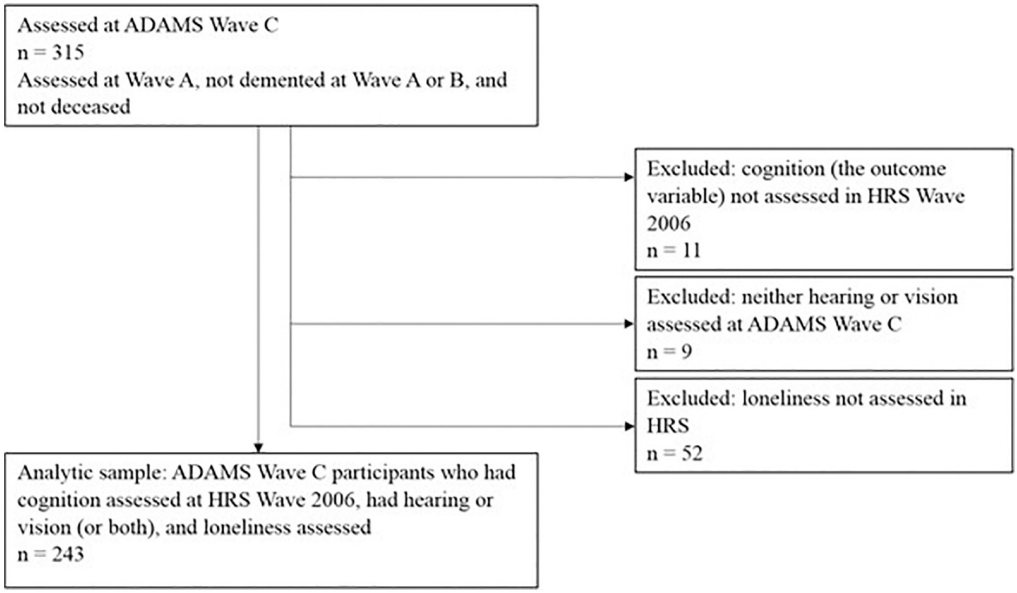

FIGURE 1
Flow chart for deriving the analytical sample from Aging, Demographics, and Memory Study (ADAMS) Wave C.

81), as opposed to wave, was used as the time-varying random factor. We controlled "wave" to account for attrition represented by the status of a participant being measured or unmeasured for whatever the reason at the time of each wave. Thus, the intercept of cognitive function represents the average status of cognitive function at age 81. The slope represents the rate of change in cognitive function as people age by 1 year. By estimating the intercept and slope of cognitive function in the first step, LPP allows us to explore both cross-sectional and longitudinal relationships between sensory impairment, loneliness, and cognitive function in the second step. At the same time, the predicted values of sensory impairment and loneliness after controlling for the covariates were processed in the first step for the following SEM modeling. Since we used 1 wave of data for sensory impairment and loneliness, the predicted values of each of these variables in the first step were produced by using SAS Proc Logistic (for hearing and vision impairment) and Proc Genmod (for loneliness) with age as the predictor controlling for covariates.

In the second step, hearing impairment and visual impairment were modeled separately in structural equation modeling (SEM) to test the mediation and moderation effects of loneliness on the longitudinal relationship between sensory impairment and cognitive function using IBM SPSS Amos (Arbuckle, 2014). The moderation effects of loneliness on the longitudinal relationship between sensory impairment and cognitive function were examined by computing two interaction terms of visual impairment*loneliness and hearing impairment*loneliness in the SEM. For the final result, we used 1-tailed tests to test our directional hypotheses because prior literature consistently reported results in one direction (Lara et al., 2019; Shukla et al., 2020).

Specifically, we first fit a full SEM model for each modality of sensory impairment (**Figure 2**) based on our hypothesis. To achieve the most parsimonious model, we removed the non-significant paths one-by-one based on their p-values and interpretability. The model fit was evaluated using the following model-fit indices: Chi-square of the estimated model (χ^2), goodness of fit index (GFI), normed fit index (NFI), incremental fit index (IFI), relative fit index (RFI), comparative fit index (CFI), and root mean square error of approximation (RMSEA). A non-significant Chi-square value ($p > 0.05$) suggests a good overall model fit to the data. For GFI, NFI, IFI, RFI, and CFI, values larger than 0.90 indicate that the model provides a good fit to the data, whereas the RMSEA value should be below.06. The fit indices and their criteria are commonly recommended in the literature (Hu and Bentler, 1999; Kline, 2015). Based on the general consensus that the number of participants needs to be 10 per estimated parameter (Schreiber et al., 2006), our analyses have a satisfactory sample size.

Results

Descriptive statistics

Characteristics of the sample are shown in **Table 1**. At baseline, in a total sample of 243 older adults, the average age was 81.08 ± 5.40. There were more females (53.5%) than males and more white participants (79.84%) than other races. For the

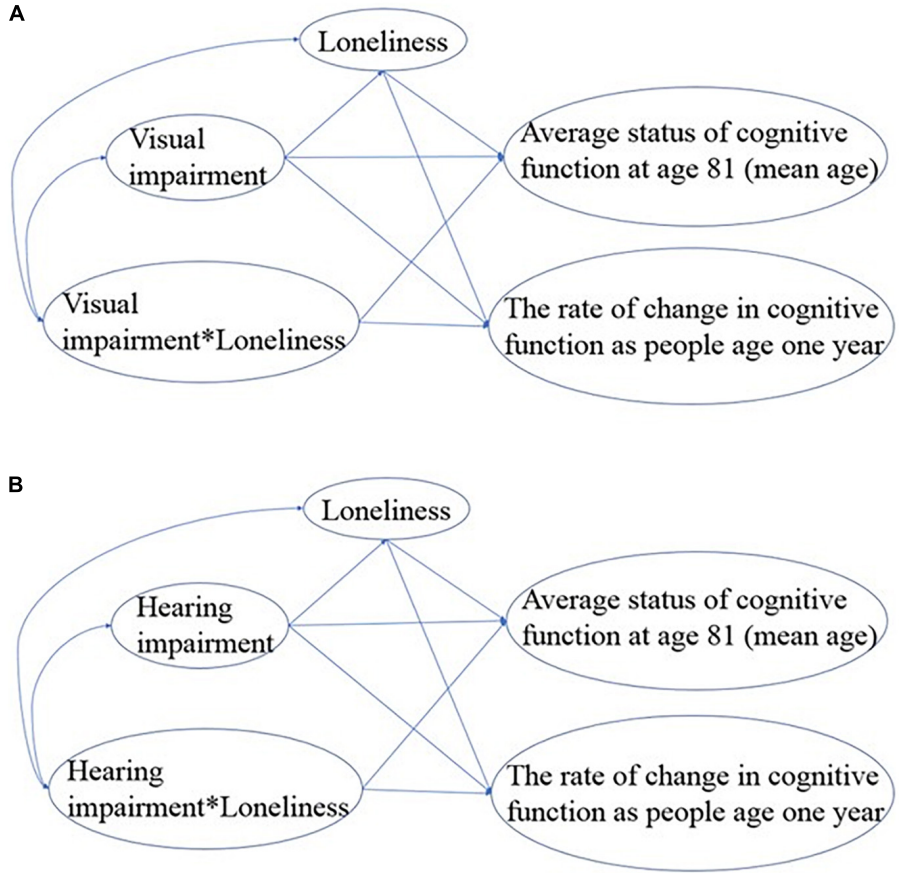

FIGURE 2
Initial mediation and moderation SEM models for **(A)** vision and **(B)** hearing impairment.

modeled variables, the average cognitive score was 19.66 ± 5.47. The average level of loneliness was 1.53 ± 0.54. One hundred and twenty-three (50.62%) of the older adults did not have hearing impairment, but 101 (41.56%) of them had hearing impairment. As for visual impairment, 154 (63.37%) of the older adults did not have visual impairment, but 84 (34.57%) had visual impairment.

Mediation and moderation effects for visual impairment

The initial model fit indices for the SEM model (Figure 2) to examine the mediation and moderation effects of loneliness were not satisfactory ($\chi^2(1) = 8.622$, $p = 0.003$; GFI = 0.986, NFI = 0.994, IFI = 0.994, RFI = 0.936, CFI = 0.994; and RMSEA = 0.177), and indicated that the model needed further improvement. The estimated path coefficients were provided in Supplementary Figure 1.

To obtain a parsimonious, best-fit model, the initial model was modified by removing non-significant paths based on statistical modification indices produced by IBM SPSS Amos as well as on theoretical interpretability. A final model was estimated as shown in Figure 3 in which the model fit indices for the final model improved and were all satisfactory ($\chi^2(4) = 3.779$, $p = 0.437$, GFI = 0.994, NFI = 0.997, IFI = 1.000, RFI = 0.993, CFI = 1.000, and RMSEA = 0.000).

Our results show that older adults who had visual impairment experienced more severe loneliness (standardized $\beta = 0.452$, $p < 0.001$). There was no significant association between loneliness and the rate of decline or the average status of cognitive function, suggesting no mediation effect of loneliness. The potential moderation effect of loneliness was represented by the interaction term of visual impairment*loneliness, which demonstrated a significant association with the rate of cognitive decline (standardized $\beta = -0.108$ [or-0.032, unstandardized], $p < 0.05$), suggesting a role of loneliness in moderating the effects of visual impairment on the rate of cognitive decline. In other words, for older adults who had visual impairment and felt lonely, their cognitive function declined by 0.032 more points per year than older adults who had visual impairment but did not feel lonely.

TABLE 1 Descriptive statistics of variables from HRS and ADAMS in this study at baseline (N = 243).

	N = 243 (%) or Mean ± SD	Range
Age	81.08 ± 5.40	73–98
Gender		
Male	113 (46.50)	
Female	130 (53.50)	
Race		
White	194 (79.84)	
Black	42 (17.28)	
Other	7 (2.88)	
Education		0–17
=12 years	152 (62.55)	
>12 years	91 (37.45)	
Annual household income (mean of each quartile)		
Highest quartile	81,899.48 (48826.46)	40,380.00–260,016.00
Second quartile	32,041.28 (4925.56)	23,492.00–39,600.00
Third quartile	18,155.59 (3279.48)	12,960.00–23,232.00
Lowest quartile	9,486.82 (2405.18)	2,400.00–12,848.00
Health conditions	2.40 ± 1.43	0–6
Physical exercise		
Yes	58 (23.87)	
No	185 (76.13)	
Cognition	19.66 ± 5.47	2–32
Loneliness	1.53 ± 0.54	1.00–3.00
Hearing impairment		
No impairment	123 (50.62)	
Impairment	101 (41.56)	
Not assessed/Don't know/Refused	19 (7.82)	
Visual impairment		
No impairment	154 (63.37)	
Impairment	84 (34.57)	
Not assessed/Don't know/Refused	5 (2.05)	

SD, standard deviation.

Mediation and moderation effects for hearing impairment

The initial model fit indices for the SEM model (Figure 2) to examine the mediation and moderation effects of loneliness were not all satisfactory ($\chi^2(1) = 7.898$, $p = 0.005$; GFI = 0.987, NFI = 0.993, IFI = 0.994, RFI = 0.931, CFI = 0.994, and RMSEA = 0.169), and indicated that the model did not fit well. The estimated path coefficients were provided in Supplementary Figure 1.

As previously described for visual impairment, we took a similar approach to obtain a parsimonious, best-fit model for hearing impairment. The initial model was modified by removing non-significant paths. A final model was reached as shown in Figure 4 in which the model fit indices for the final model improved and were all satisfactory ($\chi^2(1) = 0.172$, $p = 0.678$, GFI = 1.000, NFI = 1.000, IFI = 1.001, RFI = 0.999, CFI = 1.000, and RMSEA = 0.000).

Loneliness did not mediate or moderate the relationship between hearing impairment and cognitive decline (Figure 4). Older adults with hearing impairment had more severe loneliness (standardized $\beta = 0.170$, $p < 0.001$) than those with normal hearing. However, the path coefficients from loneliness to both the rate of change in cognitive decline (slope) and the average status of cognitive function at age 81 (intercept, centered at mean age) were non-significant, indicating no mediation effect of loneliness on the association between hearing impairment and cognitive decline. The interaction term between hearing impairment and loneliness was also not significant for either the rate of decline in cognitive function or the average cognitive status at age 81, suggesting loneliness did not moderate the relationship between hearing impairment and cognitive decline.

Discussion

Our study examined potential mediation and moderation effects of loneliness on the association between sensory impairment and cognitive decline in a national sample of older adults in the U.S. We found that loneliness moderated the association between visual impairment and the rate of decline in cognitive function, but we did not find a moderating effect of loneliness on the relationship between hearing impairment and the rate of cognitive decline. Even though we found that both hearing and vision impairment were significantly associated with increased severity of loneliness, we did not find a mediation effect of loneliness on the association between either hearing impairment or visual impairment and cognitive decline.

The potential detrimental impact of loneliness on health has been studied for decades (Cacioppo et al., 2002). In 2020, the implications of enforced social distancing during the COVID-19 pandemic has brought the adverse effects of both loneliness (i.e., perceived social isolation) and social isolation to the attention of both researchers and clinicians (Wu, 2020). The potential moderating role of loneliness on the associations among risk factors and health outcomes has been examined in other topic areas and populations such as stress and sleep among adolescents (Norman et al., 2011; Doane and Thurston, 2014; Zeligman et al., 2017), but little research has been done regarding

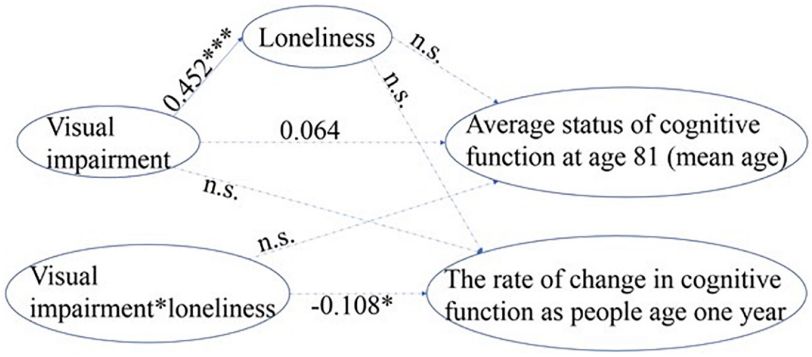

FIGURE 3
Standardized path coefficient estimates from the most parsimonious model for visual impairment. a. 1-tailed tests, *$p < 0.05$, ***$p < 0.001$. b. The error terms and correlational paths are omitted for clarity. c. The dotted paths with path coefficients shown were remained in the final model but were non-significant, the dotted paths without coefficients were deleted during the process of improving model fit (n.s.).

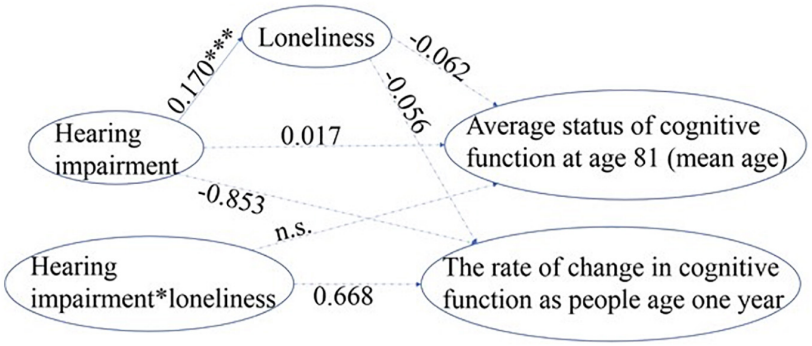

FIGURE 4
Standardized path coefficient estimates from the most parsimonious model for hearing impairment. a. 1-tailed tests, *$p < 0.05$, ***$p < 0.001$. b. The error terms and correlational paths are omitted for clarity. c. The dotted paths with path coefficients shown were remained in the final model but were non-significant, the dotted paths without coefficients were deleted during the process of improving model fit (n.s.).

the sensory-cognition associations. To our knowledge, only one recent study has explored the cross-sectional inter-relationships between sensory impairment, loneliness, and cognitive function using data from the Canadian Longitudinal Study of Aging (CLSA) (N = 30,029), but no significant moderating nor mediating effects of loneliness were found. Our study also did not find that loneliness moderated the cross-sectional associations between sensory impairment and average cognitive function (intercept, centered at mean age). However, we found loneliness moderated the longitudinal association between visual impairment and the rate of decline in cognitive function. Our findings imply that elevated levels of loneliness may exacerbate the negative impact of visual impairment on the rate of cognitive decline. Despite the increased challenges for social participation, older adults with visual impairment should try to stay engaged with family, friends, and community. For family caregivers and clinicians, our findings signal the importance of ameliorating loneliness among older adults, especially among those with visual impairment, by focusing on ensuring sufficient support and companionship.

Although we found loneliness moderated the association between visual impairment and cognitive decline, this moderating effect did not exist for hearing impairment. We suspect that this differentiated relationship is related to the different physical, social, and emotional challenges caused by vision and hearing impairment. Older adults with visual impairment may have even more limited physical mobility than those with hearing impairment. It might be easier for older adults with hearing impairment to adapt to the hearing-related challenges they face (Mick et al., 2018). For example, some physical and mental activities (e.g., walking for exercise, card games) may be still appropriate for older adults with hearing impairment but not for those with visual impairment. In addition, visual impairment may diminish older adults' opportunities for outdoor activities and social interactions by limiting transportation options, which could increase the risk of feeling stressed or frustrated.

Our study found a significant association between both types of sensory impairment and elevated loneliness severity. Our finding is consistent with previous studies (Alma et al., 2011; Mick et al., 2018). Older adults with sensory impairment are likely to encounter difficulties in communication with families and friends. Therefore, sensory-impaired older adults' social relationships can be harmed by miscommunications and misunderstandings (Crews and Campbell, 2004; Mick et al., 2014; Guthrie et al., 2016). Consequently, older adults with sensory impairment may feel negative emotions (e.g., frustration, anger, and stress) and tend to passively or intentionally withdraw from social interactions due to functional and communication difficulties (Mick et al., 2014, 2018).

The pathways connecting the association between sensory impairment and cognitive decline are largely unknown (Wayne and Johnsrude, 2015; Whitson et al., 2018). Sensory impairment has been hypothesized to cause cognitive decline through a pathway of loneliness (Lin et al., 2011a,b; Fulton et al., 2015). Our study is one of the few that has used longitudinal data to explore the potential mediating role of loneliness on the longitudinal associations between sensory impairment and cognitive decline (Maharani et al., 2019). However, we did not find a significant mediation effect of loneliness due to a lack of associations between loneliness and cognitive decline. This finding is contradictory to the findings from previous longitudinal studies (Donovan et al., 2017; Zhong et al., 2017; Maharani et al., 2019). A few factors may have contributed to this discrepancy. Previous studies that examined the longitudinal associations between loneliness and cognitive decline have primarily used memory to represent cognitive function (Donovan et al., 2017; Zhong et al., 2017) instead of using a multi-dimensional global cognition measure. These previous studies used a one-item measure of loneliness that may provide an unreliable estimate of loneliness (Donovan et al., 2017; Zhong et al., 2017). In contrast, we used the 3-item UCLA Loneliness Scale in our analysis, which has shown satisfactory reliability in our sample. However, while other studies used multiple waves of data of loneliness, we only had information on loneliness at baseline due to the study design of HRS (Smith et al., 2017). Nonetheless, our study is the first using data from the HRS and ADAMS to explore the role of loneliness in mediating the effect of objectively measured sensory impairment on cognitive decline.

Our study has some limitations. First, the measure of cognitive function in HRS was administered by a mixture of telephone and face-to-face interviews. Hearing function may have affected performance on the cognitive measure, especially for those that were conducted over the phone. Older adults with hearing impairment may also have a lower likelihood of completing the HRS TICS. However, the HRS team has found no measurable differences in cognitive performance based on the mode of the test administration (Herzog and Rodgers, 1999). Second, we did not have information about the time of onset of sensory impairment, which limits our understanding of how the length of time living with sensory impairment and adaptation to sensory impairment may influence its relationship to cognitive decline. Third, the study's generalizability should be treated with caution. Although the ADAMS Wave A sample is a representative "snapshot" of the U.S. population (as of 2002), the data from ADAMS Wave C used in the present study included the participants who were (a) without a diagnosis of dementia at Wave A or B, (b) not deceased, and (c) able to complete the HRS TICS, thus they may be healthier than the general population. Fourth, vision and hearing status are subject to change as individuals age, yet we only used one time point of measured vision and hearing impairment because relatively few individuals had multiple sensory measurements due to the study design of ADAMS. Relatedly, due to this one-time measurement of both loneliness and the sensory impairment variables, we cannot establish temporal directions or causal relationships for the identified associations. Future studies should consider collecting longitudinal data for both sensory impairment and loneliness to provide stronger evidence for the plausible relationships.

Conclusion

Our study examined the inter-relationships among sensory impairment, loneliness, and cognitive decline using longitudinal data. We used objectively measured sensory function. The measures of loneliness used in our study have also been widely used and have demonstrated satisfactory psychometric properties. Our findings suggest that vision and hearing impairment each has a different pattern of associations with cognitive decline, and loneliness may moderate the relationship between visual impairment and cognitive decline. Future studies that seek to understand the inter-relationships among sensory impairment, psychosocial factors, and cognitive decline using strong validated measures, larger sample sizes, and multiple waves of data in loneliness are warranted. Future studies should also consider examining if improving social connectedness would help slow down or even prevent future cognitive decline.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://hrs.isr.umich.edu/data-products.

Ethics statement

The studies involving human participants were reviewed and approved by the Duke University IRB. Written informed consent for participation was not required for this

study in accordance with the national legislation and the institutional requirements.

Author contributions

SG had primary responsibility for study conceptualization, data analysis, interpretation, and preparing the manuscript. EM, BW, WP, XD, and BP contributed to the study significantly by advising on the study design, reviewing the analysis results, revising the analytical strategies, and making crucial revisions to the manuscript. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by the Duke University Graduate School and the Doris Carnevali Engaging with Aging Postdoctoral Fellowship from the School of Nursing, University of Washington to SG.

Acknowledgments

SG gratefully acknowledge Basia Belza, Ph.D., registered nurse (RN), Fellow of the American Academy of Nursing (FAAN), Aljoya Endowed Professor of Aging at the School of Nursing, University of Washington for her support.

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/fnins.2022.1092297/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Initial mediation and moderation SEM full models and path estimates for **(A)** vision and **(B)** hearing impairment. a. 1-tailed tests, $^{*}p < 0.05$, $^{***}p < 0.001$. b. The error terms and correlational paths are omitted for clarity. c. The dotted paths were non-significant.

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frontiers | Frontiers in Neuroscience

TYPE Original Research
PUBLISHED 07 February 2023
DOI 10.3389/fnins.2022.1100642

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Translational Neuroscience, a section of the journal Frontiers in Neuroscience

RECEIVED 17 November 2022
ACCEPTED 30 December 2022
PUBLISHED 07 February 2023

CITATION
Wang Y, Yang Q, Tian C, Zeng J, Yang M, Li J and Mao J (2023) A dual-task gait test detects mild cognitive impairment with a specificity of 91.2%.
Front. Neurosci. 16:1100642.
doi: 10.3389/fnins.2022.1100642

A dual-task gait test detects mild cognitive impairment with a specificity of 91.2%

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Background: Mild cognitive impairment (MCI) is a valuable intervention window in the progress of senile dementia, but the question of how to easily and conveniently detect MCI in the community remains unanswered. Gait performance reflects cognitive function, but how to reliably detect MCI through gait testing is still being explored.

Objective: To develop a dual-task gait testing method that could reliably detect MCI in the community.

Methods: A cross-sectional diagnostic study was conducted in 111 older adults (mean age = 72.14 ± 6.90 years) from five communities in Wuhan, China. A novel dual-task gait testing method, walking while identifying animals in pictures (AniP-DT gait test), was developed. The participants were classified into MCI or cognitively intact based on their performance on the Montreal Cognitive Assessment Scale (MoCA). Gait performance was assessed using both single-task and the AniP-DT gait test. Multiple linear regression and binary logistic regression were used to model the association between gait speed and cognitive status, and receiver operating characteristic (ROC) curve analysis was used to assess the discrimination ability.

Results: Compared to the cognitively intact group, the gait speed of the MCI group was lower in both single-task and the AniP-DT gait tests. The gait speed of the AniP-DT gait test was significantly associated with MoCA scores after adjusting the covariates and exhibited good discrimination ability in MCI detection (AUC = 0.814), with a specificity of 91.2%. ROC analysis of the logistic models revealed better discrimination ability of dual-task gait velocity when adjusted with age and years of education (AUC = 0.862).

Conclusion: The evidence in this study suggested that the AniP-DT gait test could be an easy and reliable screening tool for MCI in community older adults.

KEYWORDS

mild cognitive impairment, gait, dual-task, older adults, AniP-DT

Introduction

Dementia is a devastating condition carrying huge social and healthcare burdens (Alzheimer's and Dementia, 2021), and will increase with the population aging. Without effective treatment for dementia, mild cognitive impairment (MCI), a transitional stage between normal aging and dementia that can be treated and even reverted (Petersen et al., 2018),

becomes a valuable window to intervene in the progress of dementia. However, symptoms of MCI are often subtle and few patients seek medical assistance before their condition worsens, Thus, identifying MCI patients in the community population would be a precondition for the MCI intervention. The current screening methods for MCI are mostly for clinical settings (Connolly et al., 2011), and effective and convenient community screening tool for MCI is still in short supply.

Motor markers of cognitive changes have gained growing attention in recent years (Montero-Odasso et al., 2009; Beauchet et al., 2013). People with cognitive impairment often demonstrate gait disturbances, and the underlying mechanism points to brain regions and networks shared between gait motor control and cognitive processes (Montero-Odasso et al., 2014). A slowing in gait velocity was found associated with cognitive impairment and progression to dementia (Montero-Odasso et al., 2005; Waite et al., 2005). Moreover, studies have suggested that gait disturbances may precede the evident cognitive symptoms in dementia (Buracchio et al., 2010; Kikkert et al., 2016). Therefore, gait tests, characterized by low cost and convenience, could be a potential screening tool for cognitive impairment. A seminal study in 1997 stated that older adults who stopped walking while talking had a higher risk of falls (Lundin-Olsson et al., 1997). Since then, the dual-task gait test, a test in which participants perform walking and a secondary cognitive task concurrently (Al-Yahya et al., 2011), has become a research topic to explore the relationship between gait and cognition. Our recent meta-analysis demonstrated that the dual-task gait test exhibited higher sensitivity in MCI detection compared with a simple walking test (Yang et al., 2020). Because of the limited attentional capacity in people with compromised cognitive abilities, interference in the performance of one or both tasks would occur when an extra task was added (Jayakody et al., 2020).

There are various forms of dual-tasking and many cognitive tasks have been used in the dual-task paradigms. These tasks differentiate from each other in their nature, content and task difficulty. More importantly, different cognitive tasks have shown varying effects in people with MCI (Hunter et al., 2018). Currently, there is no consensus about which cognitive task should be paired with walking or which has a better discriminating ability for MCI (Montero-Odasso et al., 2019). According to Al-Yahya et al. (2011), cognitive tasks can be divided into five categories: reaction time, discrimination and decision-making, mental tracking, working memory, and verbal fluency, which relate to different cognitive domains. Several tests are commonly used in dual-tasks for older adults with MCI, including serial subtractions by 1 or 7 (mental tracking) (Montero-Odasso et al., 2017; Cullen et al., 2018; Hunter et al., 2018), naming animals (verbal fluency) (Montero-Odasso et al., 2017; Cullen et al., 2018; Hunter et al., 2018), and delayed recall (working memory) (Tseng et al., 2014; Nascimbeni et al., 2015). Discrimination and decision-making tests, however, are rarely used. Studies demonstrated that increasing the complexity of the cognitive task could bring greater sensitivity for MCI detection (Bahureksa et al., 2017; Yang et al., 2020). However, raising the difficulty too much could hurt specificity. The task needs to be challenging enough so that participants are working at or near the limit of their ability to uncover deficits (Hunter et al., 2018). On the other hand, MCI patients could exhibit impairment in different cognitive domains, including executive function, attention, language, memory, and visuospatial skills (Petersen et al., 2014). People always show different proficiency in different domains, so only testing one domain could conceal the deficit of other domains. Thus, developing a comprehensive task with appropriate complexity would improve the discrimination ability of the task greatly.

Picture naming tasks, which belong to the discrimination and decision-making tasks, are wildly used to characterize cognitive impairment. This task involved the function of visual perception, semantic processing, word retrieval, and oral naming, containing multiple cognitive processes (Lin et al., 2014). The multiple processes could test multiple cognitive domains (semantic memory, executive function, language, attention). In this study, we chose animal pictures because people are reasonably well knowledgeable about animal names; hence the influence of gender, age, and education could be minimal. In this way, we have developed an AniP-DT gait test, pairing the animal picture naming task with normal walking to form a dual-task gait test. The animal picture naming task required the participants to discriminate and name the animals in pictures, impairment in any domain (visual perception, semantic processing, word retrieval, and oral naming) could result in interference in motor performance. Therefore, using the AniP-DT gait test to assess motor-cognitive interaction would detect mild impairment in different cognitive processes, and improve the MCI detection capabilities.

Materials and methods

Study design, setting, participants

This study followed the strengthening of the reporting of observational studies in epidemiology (STROBE) guidelines. A cross-sectional diagnostic study was conducted in five communities in Wuhan, China from March to July 2019. Inclusion criteria included: (1) older adults aged 60 years old and above; (2) able to follow test instructions; (3) normal vision and hearing; (4) able to walk 10 m independently (assistive walking devices including canes and walkers were allowed). Subjects were excluded if they had: (1) musculoskeletal disorders of lower limbs that affect gait performance (e.g., arthritis); (2) central or peripheral neurological diseases (e.g., Parkinsonism, stroke); (3) recent acute illness or surgery (in the past 3 months) (Nascimbeni et al., 2015). The study protocol was approved by the responsible institutional review board. Informed consent was obtained from each participant before data collection. All data has been de-identified and used only for academic purposes.

Medical and cognitive assessments

Sociodemographic information and comorbidities were collected. Sex, age, body mass index (BMI), years of education, smoking, alcohol drinking, and use of walking aids were collected as sociodemographic characteristics. BMI is a person's weight (kg) divided by the square of height (m). Current smokers were participants who smoked at least one cigarette per day for over 6 months. Current alcohol drinkers were defined as drinking alcohol every day for more than 6 months. Cognition was assessed using the Montreal Cognitive Assessment Scale (MoCA) (Nasreddine et al., 2005). The score ranges from 0 to 30, and a higher score indicates better cognitive performance.

MoCA has high sensitivity and reliability to screen MCI patients. A Chinese version of MoCA was used and adjusted with educational level (one correctional point was given to participants with less than 12 years of education except for those who already scored 30). Participants with MoCA scores less than 24 were categorized as MCI in this study. Others were classified as cognitively intact.

Psychological assessments

Previous studies have reported neuropsychiatric symptoms in cognitive decline individuals (Somme et al., 2013). Older adults' depression, anxiety, and apathy status were recorded in this study. The Chinese version of the geriatric depression scale with 15 items (GDS-15) was used to assess the depressive symptoms and a score of 8 or above indicated depression (Zhao et al., 2019). Anxiety was evaluated using the Chinese version of the geriatric anxiety inventory (GAI) (Yan et al., 2014). A score greater than 10 indicated anxiety. Apathy was assessed with the apathy evaluation scale-self (AES-s) (Marin et al., 1991). In all three scales, higher scores indicated severer psychological problems.

Gait assessments

Gait velocity of self-selected ground walking was recorded using a 10-meter-walk test. In each community, participants performed the tests in a well-lit, dry and spacious area, eliminating any dangerous objects from the ground. We adopted a stopwatch and tape measure method (Youdas et al., 2010). Four lines of tape were used on the ground to mark the start line, 2-m line, 8-m line, and finish line (**Figure 1**). The duration of each test was measured using a stopwatch, with a measurement error of 0.01 s.

While participants needed to walk through the 10-m distance, the measurement distance was in the middle, at 6-m. The examiner started the timer once the participant's first foot crossed the 2-m line and stopped the timer when the participant's first foot crossed the 8-m line. In this way, we could measure the steady gait performance without the acceleration and deceleration phases. Older adults were given rest between each trial if needed to reduce the effect of fatigue. The examiner walked slightly behind (out of their field of vision) to protect them from falling. No adverse events happened during the tests.

Each participant performed four walks, in the order of two single-task tests and two dual-task tests. In the single-task tests, older adults were instructed to walk at their preferred speed. In the dual-task tests, the cognitive task was animal picture naming. Older adults were required to name the animals in the pictures printed on paper while walking at their usual speed. The paper was A4 size and on each side, nine photographs of animals were printed, including both common (e.g., cat, rabbit) and low-familiarity animals (e.g., hedgehog, camel) for Chinese older adults (**Supplementary Figure 1**). The paper was given to participants right before the AniP-DT gait tests. All participants were given the same instructions to assure consistency and were not asked to prioritize any task over another. They had no practice trials. Gait velocities (cm/s) of single-tasks and dual-tasks were averaged from the two trials, respectively.

Data analysis

Sociodemographic, clinical, and gait characteristics were presented using either means and standard deviations (SD) or frequencies and percentages. Participants were divided into two groups (cognitively intact and MCI) based on the MoCA scores. Comparisons between the two groups were made using *t*-tests and Chi-square tests as appropriate. Spearman's rank correlation was used to explore the universal correlation between gait parameters and MoCA scores. Then we used multiple linear regression models that included the MoCA score as a dependent variable and the gait parameters, adjusted for the potential confounders, as independent variables. Binary logistic regression was performed using MCI as the dependent variable and gait performances, adjusted for age and years of education as the independent variables. Next, we applied receiver operating characteristic (ROC) analysis to explore the discrimination ability of the gait performances for screening MCI. The cut-off value of gait speeds was determined using the Youden index. All statistical analyses were implemented using SPSS v.22 (IBM, NY, USA), with statistical significance set at $P < 0.05$ (2-sided).

Results

Characteristics and gait performance of participants

In total, 114 older adults participated in the study, of whom 3 dropped out because they could only perform the single-task tests due to fatigue. Finally, 111 participants were included in the analysis. The mean age was 72.14 ± 6.90 years and 51.4% were male. Participants' characteristics, stratified by cognitive status, were presented in **Table 1**. There were 43 (38.7%) older adults classified as MCI. Participants with MCI were older and had fewer years of education. Also, older adults with MCI had a higher level of apathy.

Table 2 showed the cognitive and gait performances of participants. As expected, the MCI group had a significantly lower MoCA score than the control group. Gait velocities of AniP-DT tests in both groups were much lower than those in the single-task tests. Participants with MCI had significantly lower gait velocity in both of the tasks, with more slowing in the dual task.

Associations between participants' cognition and gait parameters

According to the spearman correlation tests, gait velocities of both single and dual-task were positively associated with the MoCA scores (single-task gait velocity, $\rho = 0.406$, $p < 0.001$; AniP-DT gait velocity, $\rho = 0.566$, $p < 0.001$). **Table 3** presented the multiple linear regression analysis results. Each analysis was adjusted with age, sex, educational level, smoking and drinking status, use of walking aid, and psychological parameters. The results also showed that both of the gait velocities were significantly correlated with MoCA, and AniP-DT gait velocity could better account for the cognition of older adults. **Table 4** reported the two logistic regression models regarding gait velocities and MCI. Controlling for age and years of education,

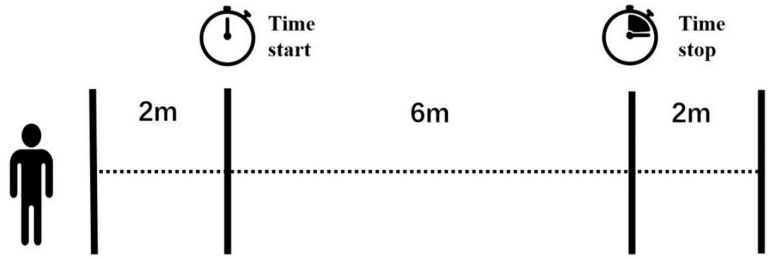

FIGURE 1
View of the 10-m gait test. Four lines of tape were marked on the ground and the two lines in the middle indicated the start and stop of a handheld stopwatch. The examiner started or stopped the timer once the participant's first foot passed these two lines.

TABLE 1 Characteristics of participants stratified by cognitive status.

	Full sample (*n* = 111)	Cognitively intact (*n* = 68)	MCI (based on MoCA) (*n* = 43)	*P*-value
Age, mean (SD), years	72.14 (6.90)	70.21 (6.08)	75.21 (7.08)	<0.001*
Male, n (%)	57 (51.4)	40 (58.8)	17 (39.5)	0.048*
BMI, mean (SD), kg/m^2	23.17 (3.49)	23.40 (2.94)	22.81 (4.23)	0.42
Years of education, mean (SD)	10.08 (4.51)	11.46 (3.41)	7.91 (5.16)	<0.001*
Use of walking aid, n (%)	9 (8.1)	5 (7.4)	4 (9.3)	0.99
Current smoker, n (%)	21 (18.9)	12 (17.6)	9 (20.9)	0.67
Current alcohol drinker, n (%)	24 (21.6)	15 (22.1)	9 (20.9)	0.89
Comorbidities, n (%)				
Hypertension	48 (43.2)	31 (45.6)	17 (39.5)	0.53
Diabetes	16 (14.4)	13 (19.1)	3 (7.0)	0.08
Hyperlipidemia	7 (6.3)	5 (7.4)	2 (4.7)	0.86
GDS-15 (depression), mean (SD)	3.38 (3.09)	3.07 (2.96)	3.86 (3.26)	0.20
GAI (anxiety), mean (SD)	2.65 (3.51)	2.29 (2.98)	3.21 (4.18)	0.18
AES-s (apathy), mean (SD)	30.23 (9.06)	28.47 (8.33)	33.00 (9.55)	0.010*

MCI, mild cognitive impairment; BMI, body mass index; GDS, geriatric depression scale; GAI, geriatric anxiety inventory; AES-s, apathy evaluation scale-self; SD, standard deviation; MoCA, Montreal cognitive assessment.
P-values are shown for differences between cognitively intact and MCI using *t*-tests or chi-square tests.
*Statistically significant value. MCI was based on the MoCA score.

TABLE 2 Cognitive and gait performance of participants.

	Full sample (*n* = 111)	Cognitively intact (*n* = 68)	MCI (based on MoCA) (*n* = 43)	*P*-value
MoCA, median (range)	25 (12–30)	26 (24–30)	19 (12–23)	<0.001*
Single-task gait velocity, mean (SD), cm/s	117.22 (27.50)	125.47 (26.20)	104.16 (24.52)	<0.001*
AniP-DT gait velocity, mean (SD), cm/s	82.54 (27.65)	92.80 (25.21)	66.31 (23.41)	<0.001*

MCI, mild cognitive impairment; SD, standard deviation; MoCA, Montreal cognitive assessment; AniP-DT, animal picture naming dual-task.
P-values are shown for differences between cognitively intact and MCI using *t*-tests or chi-square tests.
*Statistically significant value.
MCI was based on the MoCA score.

TABLE 3 Results of multiple linear regression regarding the relationship between gait velocity and MoCA score.

Dependent variable	Independent variable	Coefficient	Standard error	*P*-value	R^2	R^2 adjusted
MoCA	Single-task gait velocity	0.176	0.013	0.033*	0.471	0.418
	AniP-DT gait velocity	0.301	0.013	0.001*	0.509	0.460

MoCA, Montreal cognitive assessment; AniP-DT, animal picture naming dual-task. The linear regression model was adjusted with age, sex, educational level, smoking and drinking status, use of walking aid, and psychological parameters.
*Statistically significant value.

TABLE 4 Logistic regression models regarding gait velocities and MCI.

	Variable	OR	95% CI of OR	*P*-value
Model 1	AniP-DT gait velocity	0.964	0.941–0.988	0.004*
	Age	1.119	1.027–1.0240	0.018*
	Years of education	0.757	0.648–0.885	0.001*
Model 2	Single-task gait velocity	0.976	0.957–0.997	0.023*
	Age	1.153	1.059–1.255	0.001*
	Years of education	0.786	0.689–0.897	<0.001*

OR, odds ratio; CI, confidence interval; MCI, mild cognitive impairment; MoCA, Montreal cognitive assessment; AniP-DT, animal picture naming dual-task.
*Statistically significant value.
MCI was based on the MoCA score.

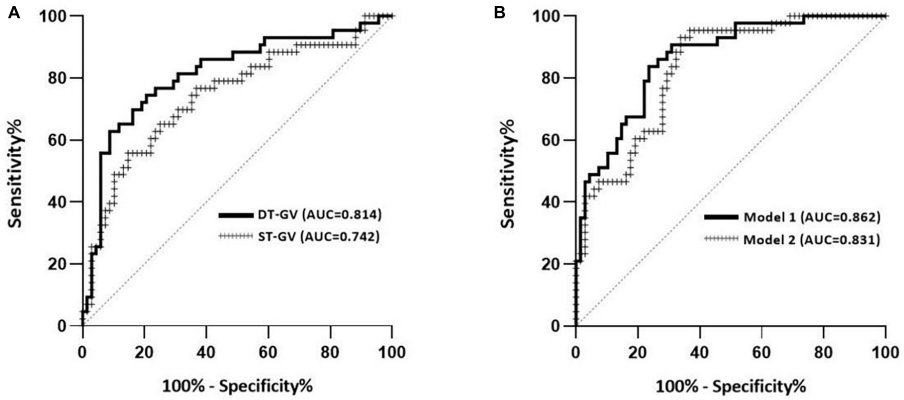

FIGURE 2
Discrimination performance of the gait parameters for screening MCI. **(A)** Receiver-operating characteristic (ROC) curves and corresponding area under the curve (AUC) for the dual-task (DT) gait velocity and single-task (ST) gait velocity to separate older adults with MCI in our study population. **(B)** ROC curves and corresponding AUC of two logistic models in **Table 3**. Model 1 contained DT gait velocity, age, and years of education. Model 2 contained ST gait velocity, age, and years of education. MCI was based on the MoCA score.

participants who had lower dual-task (OR = 0.964, 95% CI = 0.941–0.988, p = 0.004) and single-task gait speeds (OR = 0.976, 95% CI = 0.957–0.997, p = 0.023) were more likely to have MCI.

Discrimination performance of gait speeds for screening MCI

Figure 2 showed the receiver-operating characteristic (ROC) curves and area under the curve (AUC) of single and dual-task gait velocity for screening MCI. The AUC of AniP-DT gait velocity was 0.814 (95% CI = 0.727–0.900; $p < 0.001$), higher than that of single-task gait speed. The cut-off point of AniP-DT gait velocity was 65.78 cm/s (sensitivity = 0.628, 1–specificity = 0.088), and for the corresponding ROC curves of the two logistic models, the AUC of model 1 (0.862; 95% CI = 0.794–0.929; $p < 0.001$) was higher than model 2 (0.831; 95% CI = 0.757–0.905; $p < 0.001$), and improved when compared with only AniP-DT gait velocity (0.814).

Discussion

This study developed a novel dual-task gait test (AniP-DT) that contained an animal picture naming task to test the MCI detecting ability in Chinese older adults. The MCI group had deteriorated gait performance compared to the cognitively intact group in both single and dual-task. Both single and dual-task gait velocities were significantly associated with MoCA scores even after adjustment of covariates. AniP-DT gait speed exhibited higher specificity in MCI detection in older adults. We found older adults whose AniP-DT gait velocity was less than 65.78 cm/s could be considered to have possible MCI in community settings. Adjustion of age and education could further improve the discrimination ability of AniP-DT gait speed. Our results suggested that gait velocity in AniP-DT could act as a behavioral marker to detect MCI.

Researchers have attempted to develop other motor-cognitive dual-task tests to help detect cognitive impairment (Klotzbier and Schott, 2017; Nielsen et al., 2018; Osuka et al., 2020). For instance, Latorre Román et al. (2020) designed a complex gait test (CGT) which was conducted on a 4 m × 6 m ground area and involved several obstacles when participants were walking. Among the discrimination and decision-making tasks, Trail-Walking Task (TWT) has also been used in MCI detection. Klotzbier and Schott (2017) used three TWT conditions with increased difficulty in a 4 m × 4 m area to differentiate MCI from cognitively healthy controls. Considering that a screening tool should be reliable, easy to use, and applicable to as many people as possible, we chose straight-path walking as the motor task, which has the lowest environmental and professional requirements, and chose animal picture naming as the cognitive task to ensure the scope of application for people are reasonably well knowledgeable about animals. The animals chosen in our picture naming test are familiar to most Chinese people. The whole test paradigm could be performed in a variety of settings including hospital hallways, local community centers, and parks, by personnel

with simple training. On average, the test time for one person is less than 3 min.

In line with the previous findings (Montero-Odasso et al., 2014; Tseng et al., 2014), dual-task gait speed slowing was more prominent in our study and AniP-DT gait speed showed great discrimination ability of MCI from cognitively intact controls. The results suggested that the AniP-DT gait test performed well in MCI detection (AUC = 0.814), with a sensitivity of 62.8% and a specificity of 91.2%. In the complex gait test (CGT) of Latorre Román et al. (2020), obstacle negotiation could test participants' executive function and exhibit a good diagnostic ability of MCI (AUC = 0.768). In the physical function test of Abe et al. (2022), models incorporating gait speed also showed good distinguish efficacy for MCI (AUC = 0.79), with a sensitivity of 73% and a specificity of 70%. The results from Klotzbier et al. showed that one of the TWT tests, the TWT-3, which has the highest cognitive load, showed a better differentiation (AUC = 0.860), the sensitivity of this task reached 100%, and the specificity was 66.67%. With a relatively close differentiation (AUC 0.814 vs. AUC 0.860), the sensitivity (62.8 vs. 100%) and specificity (91.2 vs. 66.67%) in our test and the results from Klotzbier et al. were nearly opposite. This could be due to the increased complexity of the task since TWT-3 involved participants' cognitive flexibility, inhibition, and working memory (Klotzbier and Schott, 2017). Due to the stigma attached to dementia and cognitive impairment, screening and diagnostic decisions should be made with caution, thus particularly notable within this study is the high specificity of this test, which would be valuable in the detection of cognitive impairment in a large population. Further, we have determined the cut-off value of the gait speed. Older adults who walked slower than the cut-off value should have further evaluation of their cognition.

In widely used cognitive scales like MMSE or MoCA, age and years of education are often considered as the two factors greatly affect the performance of the participants. Xie et al. (2019) recruited MCI and cognitively normal participants in the community with matched demographic information (age, gender and education level). When adding these two parameters in our models, the ROC in our models also showed improved results, confirming the necessity of considering education and age in cognitive assessments. We think that the reason why the ajustment of age improved the differentiation ability of our test is that it is commensurate that gait velocity decreases with age, while the adjustment of education years increased the AUC of our models because we used the results from a Chinese version of MoCA, which is adjusted with educational level, as the reference in this study.

Study limitations

There are several limitations to this study. We did not make a confirmed diagnosis of cognitive impairment with the Clinical Diagnosis (DSM-5) as a criterion but used MoCA results for the categorization of the participants, which might have brought in unknown confounding factors related to MoCA. Meanwhile, several approaches could further improve the AniP-DT paradigm. First, the current test has high specificity and moderate sensitivity when detecting MCI, implying that we could modify the difficulty of the cognitive task, hence, the animal picture naming task. Possible solutions could be changing the picture sequence by putting similar animals together to increase confusion or adding more low-familiarity animals. Secondly, we only included gait velocity as an outcome. Other parameters, including gait parameters (such as gait variability or cadence) and cognitive performance (number of correct animals, error type), could be tested for their discrimination abilities. Lastly, screening methods for MCI based on gait performance are mainly focused on Western countries with fewer studies in Eastern countries. Also, future studies aiming to upgrade and validate this task in larger samples and different regions are needed due to the existence of geographical cultural differences between Eastern and Western populations.

Conclusion and implications

In summary, the AniP-DT gait test, which combined animal picture naming and straight-path walking, exhibited good discrimination ability in MCI detection in Chinese older adults in the community with a cutoff point of 65.78 cm/s. Although further exploration in a larger population is still needed, the testing paradigm showed great potential as a community screening tool for MCI in older adults, which could help identify MCI patients, thereby preventing or delaying their progression into dementia.

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 human participants were reviewed and approved by the Medical Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China (s906). The patients/participants provided their written informed consent to participate in this study.

Author contributions

QY, YW, CT, JZ, and MY: acquisition of data. YW, QY, CT, MY, and JL: analysis and interpretation of data. YW, QY, and CT: drafting of the manuscript. All authors contributed to study conception and design, critical revision of the manuscript for important intellectual content, and approved the submitted version.

Funding

This work was supported by the Humanities and Social Sciences Foundation of Ministry of Education of China (22YJC630126) and the 2021–2022 Health Research Project of Hubei Provincial Health and Health Commission (WJ2021M105).

Acknowledgments

We would like to thank all of the older adults who participated in the study.

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/fnins.2022.1100642/full#supplementary-material

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frontiers | Frontiers in Neuroscience

TYPE Systematic Review
PUBLISHED 06 April 2023
DOI 10.3389/fnins.2023.1164192

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Translational Neuroscience, a section of the journal Frontiers in Neuroscience

RECEIVED 12 February 2023
ACCEPTED 09 March 2023
PUBLISHED 06 April 2023

CITATION
Zhang Y, Qiu X, Chen J, Ji C, Wang F, Song D, Liu C, Chen L and Yuan P (2023) Effects of exercise therapy on patients with poststroke cognitive impairment: A systematic review and meta-analysis. *Front. Neurosci.* 17:1164192. doi: 10.3389/fnins.2023.1164192

Effects of exercise therapy on patients with poststroke cognitive impairment: A systematic review and meta-analysis

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Objective: To evaluate the effects of exercise therapy on patients with poststroke cognitive impairment and compare the differences in the effect of this method when compared with conventional measures, providing evidence for a more standardized and effective clinical application of exercise therapy.

Methods: A search was conducted using 7 electronic databases, including PubMed, CINAHL, Web of Science, CENTRAL, CNKI, Wanfang, SinoMed, and clinical trials registry platforms for randomized controlled trials concerning exercise therapy on patients with poststroke cognitive impairment. Two researchers independently screened the literature, evaluated the quality, and extracted information. Meta-analysis was carried out using Review Manager 5.4 software.

Results: There were 11 studies with 1,382 patients. Meta-analysis showed that exercise therapy could improve cognitive function [*SMD* = 0.67, 95% CI (0.31, 1.04), *P* = 0.0003], motor function [*SMD* = 1.81, 95% CI (0.41, 3.20), *P* = 0.01], and the activities of daily living [*MD* = 8.11, 95% CI (3.07, 13.16), *P* = 0.002] in patients with poststroke cognitive impairment.

Conclusion: Exercise therapy can not only improve cognitive function in patients with poststroke cognitive impairment but also improve motor function and the activities of daily living. Medical staff should prioritize the management of patients with poststroke cognitive impairment and carry out exercise therapy actively to improve the cognitive function of patients with stroke.

Systematic review registration: https://www.crd.york.ac.uk/prospero/, identifier: CRD42023397553.

KEYWORDS

stroke, cognitive impairment, exercise therapy, systematic review, meta-analysis

Introduction

Stroke is an important cause of cognitive impairment and dementia (Zhao et al., 2018). Poststroke cognitive impairment (PSCI) refers to cognitive impairment or dementia after a stroke. It is common in patients with stroke and usually occurs within 6 months after the stroke. The prevalence of PSCI ranges from 20 to 80% and is one of the most common complications in patients with stroke (Sun et al., 2014). PSCI is an important

factor that seriously affects patients' quality of life and survival time, and it has evolved into one of the hot topics in stroke research and intervention (Dong et al., 2017). Due to cognitive impairment, patients' cognitive abilities decline, and their adaptability to the external environment is disturbed. Therefore, patients are prone to emotional disorders such as anxiety and depression. It can also be characterized by impaired memory function, decreased computing power, and abstract thinking, which affects not only the daily lives of patients but also their rehabilitation of limbs and neurological functions. It can induce a secondary stroke and even threaten their lives, seriously affecting the overall rehabilitation process (Dong et al., 2021). Stroke survivors with moderate PSCI were six times more likely to progress to occasional dementia than stroke survivors without cognitive impairment, and up to 25% of patients with cognitive impairment were diagnosed with dementia within 3 years of stroke (Narasimhalu et al., 2009; Sachdev et al., 2009). Therefore, the rehabilitation of cognitive function in patients with stroke is an urgent issue.

Early intervention is particularly important for patients with PSCI. Studies have shown that there is a wide variation in the treatment of cognitive problems after stroke, including pharmacological and non-pharmacological interventions (Quinn et al., 2021). However, the long-term efficacy of pharmacological interventions is unclear and may be associated with adverse effects. For example, an analysis of the evidence suggests that actovegin and cerebrolysin are animal-derived nootropics that may have potential efficacy in the treatment of neurodegenerative diseases. It has a beneficial effect on improving cognitive function after stroke (Quinn et al., 2021). However, the most common adverse event was a recurrent ischemic stroke. Therefore, more researchers are inclined toward non-pharmacological interventions, such as exercise therapy, cognitive intervention, and acupuncture therapy. Early non-pharmacological exercise therapy for patients can delay the progression of the disease, sometimes even reverse the process of cognitive decline, and reduce the disability rate. Huang et al. (2022) conducted a network meta-analysis of the comparative effectiveness of different exercise interventions on cognitive function in patients with mild cognitive impairment or dementia and found that all types of exercise can effectively improve overall cognitive function in patients. However, there is a lack of effective evidence for exercise therapy in patients with PSCI.

Although routine rehabilitation training can delay the process of cognitive decline in patients and prevent the disease from progressing to dementia, there are shortcomings, such as a single form of training, low patient acceptance, and difficulty in conducting continuous and effective training, which are not conducive to the recovery of cognitive function (Yu et al., 2019). Some studies have found that exercise therapy can improve health by increasing oxygen and blood supply to the brain and indirectly improving cognitive impairment (Tang et al., 2020). Exercise therapy is defined as "a regimen or plan of physical activity designed and prescribed for specific therapeutic goals with the purpose of restoring normal physical function or reducing symptoms caused by disease or injury (Caspersen et al., 1985)". The regimen includes aerobic exercise, resistance exercise, and multiple combination exercises, as well as some traditional Chinese medicine exercises such as Baduanjin. Traditional Chinese medicine exercise therapy has been found to improve cognitive function in elderly patients with mild cognitive impairment (MCI) by regulating cognition-related brain function and structure (Su et al., 2022). Although there are many studies on the use of exercise therapy to improve PSCI, there is a relative lack of consensus, and there is no meta-analysis on the effects of exercise therapy on patients with PSCI. This study evaluated the effects of exercise therapy on patients with PSCI through a meta-analysis, aiming to provide a new evidence-based basis for intervention in patients with PSCI.

This systematic evaluation program is registered in the PROSPERO database (CRD42023397553).

Materials and methods

Search strategy

Two researchers searched PubMed, CINAHL, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), China National Knowledge Infrastructure (CNKI), Wanfang Database, Chinese Biomedical Literature Service System (SinoMed), and the clinical trials registry platform. The search was conducted from the database creation date to January 2023. In addition, the search was conducted by combining free words and subject terms. The search formula was (stroke OR cerebrovascular OR hemiplegia OR cerebral hemorrhage OR cerebral infarction OR cerebral stroke OR acute stroke) AND (cognitive dysfunction OR cognitive impairment OR cognition disorders) AND (physical activity OR physiotherapy OR fitness OR aerobic OR exercise OR resistance training OR physical fitness OR exercise). We searched both the included references and the gray literature. The results were cross-checked after each of the two researchers had completed the search independently. In case of disagreement, the decision was discussed with a third researcher.

Study design and eligibility criteria

This systematic review was completed according to the Cochrane Collaboration methodology and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (Sachdev et al., 2009).

A participant-intervention-comparison-outcome (PICO) strategy was used to structure the research questions (Stone, 2002). The inclusion criteria were as follows: (1) Participants: patients who meet the diagnostic criteria adopted by the Fourth National Conference on Cerebrovascular Diseases and were diagnosed with ischemic or hemorrhagic stroke by CT or MRI examination, are over 18 years of age, and had a cognitive decline occurring within 6 months of stroke; (2) Intervention: exercise therapy, including aerobic exercise, resistance exercise, and multiple combination exercises; (3) Comparison: routine non-pharmacological intervention, including a balanced diet, health education, and routine rehabilitation training; (4) Outcome: the main outcome indicator was cognitive function, and the assessment tools were the Minimum Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA), and the secondary outcome indicators were motor function and activities of daily living, measured by the Fugl-Meyer

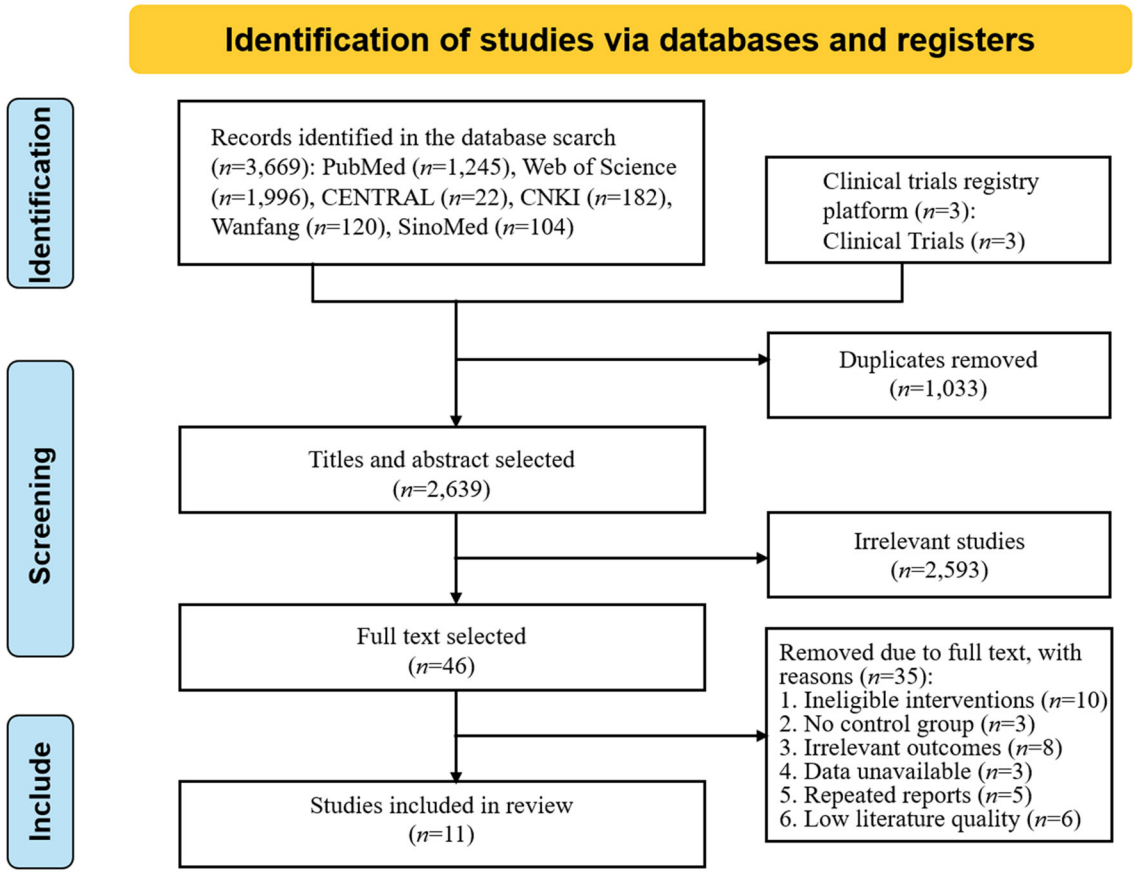

FIGURE 1
Screening process of literature selection.

Assessment (FMA) and the Modified Barthel Index (MBI). In addition, the study design must be a randomized controlled trial (RCT). The exclusion criteria were as follows: (1) data could not be extracted; (2) the full text could not be obtained; (3) the literature is a repeated publication; (4) the literature is a conference paper; and (5) the literature quality assessment was high risk.

Data extraction

Two researchers trained in evidence-based research independently searched the literature, imported the retrieved literature into the Endnote software, and deleted duplicate literature; they simultaneously and independently read the titles and abstracts for preliminary screening and carefully read the full text to determine the included literature according to the inclusion and exclusion criteria. The two researchers extracted information from the literature, including the year of publication, country, sample size, intervention measures of the experimental and control groups, intervention duration, outcome indicator, and evaluation tool. In case of disagreement, the decision was discussed with a third researcher. The researchers contacted the author by phone or email to request additional information.

Quality appraisal

The quality of included RCTs was assessed independently by two reviewers using the Cochrane Systematic Review Manual 5.1.0, with a third researcher consulted to reach a consensus in case of disagreement. The evaluation included (1) random sequence generation (selection bias), (2) allocation concealment (selection bias), (3) blinding of participants and personnel (performance bias), (4) blinding of outcome assessment (detection bias), (5) incomplete outcome data (attrition bias), (6) selective reporting (reporting bias), and (7) other biases. The bias for the abovementioned 7 aspects is low bias, high bias, and unclear (lack of relevant information or bias situation is uncertain).

Statistical analysis

The RevMan software (version 5.4; Cochrane Collaboration, Copenhagen, Denmark) was used for meta-analysis. Based on the type of extracted data, we evaluated 95% confidence intervals (CIs) for continuous variables. For a continuous variable that was measured using different scales, we used standardized mean differences (SMD) as a measure for effect size; for a

continuous variable that was measured using the same scale, we used mean differences (MD) for effect size. A *P*-value of < 0.05 (two-sided) was considered statistically significant in the estimation of effects. I^2 was used to determine the heterogeneity of the results. If the *P*-value was > 0.1 and I^2 was $< 50\%$, indicating low heterogeneity, and if all studies were from a homogeneous population, the fixed-effects model was used for meta-analysis. If the *P*-value was ≤ 0.1 and I^2 was $\geq 50\%$, indicating large heterogeneity, the source of heterogeneity was analyzed as far as possible. If the heterogeneity could not be reduced, the random-effects model was used for the meta-analysis. The inverse variance method was used to pool the effect-size measure. Clinical and methodological heterogeneity was addressed by sensitivity analysis, subgroup analysis, or descriptive analysis only.

Results

Study selection

According to the search strategy, 3,672 studies were preliminarily searched, 1,033 duplicate studies were excluded, and 11 studies (Fang et al., 2003; Studenski et al., 2005; El-Tamawy et al., 2014; Zhang et al., 2015, 2020; Fernandez-Gonzalo et al., 2016; Kim and Yim, 2017; Li, 2017; Ihle-Hansen et al., 2019; Yu et al., 2019; Zheng et al., 2020) were finally included after the preliminary screening of the title abstract and reading the full text. The literature screening process and results are shown in Figure 1.

Characteristics of the included studies

A total of 11 studies were included in this review, and the characteristics of each study are shown in Table 1. Only Chinese and English literature were included in this review, and literature in other languages was not considered. The sample sizes of the RCTs ranged from 20 to 420 participants. The total sample size for the meta-analysis was 1,382 participants, including both experimental ($n = 679$) and control ($n = 703$) participants.

Quality assessment

The 11 studies included in this analysis were RCTs, all of which had clearly defined inclusion and exclusion criteria for subjects and were comparable at baseline. The tools used to measure outcomes in the experimental and control groups were consistent, and the same statistical methods were used. The method of random sequence generation was explained in 5 studies (Fang et al., 2003; Zhang et al., 2015, 2020; Ihle-Hansen et al., 2019; Zheng et al., 2020), and allocation concealment was described in detail in only 3 studies (Fang et al., 2003; Ihle-Hansen et al., 2019; Zheng et al., 2020). The blinding of outcome evaluators was explicitly described in 3 studies (Fang et al., 2003; Studenski et al., 2005; Zheng et al., 2020), and the blinding of subjects and intervention implementers was explicitly described in 2 studies (Studenski et al., 2005; Zheng et al., 2020). Only 1 study (Fang et al., 2003) had missing data, and it did not explain the method of handling missing data; no other sources of bias were found in all studies. The literature quality assessment is shown in Table 2, Figure 2.

Results of meta-analysis

Effects of exercise therapy on cognitive function in patients with PSCI

The MMSE scale and the MoCA scale are currently widely used cognitive function assessment scales in clinical practice, both of which can be used to assess patients' cognitive function (Jia et al., 2021). Both of them are effective in diagnosing dementia and cognitive impairment (Pinto et al., 2019). The effects of exercise therapy on cognitive function in patients with PSCI were reported in 11 studies (Fang et al., 2003; Studenski et al., 2005; El-Tamawy et al., 2014; Zhang et al., 2015, 2020; Fernandez-Gonzalo et al., 2016; Kim and Yim, 2017; Li, 2017; Ihle-Hansen et al., 2019; Yu et al., 2019; Zheng et al., 2020). *SMD* was selected for the combination of effect sizes, and the results showed significant heterogeneity ($P < 0.01$, $I^2 = 89\%$). When the study by Zheng et al. (2020) was removed using sensitivity analysis, the heterogeneity was reduced, and the 95% CI was (0.20, 0.74), but I^2 was equal to 80%. The random-effects model was used for the meta-analysis. The results showed that the cognitive function of the experimental group was higher than that of the control group after the intervention, and the difference was statistically significant [$SMD = 0.67$, 95% CI (0.31, 1.04), $P = 0.0003$], as shown in Figure 3.

Subgroup analysis was performed based on the type of exercise: aerobic exercise was used in 4 studies (El-Tamawy et al., 2014; Ihle-Hansen et al., 2019; Zhang et al., 2020; Zheng et al., 2020); resistance exercise was used in 2 studies (Fang et al., 2003; Fernandez-Gonzalo et al., 2016); and aerobic exercise combined with resistance exercise was used in 5 studies (Studenski et al., 2005; Zhang et al., 2015; Kim and Yim, 2017; Li, 2017; Yu et al., 2019). In subgroup analysis (as shown in Figure 4), we found that each exercise type had a positive impact on cognitive function, with a *p*-value of < 0.05 for the overall effect for each exercise type. Moreover, aerobic exercise showed a large clinical effect in improving cognitive function [$SMD = 1.32$, 95%CI (0.30, 2.34)], while the other two exercise types exhibited a medium effect ($SMD \approx 0.5$). However, the differences were not statistically significant ($P = 0.29$ from the test for subgroup differences) (Andrade, 2020).

Effects of exercise therapy on motor function in patients with PSCI

The FMA scale is considered by many in the field of stroke rehabilitation as one of the most comprehensive quantitative measures of motor impairment after stroke (Gladstone et al., 2002). The effects of exercise therapy on motor function in patients with

TABLE 1 Characteristics of included studies in this review.

References	Country	Sample size (experiment group/control group)	Intervention		Intervention duration	Outcome indicator	Evaluation tool
			Experiment group	Control group			
Fang et al. (2003)	China	50/78	Early physiotherapy (Bobath techniques and passive movements training of the affected limb during the first week of stroke onset); 45 min/day, 5 days/week	Routine therapy without early professional physiotherapy	4 weeks	Cognitive function, motor function, activities of daily living	MMSE, FMA, MBI
Ihle-Hansen et al. (2019)	Norway	143/156	Physical activity 30 min/day, physical exercise 45 to 60 min/week, including at least 2-3 vigorous exercise	Conventional rehabilitation	18 months	Cognitive function	MMSE
Kim and Yim (2017)	South Korea	14/15	Exercise protocol for handgrip strength (grasping training with a power web exerciser + Digi-Flex repetition training) and walking speed (run on a motor-powered treadmill) for 30 min, 3 times per day	Conventional physical therapy for 60 min per day	6 weeks	Cognitive function, motor function	MoCA, Timed Up and Go
Li (2017)	China	42/42	Aerobic combined with resistance exercise, including aerobics 40 min/time, 5 times/week, balance training and use of resistance equipment for resistance training 20 min/time, 3 times/week	Routine nursing procedure	3 months	Cognitive function, activities of daily living	MMSE, MBI
El-Tamawy et al. (2014)	Egypt	15/15	Cardio on a bicycle dynamometer for "40–45" min, 3 times/week	Physiotherapy program "25–30" min/session, 3 times/week	8 weeks	Cognitive function	ACER
Fernandez-Gonzalo et al. (2016)	Switzerland	10/10	Lower extremity resistance training (using the more-affected limb, 4 sets of 7 repetitions; <2 min of contractile activity) 2 times/week	Daily routine rehabilitation training	12 weeks	Cognitive function	TMT B
Studenski et al. (2005)	USA	44/49	Home-based exercise program, supervised by an occupational or physical therapist (major muscle groups of the upper and lower extremity using elastic bands and body weight, using an exercise bicycle)	Conventional rehabilitation (health education, vital signs, and an oxygen saturation test)	12 weeks	Cognitive function, motor function, activities of daily living	FIM, MBI
Yu et al. (2019)	China	50/50	Aerobic exercise combined with resistance exercise (health care relaxation exercise and acupoint massage 40 min/time, 4 times/week +upper and lower limb exercises using elastic bands, 20 min/time, 4 times/week	Routine rehabilitation training and health education	None	Cognitive function, motor function	MoCA, FMA
Zhang et al. (2015)	China	220/200	Aerobic combined with resistance exercise (aerobics 40 min/time, 5 times/week, balance training and resistance training 20 min/time, 3 times/week	Health education and routine rehabilitation training	None	Cognitive function	MoCA
Zhang et al. (2020)	China	69/69	Indoor bicycle aerobic training, 20–30 min/ time, 4 times/week	Routine neuromuscular rehabilitation therapy and health education	12 weeks	Cognitive function, motor function, activities of daily living	MMSE, FMA, MBI
Zheng et al. (2020)	China	22/19	Baduanjin training 40 min/day, 3 days/week	Routine rehabilitative treatment and health education	24 weeks	Cognitive function, activities of daily living	MoCA, MBI

TABLE 2 Quality evaluation of the included literature.

References	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Fang et al. (2003)	Low risk	Low risk	Unclear	Low risk	Unclear	Unclear	Low risk
Ihle-Hansen et al. (2019)	Low risk	Low risk	Unclear	Unclear	Low risk	Low risk	Low risk
Kim and Yim (2017)	Unclear	Unclear	Unclear	Unclear	Low risk	Low risk	Low risk
Li (2017)	Unclear	Unclear	Unclear	Unclear	Low risk	Low risk	Low risk
El-Tamawy et al. (2014)	Unclear	Unclear	Unclear	Unclear	Low risk	Low risk	Low risk
Fernandez-Gonzalo et al. (2016)	Unclear	Unclear	Unclear	Unclear	Low risk	Unclear	Low risk
Studenski et al. (2005)	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Yu et al. (2019)	Unclear	Unclear	Unclear	Unclear	Low risk	Low risk	Low risk
Zhang et al. (2015)	Low risk	Unclear	Unclear	Unclear	Low risk	Low risk	Low risk
Zhang et al. (2020)	Low risk	Unclear	Unclear	Unclear	Low risk	Low risk	Low risk
Zheng et al. (2020)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

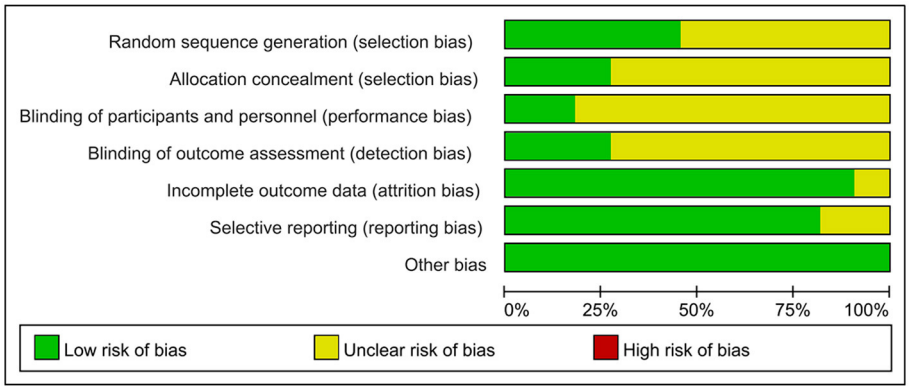

FIGURE 2
Risk assessment of bias.

PSCI were reported in 5 studies (Fang et al., 2003; Studenski et al., 2005; Kim and Yim, 2017; Yu et al., 2019; Zhang et al., 2020). *SMD* was selected for the combination of effect sizes, and the results showed significant heterogeneity ($P < 0.01$, $I^2 = 98\%$). When the study by Yu et al. (2019) was removed using sensitivity analysis, the heterogeneity was reduced, and the 95% CI was (−0.06, 0.72) but I^2 was equal to 70%. The random-effects model was used for the meta-analysis. The results showed that the motor function of the experimental group was higher than that of the control group after the intervention, and the difference was statistically significant [$SMD = 1.81$, 95% CI (0.41, 3.20), $P = 0.01$], as shown in Figure 5.

Effects of exercise therapy on activities of daily living in patients with PSCI

The effects of exercise therapy on the activities of daily living in patients with PSCI were reported in 5 studies (Fang et al., 2003; Studenski et al., 2005; Li, 2017; Zhang et al., 2020; Zheng et al., 2020). *SMD* was selected for the combination of effect sizes, and the results showed significant heterogeneity ($P < 0.01$, $I^2 = 94\%$). When the study by Studenski et al. (2005) was removed using sensitivity analysis, heterogeneity was reduced, and the 95% CI was (7.14, 14.86), but I^2 was equal to 88%. The random-effects model was used for the meta-analysis. The results showed that the

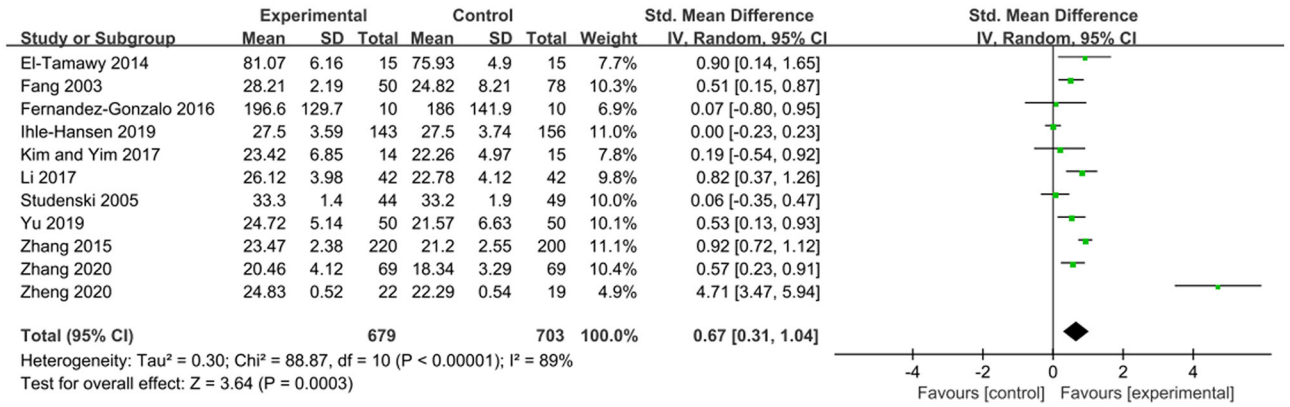

FIGURE 3
Effects of exercise therapy on cognitive function in patients with PSCI.

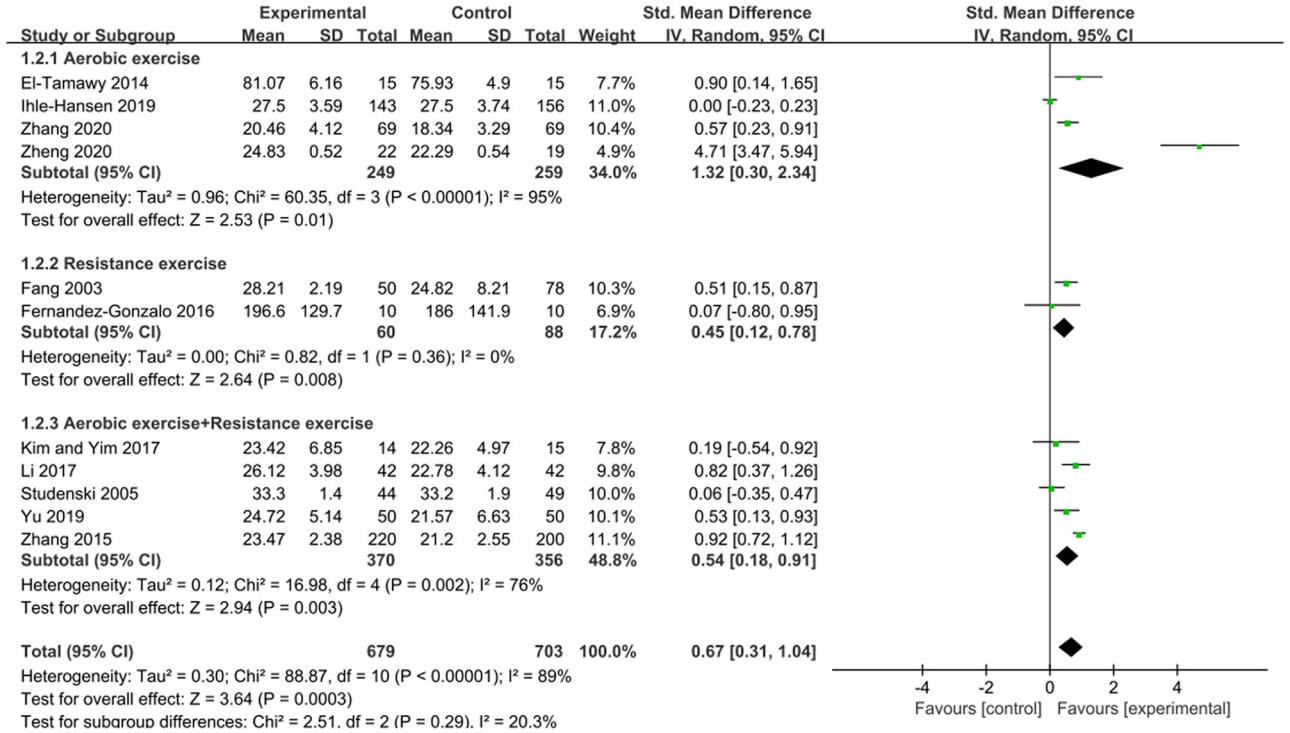

FIGURE 4
Subgroup analysis of the effects of different types of exercise on cognitive function in patients with PSCI.

activities of daily living of the experimental group were higher than those of the control group after the intervention, and the difference was statistically significant [$MD = 8.11$, 95% CI (3.07, 13.16), $P = 0.002$], as shown in Figure 6.

Publication bias

A funnel plot analysis of the included literature with cognitive function, motor function, and activities of daily living as the outcome indicators showed that the distribution was generally symmetric, and the meta-analysis results were reliable (Figure 7).

Discussion

With the understanding of stroke, people pay attention not only to the problems of motion perception caused by stroke but also to the impact of stroke on cognitive function. After a stroke, the overall cognitive function of most patients is in a state of decline due to brain damage (Li et al., 2013). Physical activity has been shown to increase brain neuronutrients, improve cerebrovascular function and cerebral perfusion, reduce stress responses, and increase brain plasticity through synaptogenesis and nerve regeneration (Li et al., 2013). The 2019 Canadian Stroke Best Practice Guidelines recommend that exercise therapy

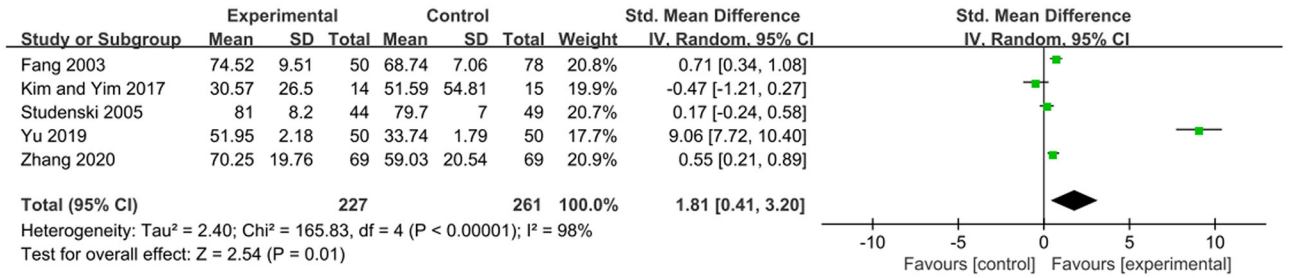

FIGURE 5
Effects of exercise therapy on monitor function in patients with PSCI.

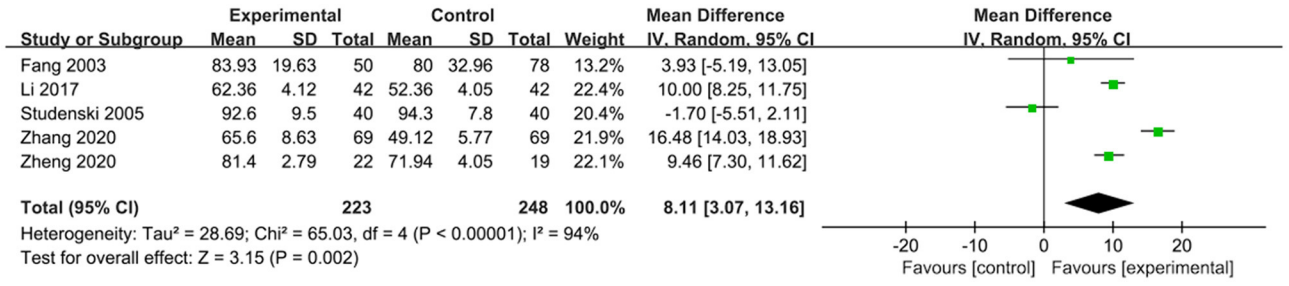

FIGURE 6
Effects of exercise therapy on activities of daily living in patients with PSCI.

be considered an adjunctive treatment for cognitive impairment, including attention, memory, and executive performance (Lanctot et al., 2020). In this study, we analyzed two current mainstream scales for comprehensive cognitive assessment and found that the cognitive function score in the exercise therapy group was higher than those in the control group, and the difference was statistically significant ($P < 0.05$). This study strongly demonstrated that exercise therapy can improve cognitive function in patients with PSCI, which is consistent with the findings of Ravichandran et al. (2020). Exercise therapy may improve PSCI for several reasons. Several studies have suggested that exercise can improve cognitive impairment in patients with mild PSCI, possibly because it can improve patients' cardiopulmonary function, reduce brain atrophy volume, increase cerebral blood flow, promote the establishment of brain neural networks, improve brain tissue metabolism, and stimulate central nervous system excitation (Szulc-Lerch et al., 2018). Moreover, exercise can also reduce or delay the occurrence of stroke risk factors such as coronary atherosclerotic heart disease, type 2 diabetes, hypertension, and other common diseases (Callisaya and Nosaka, 2017). A study found that exercise can improve cognitive performance, specifically memory and executive functions, and this was accompanied by an increase in plasma brain-derived neurotrophic factor (BDNF) levels (Sungkarat et al., 2018). In addition, exercise, especially aerobic exercise, significantly improved cortical connectivity and thus improved cognitive function in patients with PSCI (Ahlskog et al., 2011), which is consistent with the results of the subgroup analysis in this study. Studies have shown that exercise therapy can be used as a potentially effective technique to improve cognitive function in patients with PSCI.

In addition to cognitive impairment, motor impairment is a common consequence of stroke. Life becomes more difficult for patients with motor impairments who have PSCI. This study has shown that exercise therapy can improve motor function in patients with PSCI. The patients master the correct motor skills due to repeated, regular coordination training during the exercise. The movement of the cerebral cortex motor area is "set" through the input of repeated and intensified normal movement mode to the brain for stimulation so that the patient's body movements achieve maximum coordination and randomness and then promote the recovery of the affected limb movement ability and effectively reduce the occurrence of hemiplegic limb disuse and misuse atrophy deformation (Li et al., 2016). Many molecular signaling pathways are involved in this process, but among them, the brain-derived neurotrophic factor is a key promoter of neuroplasticity involved in motor learning and rehabilitation after stroke. Exercise, especially aerobic exercise, can upregulate neuronutrients (such as BDNF) to enhance the plasticity of the motor system (Mang et al., 2013). At the same time, exercise therapy can train the limbs of patients with PSCI, improve the condition of their movement impairment, and make their activities more coordinated.

Studies have shown that exercise can improve patients' ability to undertake the activities of daily living and prevent the occurrence of falls in elderly people, especially exercise to maintain physical balance (Sherrington et al., 2017), which is consistent with the findings of this study. García-Rudolph et al. (2019) also found that physical activity can improve the quality of life after a stroke. Exercise promotes the recovery of motor function and improves the activities of daily living. Improving upper extremity function can improve the ability to eat, dress, and use utensils; rehabilitating the

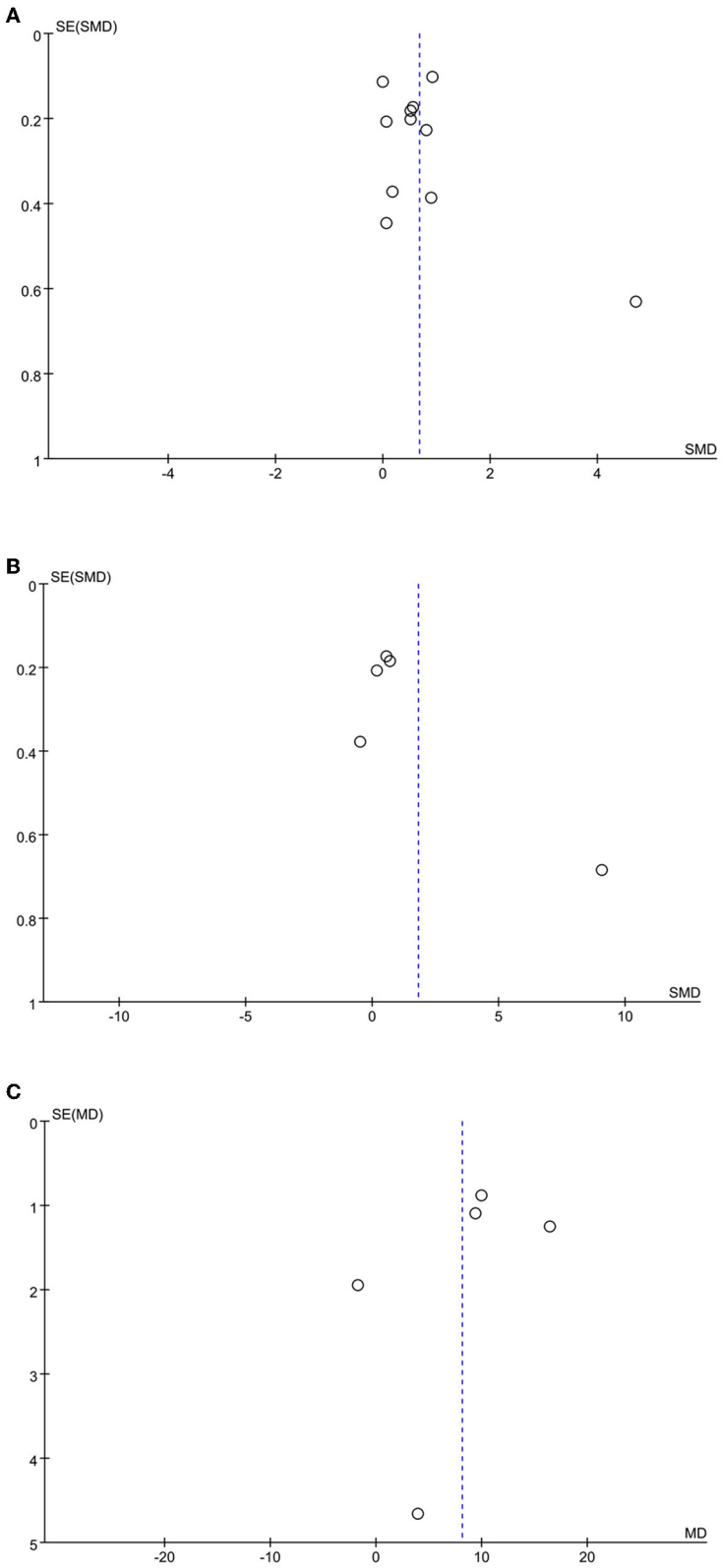

FIGURE 7
Funnel plot of the included studies. **(A)** cognitive function; **(B)** motor function; **(C)** activities of daily living.

back, waist, and lower extremities can promote the rehabilitation of turning, sitting, and standing transfer abilities. Improvements in balance and gait can improve patients' ability to walk and climb stairs (Shiraishi et al., 2017). Therefore, medical staff can improve the activities of daily living in patients with stroke by strengthening exercise therapy.

Strengths and limitations

The main advantage of this meta-analysis review is that only RCTs were selected. RCTs have the highest level of research evidence, and most high-quality clinical trials use the RCT design method. At present, there are still limitations to this study. First, although we used a rigorous method to search and select literature, publication bias was inevitable because the eligible studies included were Chinese and English literature only. In addition, many Chinese studies on blind methods, allocation, and concealment provided insufficient information, which was a hidden danger. Second, since the study did not strictly screen patients for the time of onset and diagnosis of PSCI, our results may be influenced by inevitable heterogeneity. Third, due to the limited number of eligible studies, no further subgroup analysis of the effects of exercise duration was performed in this study, which could be considered more carefully in subsequent studies.

Conclusion

In conclusion, exercise therapy can not only significantly improve the cognitive function of patients with PSCI but also improve the motor function and activities of daily living of patients to some extent. However, as the intensity and frequency of exercise therapy are still heterogeneous, the intensity and frequency of exercise therapy should be further discussed. In addition, if exercise therapy has the advantages of feasibility, economy, and safety to improve the quality of life of patients with PSCI, it is worth exploring how it might be promoted further.

Data availability statement

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

Author contributions

YZ, XQ, JC, CJ, FW, and DS contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by YZ, XQ, CJ, and CL under the supervision of LC and PY. The first draft of the manuscript was written by YZ, XQ, and JC. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding

This study was supported by Postgraduate Research & Practice Innovation Program of Jiangsu Province (grant number SJCX22_0815) and funding for Clinical Trials from the Affiliated Drum Tower Hospital, Medical School of Nanjing University (grant number 2021-LCYJ-MS-05).

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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frontiers | Frontiers in Neuroscience

TYPE Original Research
PUBLISHED 17 April 2023
DOI 10.3389/fnins.2023.1180782

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Translational Neuroscience, a section of the journal Frontiers in Neuroscience

RECEIVED 06 March 2023
ACCEPTED 15 March 2023
PUBLISHED 17 April 2023

CITATION
Deng Y, Lin X, Zhou J, Li M, Fu Z and Song D (2023) Concurrent serum lead levels and cognitive function in older adults. *Front. Neurosci.* 17:1180782. doi: 10.3389/fnins.2023.1180782

Concurrent serum lead levels and cognitive function in older adults

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Introduction: In this study, we investigated the relationship between serum lead levels and cognitive functioning in a sample of older adults in the US.

Method: Using the National Health and Nutrition Examination Survey (NHANES) 2011–2013, a total of 768 older adults aged ≥60 years were included in the analysis. Lead concentrations in the whole blood samples were assessed using mass spectrometry. We used the immediate and delayed memory portions of the Consortium to Establish a Registry for Alzheimer's Disease Word Learning Subtest (CERAD-WL), the Animal Fluency Test (AFT), and the Digit Symbol Substitution Test (DSST) to assess the participants' cognitive performance. Using sample averages and standard deviations (SDs), we computed test-specific and global cognition z-scores. To assess the relationships between the quartiles of serum lead levels and cognitive performance, we built multiple linear regression models and adjusted for covariates, including age, sex, race/ethnicity, education, depressive symptoms, alcohol usage, and body mass index.

Results: The average age of the participants was 69.6 (SD 6.6) years. Approximately half of the participants were women (52.6%), non-Hispanic white (52.0%), and had completed at least some college education (51.8%). The average serum lead concentration was 1.8 g/dL (SD 1.6) for these participants. The results of multiple linear regression using individuals in the lowest serum lead quantile as a reference group revealed that the serum lead level was not associated with test-specific (CERAD-WL, AFT, and DSST) or global cognitive z-scores.

Conclusions: In older adults, concurrent serum lead concentration is not related to cognitive performance. Early or continuous lead exposure may exert a greater effect on the etiology of accelerated cognitive decline with old age.

KEYWORDS

biomarker, lead, cognition, seniors, heavy metal

Introduction

Lead is a naturally occurring toxic metal in the Earth's crust. Because of the massive environmental contamination caused by the widespread use of lead, lead exposure has become a serious public health problem. Humans can be exposed to lead by breathing in lead particles and consuming dust, water, and food that have been contaminated with lead. According to the World Health Organization's 2021 update on the public health impact of

chemicals: knowns and unknowns, lead exposure is estimated to be responsible for a loss of 21.7 million disability-adjusted life years globally, highlighting its long-term impact on people's health. Lead has a half-life that ranges from a month in the blood to 25-30 years in the bones. Because lead builds up in the bones during a person's lifetime and because bones hold the majority of the body's burden of lead, lead in the bones is often used as a biomarker of cumulative exposure. The nervous system is particularly sensitive to lead exposure (Wani et al., 2015). Some studies have suggested that cumulative exposure to lead, as measured by the lead level in the bones, is associated with accelerated cognitive decline at an older age. However, it is presently unclear whether concurrent plasma lead levels are associated with worse cognitive function in older adults. Some studies have reported significant associations with cognitive function measured by the Mini-Mental State Examination (MMSE) (Wright et al., 2003), verbal ability, and memory (Payton et al., 1998; Weisskopf et al., 2007). However, the findings of other studies did not support these conclusions (Weisskopf et al., 2004; Shih et al., 2006; Weisskopf et al., 2007; Weuve et al., 2009).

There is a research gap on whether accumulative lead exposure, concurrent lead exposure, or both is associated with cognitive function in older adults. Thus, this study investigated the relationship between concurrent plasma lead levels and cognitive function in a nationally representative group of older participants in the National Health and Nutrition Examination Survey (NHANES) 2013–2014. The findings of this study will help elucidate the effect of concurrent exposure to lead on cognitive function among older adults.

Methods

The parent study design

The NHANES is a program of studies based on continuous cross-sectional surveys designed to assess the health and nutrition status of the population in America, led biannually by the National Center for Health Statistics of the Centers for Disease Control and Prevention. The NHANES program began in the early 1960s and currently focuses on various health and nutrition measurements. Instead of utilizing simple random sampling, the NHANES data were collected using a complex and multistage probability design to represent the census makeup of civilian, noninstitutionalized populations (Johnson et al., 2013). Medical, dental, and physiological measurements and laboratory tests carried out by qualified doctors, medical and health technicians, and dietary and health interviewers were used to evaluate participants' demographic, socioeconomic, dietary, and health-related statuses. In-person interviews and physical examinations were conducted at participants' residences and mobile exam centers with special settings.

The inclusion criteria in this study specified individuals who were 60 years of age or older and had available information on both their plasma lead levels and cognitive function. The NHANES 2013–2014 survey included a total of 9,813 participants. Those older than 60 ($n = 768$) and those with no available information about their plasma lead levels ($n = 0$) or cognitive performance ($n = 0$) were excluded. Eventually, this study comprised a total of 768 older adults aged 60 years and above.

Ethical considerations

The National Center for Health Statistics Research Ethics Review Board approved NHANES.

Measures

Independent variable: quartile of plasma lead level (1st quartile [reference group], 2nd quartile, 3rd quartile, and 4th quartile)

Before being sent to Georgia Regents University for testing, the samples were stored at freezing temperatures (−70°C). After a quick dilution sample preparation process, mass spectrometry was used to directly evaluate the lead content in whole plasma specimens. The diluted plasma sample in liquid form was blasted through a nebulizer, which dispersed the large droplets of liquid into an argon aerosol. A stream of flowing argon was used to selectively transport the smaller aerosol particles past the spray chamber and into inductively coupled plasma. Plasma with a temperature of 6,000–8,000 K and a predominance of positive argon ions and electrons was produced by connecting radio-frequency power into flowing argon. The complete, detailed method has been published in a previous publication (National Health Nutrition Examination Survey, 2016). This method had a limit of detection (LOD) of 0.07 μg/dL for plasma lead levels. For values below the LOD, an imputed value was filled as the analyte. This value was the LOD divided by the square root of 2. The NHANES employed several techniques to check the accuracy of the analyses carried out by the contract laboratories, including performing blind split samples obtained during "dry run" sessions in the MEC.

Moreover, 2.0% of all specimens underwent random repeat testing at contract laboratories. A review of the results was done. Uncertain values or incomplete data were forwarded to the performing laboratory for verification. In the present study, we categorized participants' plasma levels of lead into four groups based on quartile and used the 1st quartile (the lowest quartile) as a reference. This is consistent with prior NHANES-based epidemiological studies (Fu et al., 2022a,b; Li et al., 2023).

Dependent variable: cognitive function

The NHANES team assessed cognitive function with three cognitive performance tests, including the Consortium to Establish a Registry for Alzheimer's Disease Word Learning Subtest (CERAD-WL), the Animal Fluency Test (AFT), and the Digit Symbol Substitution Test (DSST). All the surveys were completed on the same day and were administered by two trained interviewers in a mobile examination center. The participants were given the option to take the surveys in their preferred language.

The CERAD-WL has been widely used for various clinical purposes, including assessment for Alzheimer's disease (Reid et al.,

2002), identification of mild cognitive impairment, differential diagnosis of recently identified dementias, cognitive assessment of modifiable risk factors for AD, and has been used in major epidemiological surveys worldwide (Morris et al., 1989; Prince et al., 2003; Gao et al., 2009). In NHANES, CERAD-WL was used to assess the participants' immediate and delayed learning ability for new verbal information (memory sub-domain) and included an immediate recall test after each of the three successive immediate learning trials and a delayed recall test (Davis et al., 1992; Fillenbaum et al., 2008). During each of the three learning trials, 10 words appeared on the screen one at a time in large and bold letters, and the participants were asked to read the words out loud after each word appeared. Each learning trial displayed the same set of 10 words in different sequences and colors. For the immediate recall test, the participants were asked to recall as many as 10 words as possible right after each learning trial. The scores ranged from 0 to 10 for each of the three learning trials and were added up to calculate the total immediate recall score, ranging from 0 to 30 points. For the delayed recall tests, the participants were asked to recall as many words from the same 10-word list as possible after completing the other two cognitive tests (the DSST and the AFT). The number of words correctly recalled by the participant was recorded as the delayed test score, ranging from 0 to 10. The final CERAD-WL scores consist of both the immediate recall scores and the delayed recall scores.

The AFT is a test commonly used for cognition research that measures participants' categorical verbal fluency, a component of the executive function (Strauss et al., 2006). The participants were asked to name as many animals as possible in 1 min, with one point given for each unique animal identified. The participants in NHANES were given a practice verbal fluency test with the clothing category to become familiar with the rules. The AFT has been shown to differentiate between normal cognition, mild cognitive impairment, and probable Alzheimer's disease in older people with a sensitivity of 98.8% (García-Herranz et al., 2020). A score of fewer than 15 points indicates Alzheimer's disease following dementia in the memory clinic setting (Canning et al., 2004). The AFT has been used in large-scale screenings and epidemiologic studies (Clark et al., 2009).

The DSST is a paper-and-pencil cognitive test administered on a single sheet of paper that requires the participants to match symbols to numbers according to a key located on the top of the page (Jaeger, 2018). The DSST test evaluated participants' processing speed, sustained attention, and working memory (Ryan and Schnakenberg-Ott, 2003). During the DSST test, a total of 133 boxes were printed on a paper with the numbers on top of each box. The participants were asked to draw the symbols in each box corresponding to each number based on the key provided. The DSST total score was calculated using the number of correct matches, ranging between 0 and 133. The DSST has been used in large screening, epidemiological, and clinical studies (Plassman et al., 2007; Proust-Lima et al., 2007; Rosano et al., 2016).

Covariates

To minimize potential confounding between plasma lead levels and cognitive function, we reviewed the literature (Ge et al., 2018, 2020; Li et al., 2019; Fu et al., 2022a) and adjusted for covariates, including age (years), sex (male or female), race/ethnicity (Mexican Americans, other Hispanics, non-Hispanic white, or non-Hispanic Black), an education level (below high school, high school graduate, or some college or above), depressive symptoms, body mass index (kg/m^2) (<18.5, 18.5-24.9, 25-29.9, or ≥30), and alcohol use (drinks per day) (0–1, 2, or 3 and more). Depressive symptoms were measured using the Patient Health Questionnaire, whose total score ranges between 0 and 27. A higher score indicates more severe depressive symptoms (Kroenke et al., 2001).

Statistical analysis

The averages and standard deviations (SD) of the values from the cognitive tests were used to compute the standardized z-scores for the CERAD-WL immediate recall, the CERAD-WL delayed recall, the AFT, and the DSST. The averages and SDs of the test-specific z-scores were then used for the calculation of global cognition z-scores. Multivariate linear regression models were developed to investigate the independent connection between plasma lead quartiles (reference: the 1st quartile) and test-specific and global cognitive z-scores while controlling the abovementioned confounders. We checked both the z-scores to determine if the covariates were multicollinear before building the regression models. There was no multicollinearity, as indicated by the variance inflation factor of <10. Statistical significance was defined as a confidence interval (CI) of 95%, excluding zero. All analyses were carried out using SPSS.

Results

Table 1 shows the characteristics of the participants. Of the 768 participants (average age 69.6; standard deviation [SD] 6.6), approximately half of the participants were women (52.6%), non-Hispanic white (52.0%), completed some college education or above (51.8%), and had a BMI of ≥30kg/m^2 (36.8%). Their average plasma lead level was 1.8 μg/dL (SD 1.6). The participants' average CERAD-WL immediate memory, CERAD-WL delayed memory, AFT, and DSST score was 19.6 (SD 4.6), 6.2 (SD 2.4), 16.6 (SD 5.3), and 45.8 (SD 17.2), respectively.

Table 2 shows the averages and 95% CIs of the cognitive test-specific z-scores stratified by plasma level quartiles. For participants in the 1st quartile, their CERAD W-L immediate recall, CERAD W-L delayed recall, the AFT, and the DSST average z-scores were 0.03 (95% CI −0.11, 0.17), 0.03 (95% CI −0.11, 0.17), −0.01 (95% CI −0.15, 0.12), and 0.04 (95% CI −0.10, 0.19), respectively. For the participants in the 2nd quartile, their CERAD W-L immediate recall, CERAD W-L delayed recall, the AFT, and the DSST average z score were 0.03 (95% CI −0.11, 0.17), −0.01 (95% CI −0.15, 0.13), 0.05 (95% CI −0.11, 0.20), and 0.10 (95% CI −0.04, 0.24), respectively. For participants in the 3rd quartile, their CERAD W-L immediate recall, CERAD W-L delayed recall, the AFT, and the DSST average z-scores were 0.04 (95% CI −0.10, 2.020.18), 0.10 (95% CI −0.04, 0.23), 0.06 (95% CI −0.08, 0.21), and 0.05 (95%

TABLE 1 Characteristics of the participants by plasma lead level quartile.[a]

Variables	Quartile 1 ≤0.960 ug/dl (*n* = 196)	Quartile 2 0.960–1.350 ug/dl (*n* = 189)	Quartile 3 1.350–2.065 ug/dl (*n* = 191)	Quartile 4 >2.065 ug/dl (*n* = 192)	Total (*n* = 768)
Age, years	68.3 (5.8)	69.6 (6.7)	70.7 (6.4)	69.6 (7.0)	69.6 (6.6)
Sex, n (%)					
Men	79 (40.3%)	85 (45.0%)	88 (46.1%)	112 (58.3%)	364 (47.4%)
Women	117 (59.7%)	104 (55%)	103 (53.9%)	80 (41.7%)	404 (52.6%)
Race/ethnicity, n (%)					
Mexican Americans	31 (15.8%)	22 (11.6%)	22 (11.5%)	12 (6.3%)	87 (11.3%)
Other Hispanics	22 (11.2%)	8 (4.2%)	16 (8.4%)	17 (8.9%)	63 (8.2%)
Non-Hispanic Whites	99 (50.5%)	104 (55.0%)	101 (52.9%)	95 (49.5%)	399 (52.0%)
Non-Hispanic Blacks	23 (11.7%)	33 (17.5%)	38 (19.9%)	50 (26.0%)	144 (18.8%)
Other	21 (10.7%)	22 (11.6%)	14 (7.3%)	18 (9.4%)	75 (9.8%)
Education, n (%)					
Below high school	58 (29.6%)	35 (18.5%)	39 (20.4%)	45 (23.4%)	177 (23.0%)
High school graduate	48 (24.5%)	52 (27.55)	37 (19.4%)	56 (29.2%)	193 (25.1%)
Some colleges or above	90 (45.9%)	102 (54.0%)	115 (60.2%)	91 (47.4%)	398 (51.8%)
Body mass index, n (%)					
<18.5 kg/m^2	3 (1.5%)	3 (1.6%)	4 (2.1%)	4 (2.1%)	14 (1.8%)
18.5–24.9 kg/m^2	38 (19.55)	42 (22.3%)	51 (27.1%)	63 (33.3%)	194 (25.5%)
25.0–29.9 kg/m^2	63 (32.3%)	76 (40.4%)	64 (34.0%)	69 (36.5%)	272 (35.8%)
≥30 kg/m^2	91 (46.7%)	67 (35.6%)	69 (36.7%)	53 (28.0%)	280 (36.8%)
Plasma lead levels, μg/dL	0.74 (0.16)	1.15 (0.11)	1.66 (0.21)	3.49 (2.37)	1.76 (1.59)
Depressive symptoms	5.6 (5.3)	5.5 (5.2)	5.2 (4.9)	5.5 (4.7)	5.5 (5.0)
Alcohol use, number of drinks/day	1.7 (1.0)	1.7 (1.7)	10.8 (94.2)	2.1 (1.8)	4.1 (47.4)
CERAD W-L immediate recall	19.8 (4.7)	19.8 (4.5)	19.8 (4.6)	19.1 (4.8)	19.6 (4.6)
CERAD W-L delayed recall	6.5 (2.3)	6.6 (2.3)	6.7 (2.2)	6.2 (2.3)	6.2 (2.4)
Animal fluency test	16.9 (5.1)	18.1 (5.8)	17.7 (5.8)	16.3 (4.8)	16.6 (5.3)
Digit symbol substitution test	51.0 (18.5)	52.1 (16.2)	49.8 (17.7)	44.4 (16.1)	45.8 (17.2)

[a]Data were presented as the average (standard deviation) for continuous variables and n (%) for categorical variables.

CI −0.09, 0.20), respectively. The CERAD W-L immediate recall, CERAD W-L delayed recall, the AFT, and the DSST average z-scores were −0.10 (95% CI −0.25, 0.05), −0.10 (95% CI −0.25, 0.05), −0.08 (95% CI −0.22, 0.06), and −0.18 (95% CI −0.32, −0.05), respectively, among participants in the 4th quartile. The global cognition average z–score from the lowest to the highest quartiles was 0.09 (95% CI −0.36, 0.53), 0.17 (95% CI −0.30, 0.63), 0.25 (95% CI −0.19, 0.70), and −0.46 (95% CI −0.90, −0.01), respectively.

Multiple linear regression with a reference group being those in the 1st quantile of plasma lead level showed that concurrent plasma cotinine level is not associated with test-specific (CERAD-WL, AFT, and DSST) or global cognitive z-scores (all the 95% CIs included 0) (Table 3).

Discussion

This study's findings suggest that concurrent lead levels are not associated with cognitive function in older adults. However, it is possible that lead exposures during early life or over a long duration may have a greater impact on the etiology of accelerated cognitive deterioration in later years. The findings of this study contribute to the literature and add evidence to the controversial question of whether concurrent plasma lead levels are associated with cognitive function in older adults.

A growing body of evidence shows that lead is associated with worse cognitive function in older adults (Shih et al., 2006). However, it is unclear whether cumulative exposure to lead as measured by tibia lead level or recent exposure to lead as measured

TABLE 2 Cognitive z-scores and 95% confidence intervals by the plasma lead level quartile.

	Quartile 1 ≤0.960 ug/dl ($n = 196$)	Quartile 2 0.960–1.350 ug/dl ($n = 189$)	Quartile 3 1.350–2.065 ug/dl ($n = 191$)	Quartile 4 >2.065 ug/dl ($n = 192$)
CERAD W-L immediate recall	0.03 (−0.11, 0.17)	0.03 (−0.11, 0.17)	0.04 (−0.10, 0.18)	−0.10 (−0.25, 0.05)
CERAD W-L delayed recall	0.03 (−0.11, 0.17)	−0.01 (−0.15, 0.13)	0.10 (−0.04, 0.23)	−0.10 (−0.25, 0.05)
Animal fluency test	−0.01 (−0.15, 0.12)	0.05 (−0.11, 0.20)	0.06 (−0.08, 0.21)	−0.08 (−0.22, 0.06)
Digit symbol substitution test	0.04 (−0.10, 0.19)	0.10 (−0.04, 0.24)	0.05 (−0.09, 0.20)	−0.18 (−0.32, −0.05)
Global cognition	0.09 (−0.36, 0.53)	0.17 (−0.30, 0.63)	0.25 (−0.19, 0.70)	−0.46 (−0.90, −0.01)

TABLE 3 The independent associations of plasma lead level quartile (reference: ≤0.960 ug/dl) with cognitive specific test and global cognition z-scores.[a]

	Quartile 1 ≤0.960 ug/dl ($n = 196$)	Quartile 2 0.960–1.350ug/dl ($n = 189$)	Quartile 3 1.350–2.065ug/dl ($n = 191$)	Quartile 4 >2.065 ug/dl ($n = 192$)
CERAD W-L immediate recall	Reference	−0.037 (−0.298, 0.223)	0.054 (−0.206, 0.314)	−0.105 (0.361, 0.150)
CERAD W-L delayed recall	Reference	0.037 (−0.218, 0.292)	0.215 (−0.0390, 0.469)	−0.001 (−0.251, 0.249)
Animal fluency test	Reference	0.128 (−0.131, 0.387)	0.205 (−0.053, 0.463)	0.000 (−0.254, 0.254)
Digit symbol substitution test	Reference	−0.100 (−0.320, 0.120)	−0.003 (−0.221, 0.216)	−0.228 (−0.444, −0.013)
Global cognition	Reference	0.015 (−0.724, 0.755)	0.472 (−0.263, 1.206)	−0.334 (−1.058, 0.389)

[a]The models were adjusted for sex, race/ethnicity, education, alcohol use, and BMI.

by plasma lead level or both are associated with cognitive function in older adults. The finding of this study is consistent with two prior studies on plasma lead levels in which the researchers did not detect a significant association between plasma lead levels and cognitive function in older adults (Shih et al., 2006; van Wijngaarden et al., 2011). In a systematic review of 21 studies contrasting and evaluating the relationships between recent (in the plasma) and cumulative (in the bone) lead exposures and neurobehavioral outcomes (Shih et al., 2007), researchers found that associations with biomarkers of cumulative dosage were higher and more consistent than those with plasma lead levels. In another meta-analysis including 22 studies, researchers found that neurobehavioral deficits existed at the current plasma lead concentration of 40 lg/100 ml (Meyer-Baron and Seeber, 2000). To summarize, findings regarding the relationship between plasma lead levels and adult neurobehavioral outcomes are controversial.

Lead is a known neurotoxin that accumulates and persists longer in the brain tissue than in other body parts. The half-life of lead in the plasma is approximately 35 days, but it lasts ∼2 years in the brain tissues (Heidari et al., 2021). Lead interferes with several neurochemical pathways, such as the plasma-brain barrier capillary integrity, synaptogenesis, the formation of myelin, and catecholamine metabolism in the central nervous system (Solon et al., 2008). The biologically plausible mechanisms for the association between plasma lead and cognitive function found in other studies are complicated. First, as a redox-inactive metal, lead induces oxidative stress through depleting thiols and impairing antioxidant defense systems (Ercal et al., 2001). Excessive oxidative stress leads to endoplasmic reticulum stress, mitochondrial damage, and neuronal apoptosis (Sanders et al., 2009). Second, lead disrupts the body's homeostatic levels of essential metals and alters normal metal signaling (Zhu et al., 2013). Lead exposure results in calcium hyperactivation, which causes neurons to experience excitotoxic damage (Sanders et al., 2009). It may disrupt zinc-dependent transcription factors and modify the regulation of gene transcription (Zawia et al., 2000). Third, exposure to lead results in epigenetic modifications in the brain regions and alterations of the epigenetic regulator (Bakulski et al., 2020). Finally, lead inhibits crucial enzymes involved in the heme synthesis process (Piomelli, 2002). Anemia caused by cerebral hypoxia is also believed to greatly impair cognition (Petranovic et al., 2008). Besides, several other mechanisms have also been proposed, such as affecting neurotransmitter storage and releasing and damaging the mitochondria (van Wijngaarden et al., 2011).

The study has several advantages. First, the study population consists of a nationally representative sample of older adults and thus has good generalizability. Moreover, to minimize residual confounding, we adjusted a comprehensive list of sociodemographic, lifestyle, mental health, and physical health covariates. In addition, older adults are vulnerable to cognitive impairment; thus, this study focused on a vulnerable group of older people. The limitation of this study is mainly the cross-sectional design. As a result, we could not establish causality or assess changes in plasma lead levels and cognitive function over time.

Moreover, even though plasma lead levels have a relatively long half-life, they still only measure a person's recent exposure to lead and do not reflect his/her long-term exposure to lead. In addition, we may not have assessed all cognitive domains with three cognitive tests. Finally, the NHANES survey may not fully represent some sub-populations, such as rural populations, homeless people, and non-English speaking individuals. Future studies are expected to use longitudinal studies to examine the temporal relationship between plasma and bone lead levels and full cognitive domains in older adults, especially those from non-western countries. Such

studies would shed light on whether long-term lead accumulation in the body is associated with worse cognitive function among older adults.

To conclude, in this study, we did not find an association between concurrent plasma lead levels and cognitive function in a nationally representative sample of older adults. Our finding indicates that lead exposures in early life or over a long duration may have more of an impact on the etiology of accelerated cognitive deterioration in older adults.

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 human participants were reviewed and approved by the National Center for Health Statistics Research Ethics Review Board approved the NHANES. The patients/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

YD, ML, XL, ZF, and DS designed this study, drafted the initial manuscript, and searched for literature. JZ conducted the statistical analysis. All authors critically revised the manuscript and approved the final version of the manuscript.

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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frontiers | Frontiers in Neuroscience

TYPE Original Research
PUBLISHED 03 May 2023
DOI 10.3389/fnins.2023.1200763

OPEN ACCESS

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RECEIVED 05 April 2023
ACCEPTED 13 April 2023
PUBLISHED 03 May 2023

CITATION
Wang S, Lin X, Zhou J, Li M and Song D (2023) Association between serum cystatin C level and cognition in older adults: a cross-sectional analysis.
Front. Neurosci. 17:1200763.
doi: 10.3389/fnins.2023.1200763

Association between serum cystatin C level and cognition in older adults: a cross-sectional analysis

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Introduction: Serum Cystatin C level, an indication of kidney function, has been implicated in the pathogenesis of Alzheimer's disease and cognitive impairment. In this cross-sectional study, we looked into the relation between serum Cystatin C levels and cognition in a group of U.S. older adults.

Method: The data of this study were from the National Health and Nutrition Examination Survey (NHANES) 1999–2002. A total of 4,832 older adults aged ≥60 who met the inclusion criteria were included. The Dade Behring N Latex Cystatin C assay, which is a particle-enhanced nephelometric assay (PENIA), was utilized to assess Cystatin C levels in participants' blood samples. Participants' cognition was examined using the digit symbol substitution test (DSST). *Z*-scores of the DSST were calculated based on sample means and standard deviations (SD). To investigate the relationships between the quartiles of serum Cystatin C level and DSST *z* scores, multiple linear regression models were developed while controlling for age, sex, race/ethnicity, and education.

Results: The average age of the participants was 71.1 (SD 7.8). The participants were about half female (50.5%), non-Hispanic White (61.2%), and (36.1%) who had completed at least some college. They had an average serum Cystatin C level of 1.0mg/dl (SD 0.44). After performing multiple linear regression with a reference group consisting of participants in quartile one of plasma Cystatin C levels, we found that serum Cystatin C levels in quartiles three and four were independently associated with lower DSST *z* scores (β=−0.059, 95% CI −0.200 to −0.074 and β=−0.108, 95% CI −0.319 to −0.184, respectively).

Conclusion: Higher serum Cystatin C level is associated with worse processing speed, sustained attention, and working memory in older adults. Cystatin C level may be a biomarker for cognitive decline in older adults.

KEYWORDS

biomarker, cystatin C, psychomotor test, gerontology, national survey, kidney function

Introduction

The global population is aging dramatically. With the proportion of the older population expanding, promoting the health and independence of older adults is an ongoing challenge to families and society. Being old is associated with a decrease in cognitive health that ultimately impairs living independence and quality of life (Song et al., 2019). A comprehensive understanding of the potential risk factors and biomarkers of cognitive deterioration among older adults is of utmost importance to help to screen high-risk individuals and determine strategies to alleviate these effects on the population and reduce the burden of cognitive impairment on individuals and society.

A group of socio-demographic factors such as older age and lower education and psychosocial factors (such as depressive symptoms and social isolation) have been established as risk factors for cognitive decline in older adults (Song et al., 2018; Warren and Bamiou, 2018; Livingston et al., 2020). Biomarkers of cognitive decline in the older population are not fully studied. Cystatin C has received increasing attention as a potential biomarker for cognitive impairment in the older population because studies found that cystatin C colocalizes with β-amyloid in the brains of individuals with Alzheimer's disease (AD; Levy et al., 2001; Sastre et al., 2004). Cystatin C is a protein that belongs to a group of cysteine proteases inhibitors generated mainly by nucleated cells (Mussap and Plebani, 2004). The serum concentration of cystatin C is independent of gender and age; therefore, it has been widely studied as an endogenous marker of glomerular filtration rate (Filler et al., 2005). In addition to its role as a marker for renal function, cystatin C plays various biological roles, ranging from cell proliferation and growth to modulating potentially pathogenic events, including neurodegenerative disorders (Mathews and Levy, 2016). Cystatin C is linked to the risk of cognitive impairment through genetic and neuropathological pathways. Genetically, the CST3 B haplotype of cystatin C was considered to be a risk factor for AD, frontotemporal dementia, and Lewy body dementia (Finckh et al., 2000; Benussi et al., 2010; Maetzler et al., 2010). In addition, cystatin C colocalizes with β-amyloid in the brain, especially in areas involved in AD pathology (Sastre et al., 2004).

The association between Cystatin C levels and cognitive impairment among general older adults has revealed different results in previous studies (Sundelöf et al., 2008; Wang et al., 2017; Zhang et al., 2019; Chen et al., 2021). A recent review conducted a subgroup analysis based on ethnicity and revealed that the increased level of Cystatin C was associated with the risk of cognitive impairment in the Asian population but not in the Caucasian population (Nair et al., 2020). Furthermore, the association between cystatin C and cognitive decline has not been fully investigated in community-based older adults.

Therefore, the aim of the present study is to investigate the relationship between cystatin C level and cognitive function in a nationally representative group of older participants in the National Health and Nutrition Examination Survey (NHANES) 2000–2002. The findings of this study will help elucidate the effect of cystatin C on cognitive function among older adults, which has significant benefits in diagnostic as well as therapeutic implications for cognitive impairment among older adults.

Methods

The parent study design

The NHANES program is a biannual series of continuous cross-sectional surveys designed to assess the health and nutrition of people in the USA. It is administered by the National Center for Health Statistics, which is part of the Centers for Disease Control and Prevention. The program has evolved to encompass a wide range of health and nutrition measurements. To ensure that the data collected is representative of the civilian, noninstitutionalized population, the NHANES employs a complex, multistage probability design instead of a simple random sampling method (Johnson et al., 2013). A team of qualified doctors, technicians, and interviewers performed a range of measurements to evaluate the demographic, socioeconomic, nutrition, and health-related status of the participants. In-person interviews and physical examinations were conducted at participants' residences and mobile exam centers, respectively, with specialized settings. The inclusion criteria for this study were being at least 60 years old and having information available on both serum Cystatin C level and cognition. Data from the NHANES 1999–2000 ($n = 25,232$) and 2001–2002 cycles ($n = 24,896$) were combined. We excluded those under 60 years old ($n = 44,737$), those without available information on serum Cystatin C level ($n = 559$), and those without cognitive performance data ($n = 0$). The final sample for this study consisted of 4,832 older adults aged 60 years and above.

Ethical considerations

The NHANES study was granted approval by the Research Ethics Review Board of the National Center for Health Statistics. Informed written consent was obtained from all participants prior to their enrollment in the study.

Measures

Independent variable: quartile of serum cystatin C level [quartile one (reference group), quartile two, quartile three, and quartile four]

The Dade Behring N Latex Cystatin C assay is a particle-enhanced nephelometric assay (PENIA). It was utilized to assess Cystatin C levels in blood samples. This assay was performed on the Dade Behring Nephelometer II (BNII; Finney et al., 1997). According to Newman's (2002) assessment of various assay methodologies, the current assay is the most accurate and precise among automated assays across the clinical concentration range, with an intra-assay imprecision range between 2.0 and 3.0% coefficient of variation. The inter-assay imprecision range is between 3.2 and 4.4% coefficient of variation. Additionally, the assay range is between 0.23 and 7.25 mg/dl. Newman also found that this assay had superior sensitivity and lacked analytical interference compared to other automated assays. The participants' serum Cystatin C level was categorized into four groups (quartile one, quartile two, quartile three, and quartile four).

Dependent variable: cognitive function

In NHANES 1999–2002, with the Digit Symbol Substitution Test (DDST), participants' processing speed, sustained attention, and

TABLE 1 The participants' characteristics, total and by serum Cystatin C level quartile.[a]

Variables	Quartile 1≤0.786mg/dl (*n*=1,214)	Quartile 2 0.786–0.903mg/dl (*n*=1,204)	Quartile 3 0.903–1.07mg/dl (*n*=1,220)	Quartile 4>1.07mg/dl (*n*=1,194)	Total (*n*=4,832)
Age, years	67.1 (6.1)	69.2 (6.8)	72.1 (7.5)	76.3 (7.4)	71.1 (7.8)
Sex, *n* (%)					
Male	534 (44.0%)	574 (47.7%)	650 (53.3%)	634 (53.1%)	2,392 (49.5%)
Female	680 (56.0%)	630 (52.3%)	570 (46.7%)	560 (46.9%)	2,440 (50.5%)
Race/ethnicity, *n* (%)					
Hispanics and others	446 (36.7%)	346 (28.7%)	248 (20.3%)	182 (15.2%)	1,222 (25.3%)
Non-Hispanic Whites	544 (44.8%)	714 (59.3%)	800 (65.6%)	900 (75.4%)	2,958 (61.2%)
Non-Hispanic Blacks	224 (18.5%)	144 (12.0%)	172 (14.1%)	112 (9.4%)	652 (13.5%)
Education, *n* (%)					
Below high school	490 (40.4%)	456 (38.0%)	470 (38.6%)	494 (41.4%)	1,910 (39.6%)
High school graduate	270 (22.3%)	300 (25.0%)	296 (24.3%)	308 (25.8%)	1,174 (24.3%)
College graduate or above	452 (37.3%)	444 (37.0%)	452 (37.1%)	392 (32.8%)	1,740 (36.1%)
Serum Cystatin C level, mg/dl	0.7 (0.07)	0.8 (0.03)	1.0 (0.05)	1.4 (0.70)	1.0 (0.44)
Digit symbol substitution test	44.9 (19.4)	45.3 (18.1)	40.9 (18.6)	36.3 (16.7)	41.9 (18.6)

[a]The data for continuous variables were presented as mean (standard deviation), while categorical variables were presented as *n* (%).

working memory were examined (Ryan and Schnakenberg-Ott, 2003). Two experienced interviewers in a mobile physical examination center conducted all of the questionnaires on the same day. The surveys gave participants the option of taking them in their favorite language. The DSST is a cognitive test that uses paper and pencil and is given on a single sheet of paper. Participants must match symbols with numbers using a key at the top of the page (Jaeger, 2018). The DSST required participants to draw symbols in one hundred thirty-three numbered boxes based on a provided key. The score for the test was calculated based on the number of correct matches, which could range from 0 to 133. This test has been utilized widely in public health research studies (Plassman et al., 2007; Proust-Lima et al., 2007; Rosano et al., 2016).

Covariates

In order to reduce the possible confounding impact of serum Cystatin C levels on cognition, we accounted for several variables, including age (in years), gender (male or female), race/ethnicity (Mexican Americans, other Hispanics, non-Hispanic White, or non-Hispanic Black), and education (below high school, high school graduate, or some college or above).

Statistical analysis

Descriptive statistics were used to summarize the data. Means and standard deviations (SD) were used for continuous data, while frequency and percentages were used for categorical data. To investigate the independent association between serum Cystatin C level quartile and cognition, we developed a multivariate linear regression model while controlling for the previously mentioned confounding variables. The independent variable was Cystatin C quartile (with quartile one as the reference) and the dependent variable was the DSST *z* scores. Before constructing the regression model, we evaluated multicollinearity among the covariates, with no multicollinearity being observed (variance inflation factor < 10). We set statistical significance at a 95% confidence interval (CI) that excluded zero. All analyses were performed using SPSS 25.0.

Results

Table 1 showed the sociodemographic and health characteristics of the participants. Of the 4,832 participants (average age 71.1, standard deviation [SD] 7.8). Roughly half were female (50.5%), non-Hispanic White (61.2%), and completed some college or above (36.1%). Their mean plasma Cystatin C level was 1.0 μg/dl (SD 0.44). Their mean DSST score was 41.9 (SD 18.6).

Table 2 showed the averages and 95% CIs of the cognitive test-specific *z* scores stratified by plasma Cystatin C level quartiles. For participants in quartile one of plasma Cystatin C level, their average DSST *z* score was 0.16 (95% CI 0.10, 0.22). For participants in quartile two, their average DSST *z* score was 0.18 (95% CI −0.12, 0.23). For participants in quartile three, their average DSST *z* score was −0.05 (95% CI −0.11, 0.004). The average DSST *z* score was −0.30 (95% CI −0.30, −0.25) among participants in quartile four.

After performing multiple linear regression with a reference group consisting of participants in quartile one of plasma Cystatin C levels, we found that serum Cystatin C levels in quartiles three and quartile four were independently associated with lower DSST *z* scores (β = −0.059, 95% CI −0.200 to −0.074 and β = −0.108, 95% CI −0.319 to −0.184, respectively), as demonstrated in Table 3.

Discussions

Our finding is that higher serum Cystatin C level is associated with worse processing speed, sustained attention, and working memory in older adults as measured by DSST *z* scores. The findings of this study indicate that Cystatin C level may be a biomarker for cognitive decline in older adults.

Cystatin C is a protein commonly utilized as a biomarker for assessing kidney function and Alzheimer's disease (Shlipak et al., 2013). Upon its synthesis by nucleated cells, Cystatin C is secreted into the bloodstream and participates in various neurological pathways, such as suppressing the production of cysteine protease, reducing Amyloid-beta accumulation, and regulating the generation of neural

TABLE 2 The DSST *z*-scores and their corresponding 95% confidence intervals were stratified by quartiles of serum Cystatin C levels.

	Quartile 1≤0.786mg/dl (*n*=1,214)	Quartile 2 0.786–0.903mg/dl (*n*=1,204)	Quartile 3 0.903–1.07mg/dl (*n*=1,220)	Quartile 4>1.07mg/dl (*n*=1,194)
Digit symbol substitution test	0.16 (0.10,0.22)	0.18 (0.12,0.23)	−0.05 (−0.11,0.004)	−0.30 (−0.35,-0.25)

TABLE 3 Independent associations between quartiles of serum Cystatin C levels (reference: ≤0.786mg/dl) and DSST *z*-scores.[a]

	Quartile 1≤0.786mg/dl (*n*=1,214)	Quartile 2 0.786–0.903mg/dl (*n*=1,204)	Quartile 3 0.903–1.07mg/dl (*n*=1,220)	Quartile 4>1.07mg/dl (*n*=1,194)
Digit symbol substitution test	Reference	0.005(−0.056, 0.066)	**−0.059 (−0.200, −0.074)**	**−0.108 (−0.319, −0.184)**

Bolded values mean statistical significance (95% confidence interval excluding zero). [a]Age, sex, race/ethnicity, and education were adjusted in the model.

cells (Mathews and Levy, 2016). Recent research has explored the relationship between Cystatin C levels and cognitive health, with some studies indicating that elevated levels of Cystatin C in the cerebrospinal fluid (CSF) may be linked to a higher likelihood of cognitive decline and dementia in older adults (Yaffe et al., 2014). Additionally, there have been reports suggesting an association between the levels of Cystatin C in the blood and the risk of developing dementia, as well as cognitive impairment (Sarnak et al., 2008; Maetzler et al., 2010).

The precise mechanism underlying the association between Cystatin C levels and cognitive function remains under investigation. Several hypotheses have been proposed in studies exploring the potential pathogenic role of Cystatin C levels in cognitive diseases. One proposed hypothesis posits that amyloid plaques, which are a hallmark of Alzheimer's disease, are primarily composed of the protein amyloid beta. In this context, Cystatin C belongs to a type of cysteine proteinase inhibitor, which functions by binding to enzymes and reducing their ability to degrade amyloid beta protein (Murphy and LeVine, 2010; Mathews and Levy, 2016). By inhibiting the degradation of Amyloid-beta, Cystatin C can potentially prevent the accumulation of toxic Amyloid-beta aggregates in the brain, which may contribute to the preservation of cognitive function (Mi et al., 2007). Another hypothesis is the anti-inflammatory properties of Cystatin C, which have demonstrated the ability to regulate immune response and mitigate oxidative stress, thus aiding in the prevention of cognitive decline (Xu et al., 2015). Cystatin C also has the potential to affect cognitive function by modulating synaptic plasticity involved in the formation of memory (Sun et al., 2008).

This study has several strengths. Firstly, the study population is a nationally representative sample of older adults, enhancing the generalizability of the findings. Secondly, this study focuses on a vulnerable group of people, older adults who are at high risk of cognitive impairment. However, the major weakness of this study is its cross-sectional design. Therefore, we cannot establish causality or determine changes in plasma Cystatin C level and cognition over time. Third, certain confounders, such as depressive symptoms, may exist in this study. However, depressive symptoms were not measured in NHANES 1999–2002. Thus, we could not adjust depressive symptoms in the analysis. Moreover, plasma Cystatin C level with a half-life of about 1.5 h (Sjöström et al., 2004) only reflects recent levels and may not accurately reflect long-term kidney function. Furthermore, we only assessed one cognitive domain, which may limit the scope of the findings. Since the data were collected between 1999 and 2002, they might be outdated and did not reflect older adults' current Cystatin C level and cognition. Finally, the NHANES survey may not be fully representative of certain sub-populations, such as rural populations, homeless individuals, and non-English speakers. Future studies should consider using longitudinal designs to investigate the relationship between plasma cystatin level and cognitive function across all domains in older adults, particularly those in non-western countries.

To conclude, in this study, we found a negative association between serum Cystatin C level and cognitive function in a large sample of older adults. Our finding indicates that Cystatin C level may serve as a biomarker for cognitive decline in older adults.

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 human participants were reviewed and approved by the NHANES has been approved by the National Center for Health Statistics Research Ethics Review Board. The patients/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

SW, ML, and DS designed this study, drafted the initial manuscript, and searched for literature. XL and JZ conducted the statistical analysis. All authors contributed to the article and approved the submitted version.

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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frontiers | Frontiers in Aging Neuroscience

TYPE Original Research
PUBLISHED 24 May 2023
DOI 10.3389/fnagi.2023.1203920

OPEN ACCESS

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RECEIVED 11 April 2023
ACCEPTED 02 May 2023
PUBLISHED 24 May 2023

CITATION
Yang M, Liu Y, Hu X, Ren D, Yang Q, Mao J and Chen J (2023) Association of Life's Simple 7 with mild cognitive impairment in community-dwelling older adults in China: a cross-sectional study.
Front. Aging Neurosci. 15:1203920.
doi: 10.3389/fnagi.2023.1203920

Association of Life's Simple 7 with mild cognitive impairment in community-dwelling older adults in China: a cross-sectional study

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Background: Life's Simple 7 (LS7), a metric composed of seven intervenable cardiovascular risk factors, is initiated by the American Heart Association to improve cardiovascular health. The components of LS7 have been reported as risk factors for dementia. However, few studies investigated the association between LS7 metric and mild cognitive impairment (MCI).

Methods: The study was carried out in a primary care facility between 8 June and 10 July 2022. A total of 297 community-dwelling residents aged 65 years or older were recruited. Sociodemographic, comorbidity, and lifestyle characteristics were collected through the questionnaires, and biological parameters were obtained from blood sample examinations. Logistic regression was used to analyze the association between LS7 scores (overall, behavioral, and biological) and individual components with MCI, adjusting sex, age, education, and cardiovascular disease (CVD).

Results: In comparison with the cognitively intact group ($n = 195$), the MCI group ($n = 102$) had a lower education level and a higher proportion of hypertension. Multivariate logistic regression analysis, adjusting sex, age, education, and CVD demonstrated a significant association between MCI and overall LS7 score [odd ratio = 0.805, 95% confidence interval (0.690, 0.939)] and biological score [odd ratio = 0.762, 95% confidence interval (0.602, 0.965)].

Conclusion: Life's Simple 7 was associated with MCI in community-dwelling older adults, indicating that LS7 could be used as guidance in the prevention of dementia in the community.

KEYWORDS

Life's Simple 7, cardiovascular health, mild cognitive impairment, dementia, cardiovascular disease, risk factors

Introduction

With global aging, dementia cases are projected to reach 78 million by 2030, costing US$2.8 trillion annually (Zhang et al., 2021). Although the pathogenesis of dementia remains unclear, it is widely recognized as a multifactorial disease with various risk factors, including obesity, smoking, physical inactivity, poor diet, depression, hypertension, diabetes, hyperlipidemia, and coronary heart disease (Deckers et al., 2015). Some of these risk factors

may be interrelated and unchangeable, and current evidence on the combined effect of multiple risk factors is limited, primarily focusing on individual risk factors (Cooper et al., 2015; Xu et al., 2015) or lifestyle factors (Flicker, 2010; Gelber et al., 2012; Sabia et al., 2017; Samieri et al., 2018). Therefore, identifying and addressing the key modifiable risk factors are essential for effective dementia management.

The Lancet Commission and the World Dementia Council recommended targeting cardiovascular risk factors in their guidelines for preventing dementia (Winblad et al., 2016; Livingston et al., 2020). Life's Simple 7 (LS7) metric was first proposed by the American Heart Association (AHA) to define and monitor the prevalence of ideal cardiovascular health (CVH) and reduce the morbidity and mortality from cardiovascular disease (CVD) in the US population. LS7 metric focuses on modifiable cardiovascular risk factors, including four behavioral factors [smoking, diet, physical activity, and body mass index (BMI)] and three biological factors (untreated blood pressure, total cholesterol, and fasting plasma glucose), and the status of these factors are classified into levels of poor, intermediate, and ideal (Lloyd-Jones et al., 2010). In a dose-response meta-analysis by Aneni et al., each increase in the number of ideal CVH components was associated with a pooled hazard ratio for CVD mortality of 0.81 [95% confidence interval (CI), 0.75–0.87; Aneni et al., 2017]. In a meta-analysis by Fang et al., achieving the greatest number of ideal CVH components was associated with a lower risk of CVD (risk ratio = 0.20; 95% CI, 0.11–0.37) and cardiovascular mortality (risk ratio = 0.25; 95% CI, 0.10–0.63; Fang et al., 2016), suggesting LS7 a useful tool for cardiovascular risk assessment. There was a potential mechanism that cardiovascular risk factors were believed to have deleterious effects on the structure and function of cerebral blood vessels, leading to a decrease in cerebral perfusion and promoting disturbances in amyloid clearance, resulting in neurovascular dysfunction and sub-optimal brain health (Gorelick et al., 2017). Moreover, cardiovascular risk factors in LS7 emerge in the aforementioned risk factors for dementia, implicating that LS7 may be put forward as a potential tool for the prevention of dementia.

In 2017, LS7 was identified as the practical criteria for defining brain health, which encompasses cognitive processes such as learning, judgment, communication, and memory (Gorelick et al., 2017). Recently, a statement based on LS7 was issued by AHA, providing an up-to-date summary for primary care physicians to evaluate cardiovascular risk factors, preserve brain health, and prevent cognitive impairment (Lazar et al., 2021). In the previous studies related to dementia, Janice L. Atkins et al. demonstrated that individuals with optimal LS7 profiles had a 33% reduction in risk of incident hospital-diagnosed dementia using population-representative medical records of the UK, where incident CVD events occurred (Atkins et al., 2019). As for preventing cardiovascular morbidity, Langa et al. reported a significant decline in the prevalence of dementia among the US population aged 65 years or older (8.8% in 2012 vs. 11.6% in 2000) in the presence of self-reported heart disease (Langa et al., 2017). As mentioned above, the relationship between CVH and dementia is necessarily linked to the development of CVD. Although most cases of cognitive decline have similar pathogenesis being mixed with contributions by neurodegenerative disease, comorbidities, and CVD (Schneider et al., 2007; Langa and Levine, 2014; Arvanitakis et al., 2019), whether CVH can directly influence cognitive status in the absence of CVD is unclear.

Mild cognitive impairment (MCI) is a clinical diagnosis of a syndrome on the continuum of cognitive decline between normal cognition and dementia (Petersen, 2011; Langa and Levine, 2014). In the symptomatic predementia stage, a consensus has been established that primary intervention in this population can thwart or delay the progression of cognitive deterioration to dementia and decrease the incidence or prevalence of dementia (Jia et al., 2020). However, few studies using LS7 identified the association between the LS7 metric and MCI. Meanwhile, fewer studies have been conducted in Asian countries such as China (Gildner et al., 2018), where the prevalence and growth rate of dementia are the highest, accounting for nearly 25% of all dementia cases worldwide (GBD 2016 Neurology Collaborators, 2019; Zhou et al., 2019). This study aims to investigate whether the LS7 metric, as the combination of changeable risk factors, is associated with the incidence of MCI without CVD in community elderlies in China, providing further evidence for the assessment and management of cognitive risk.

Methods

Study design

The study is a cross-sectional, population-based survey carried out in the primary care setting from 8 June to 10 July 2022.

Study participants

In this study, the community where 2,618 adults live has seven subdivisions. A total of 318 participants in Wuhan, Hubei, China were recruited through convenience sampling.

Inclusion criteria

Participants were included if they (1) were aged 65 years or older; (2) accomplished the health check-ups; and (3) signed informed consent.

Exclusion criteria

Participants were excluded if they (1) had an acute illness or undergone surgery in recent 3 months; (2) were unable to cooperate in completing psychological tests due to visual impairment, hearing impairment, or other impairment; (3) were taking medications that might affect cognition or taking anti-psychotic medications (e.g., antidepressants for severe depression); and (4) had a self-reported or recorded diagnosis of neurological disorders (e.g., parkinsonism or incident dementia; see Figure 1).

Data collection

Sociodemographic characteristics including sex, age, education level, and marital status were collected through the questionnaire.

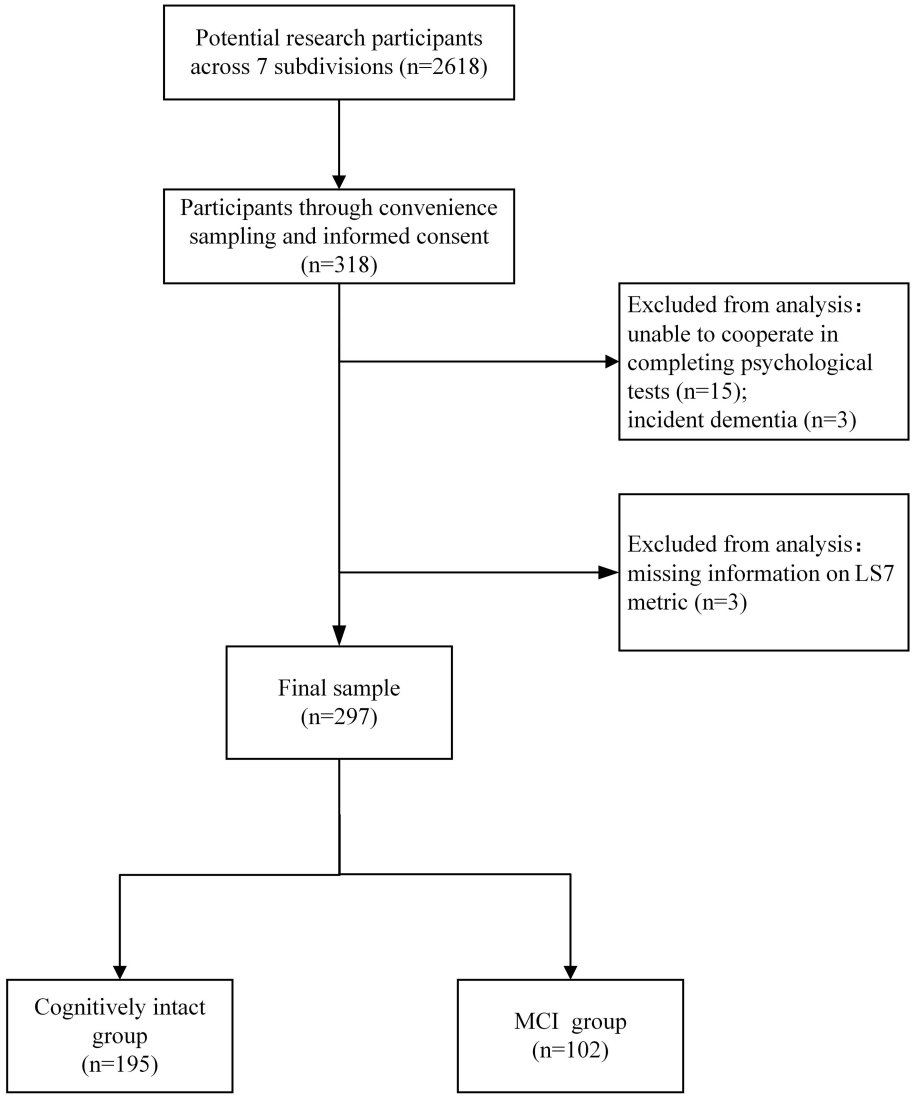

FIGURE 1
Flow chart of participants.

Former alcohol drinkers were defined as participants who quit drinking within <12 months, while those who never drank or quit drinking for more than 12 months were considered non-alcohol drinkers. Similarly, former smokers were defined as participants who quit smoking within <12 months, and those who never smoked or quit smoking for more than 12 months were considered non-smokers. Information on hypertension, diabetes, hyperlipidemia, and CVD was self-reported by participants through the questionnaire and then can be determined by the research team in their medical records. LS7 metric was calculated using de-identified data for all the participants.

Diagnostic criteria

Mild cognitive impairment scored 0.5 on the global Clinical Dementia Rating scale and was diagnosed according to the following criteria by a physician: (1) the presence of spontaneous cognitive complaints; (2) suggested objective impairment in cognitive domains of memory, executive function, attention, and language by cognitive tests such as Montreal Cognitive Assessment; (3) preserved activities of daily living on the disability scale confirmed by clinician's interviews; and (4) no dementia according to the Diagnostic and Statistical Manual of Mental Disorders (Petersen, 2011). The Chinese version of the Montreal Cognitive Assessment scale (version 7.1) was used in this study. To correct for literacy, participants with ≤12 years of education were added 1 point to their overall scores. The MCI group was scored with <26 points.

Dementia was determined by scoring more than 0.5 on the global Clinical Dementia Rating scale and meeting the Diagnostic and Statistical Manual of Mental Disorders (fifth edition), which required those as follows: (1) memory impairment and impairment in at least one of the other domains such as aphasia, apraxia,

agnosia, or executive functioning; (2) impairment and decline in social or occupational function; and (3) cognitive deficits that do not occur exclusively during the course of a delirium episode.

Participants without MCI and dementia were classified as cognitively intact.

Measurements of LS7 metric

Blood pressure was defined as the average of two consecutive blood pressure readings in the right arm in the seating position. Total cholesterol and fasting plasma glucose were determined using a peripheral blood sample after a minimum of 5 h of fasting. BMI was calculated as weight divided by the square of height (kg/m^2). Diet, smoking status (current, former, and never), and physical activity (time of moderate and vigorous activity per week) were self-reported. According to the AHA definition and criteria (Lloyd-Jones et al., 2010), each individual component in LS7 was given a score of poor (coded as 0), intermediate (coded as 1), or ideal (coded as 2). In addition, the scoring criteria for diet was modified to the intake of fruit, vegetables and fishes since they may be more available to collect in health check-ups (Samieri et al., 2018; see Supplementary Table 1). Behavioral score, defined as the summarization of scores of diet, smoking, physical activity, and BMI ranges from 0 (worst) to 8 (best). The biological score, defined as the summarization of the scores of blood pressure, total cholesterol, and fasting plasma glucose ranges from 0 (worst) to 6 (best). The overall score of LS7, which ranged from 0 to 14, was divided into three categories: poor [< mean − standard deviation (SD)], intermediate (≥ mean − SD and < SD + mean), and optimal (≥ mean + SD; Sabia et al., 2019).

Covariates

Covariates included in the analysis were sex, age, education, and related clinical factors. Education level was categorized as "high" (college degree and above) or "low" (high school degree and below).

Statistical analysis

Participants with missing data were further excluded from data analysis. The Kolmogorov–Smirnov test was used to determine the distribution of continuous variables, demonstrating that age was normally distributed ($P = 0.579$). In univariate analysis, the *t*-test and chi-square test were used for the comparison of continuous variables and categorical variables, respectively. In multivariate analysis, the association of MCI for LS7 metric and individual components was assessed using logistic regression analysis. Interaction analysis was used to evaluate the potential interaction among components by adding a product term. A sensitivity analysis was performed by adjusting for CVD, which was defined as self-reported (verified in medical records) stroke and coronary heart disease and heart failure (Malik et al., 2021; Tin et al., 2022). Meanwhile, collinearity analysis was used to examine the accuracy of the regression model based on LS7. Results of the logistic regression models were reported as odd ratio and 95% CI. All the statistical analyses were performed with SPSS v.26 (IBM, NY, USA).

This study followed the strengthening of the reporting of observational studies in epidemiology (STROBE) guidelines (Vandenbroucke et al., 2007), and the study protocol was approved by the Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology (s906).

Results

Demographic characteristics of participants

A total of 297 participants (70.9 ± 4.8 years) were included in this study, with 195 in the cognitively intact group and 102 in the MCI group. The MCI group had a lower education level ($p < 0.01$) and a higher proportion of hypertension ($p < 0.05$) than the cognitively intact group. There were no other significant differences between the two groups (Table 1).

Association between MCI and LS7

In the categorical analysis, the optimal CVH status was associated with a 66.0% lower risk of MCI in comparison with the poor status, while no statistically significant association was found in the intermediate. When the scores (continuous) were used in the analysis, the risk for MCI was reduced by 19.4% per 1-point increment in the overall LS7 score and was reduced by 23.7% per 1-point increment in the biological score after adjustment for sex, age, and education (Table 2).

Association between MCI and each individual component

All the participants reached the ideal level for diet according to their self-reported dietary status, and there were no former smokers among the participants. In the adjusted logistic regression models, achieving an ideal level of fasting plasma glucose reduced the risk of MCI by 56.2%, but no other components showed a significant association with MCI (Table 3). Interactions between levels of individual components (categorical) were tested, but no significant interactions are found in Supplementary Table 2.

Sensitivity analysis

In the sensitivity analysis (Table 4), adjusting for CVD as another covariate showed that the overall score, biological score, and ideal fasting plasma glucose were significantly associated with MCI (per 1-point increment of overall LS7 score reduced by 19.5% lower risk, biological score with 23.8% risk for MCI, fasting plasma glucose with 56.4% risk of MCI). The beta coefficients for the overall score, behavioral score, and biological score are shown in Supplementary Table 3. The results were similar to the prior logistic regression models, demonstrating the robustness and accuracy of

TABLE 1 Demographic characteristics of participants.

Variables	Cognitively normal group ($n = 195$)	MCI group ($n = 102$)	t/χ^2-value	P
Sex, *n* (%)			2.680	0.102
Female	103 (52.8)	64 (62.7)		
Age, years (mean ± SD)	70.6 (4.6)	71.4 (5.2)	−1.330	0.185
Education level, *n* (%)			19.820	**0.000**
Low (high school degree and below)	138 (70.8)	95 (93.1)		
High (college degree and above)	57 (29.2)	7 (6.9)		
Married, *n* (%)	171 (87.7)	94 (92.2)	1.389	0.239
Alcohol consumption, *n* (%)			0.098	0.952
Current	12 (6.2)	6 (5.9)		
Former	7 (3.6)	3 (2.9)		
Never	176 (90.3)	93 (91.2)		
Smoking, *n* (%)			0.149	0.699
Current	24 (12.3)	11 (10.8)		
Never	171 (87.7)	91 (89.2)		
Hypertension, *n* (%)	83 (42.6)	56 (54.9)	4.094	**0.043**
Diabetes, *n* (%)	27 (13.8)	22 (21.6)	2.899	0.089
Hyperlipidemia, *n* (%)	18 (9.2)	9 (8.8)	0.013	0.908
CVD, *n* (%)	16 (8.2)	9 (8.8)	0.033	0.855

SD, standard deviation; CVD, cardiovascular disease (stroke, coronary heart disease, and heart failure).
Values in bold mean statistically significant ($p < 0.05$).

TABLE 2 Logistic regression modeling the association between MCI and LS7.

	OR	95% CI of OR
LS7, per 1-point increment		
Overall LS7 score	**0.806**	**(0.691, 0.940)**
Behavioral score	0.833	(0.680, 1.021)
Biological score	**0.763**	**(0.603, 0.966)**
LS7, categories		
Poor, 0–9	Reference	
Intermediate, 10–12	0.660	(0.351, 1.242)
Optimal, 13–14	**0.340**	**(0.134, 0.860)**

MCI, mild cognitive impairment; LS7, Life's Simple 7; OR, odd ratio; CI, confidence interval.
Models were adjusted for sex, age, and education.
Values in bold mean statistically significant ($p < 0.05$).

this study. We also found no collinearity between CVD and LS7 metrics with all VIFs < 5 (see Supplementary Table 4).

Discussion

Results from this cross-sectional study demonstrated that the optimal category of LS7 reduced the odds of MCI by 66.0% compared with the poor category. The risk for MCI was reduced by 19.4% per 1-point increment in the overall LS7 score and 23.7% per 1-point increment in the biological score. Among the components of LS7, the ideal level of fasting plasma glucose reduced the risk of MCI by 56.2%.

Since dementia is a multifactorial disease with various risk factors, its disease-modifying medications lack effectiveness. For example, aducanumab is only suitable for early dementia patients, but it is still unable to intervene when the disease progresses to the middle and late stages (Sevigny et al., 2016). Identifying and addressing the key modifiable risk factors are of great importance in the prevention of it. This study demonstrated that a higher LS7 score was associated with a reduced risk of MCI, a preclinical stage of dementia, suggesting that the LS7 metric can provide valuable guidance in the risk management of dementia. In consistence, a cohort study in France found that community dwellers aged at least 65 years with a higher LS7 score were linked to a lower risk of attenuated cognitive decline (Samieri et al., 2018). Retrolongitudinal studies demonstrated that higher LS7 overall and biological scores in midlife (aged 45–65 years) were associated with a lower incidence of cognitive impairment at an older age (Thacker et al., 2014; Gonzalez et al., 2018; Malik et al., 2021).

In the categorical analysis of our study, the optimal category (13–14) of LS7 demonstrated a substantial reduction in the risk of MCI, but no significant change in the risk of MCI was found in the intermediate category (10–12) in community-dwelling old adults. A study in adults aged 65 years or older in Northern Manhattan showed that both intermediate (6–9) and optimal category (10–14) of LS7 were associated with reduced incidence of dementia (Guo et al., 2021). We guess that the difference in the outcome variable

TABLE 3 Logistic regression modeling the association between MCI and each individual component (the final independent variable entered in each model).

Components	Adjusted OR	95% CI of OR
Smoking		
Poor	Reference	
Ideal	1.042	(0.439, 2.472)
Physical activity		
Poor	Reference	
Intermediate	0.994	(0.391, 2.525)
Ideal	0.613	(0.343, 1.096)
Body mass index		
Poor	Reference	
Intermediate	0.448	(0.112, 1.794)
Ideal	0.363	(0.094, 1.406)
Total cholesterol		
Poor	Reference	
Intermediate	1.393	(0.547, 3.545)
Ideal	1.896	(0.784, 4.517)
Blood pressure		
Poor	Reference	
Intermediate	1.127	(0.616, 2.061)
Ideal	0.642	(0.335, 1.231)
Fasting plasma glucose		
Poor	Reference	
Intermediate	0.708	(0.368, 1.363)
Ideal	**0.438**	**(0.206, 0.932)**

OR, odd ratio; CI, confidence interval.
Models were adjusted for sex, age, and education.
Values in bold mean statistically significant ($p < 0.05$).

TABLE 4 Results of sensitivity analysis adding CVD as a covariate.

	Adjusted OR	95% CI of OR
LS7, per1-point increment		
Overall score	**0.805**	**(0.690, 0.939)**
Behavioral score	0.832	(0.679, 1.020)
Biological score	**0.762**	**(0.602, 0.965)**
LS7, categories		
Poor, 0–9	Reference	
Intermediate, 10–12	0.661	(0.351, 1.243)
Optimal, 13–14	**0.340**	**(0.135, 0.861)**
Smoking		
Poor	Reference	
Ideal	1.054	(0.442, 2.510)
Physical activity		
Poor	Reference	
Intermediate	1.014	(0.397, 2.586)
Ideal	0.611	(0.342, 1.093)
Body mass index		
Poor	Reference	
Intermediate	0.438	(0.109, 1.755)
Ideal	0.353	(0.091, 1.372)
Total cholesterol		
Poor	Reference	
Intermediate	1.387	(0.545, 3.528)
Ideal	1.931	(0.802, 4.650)
Blood pressure		
Poor	Reference	
Intermediate	1.075	(0.591, 1.954)
Ideal	0.616	(0.323, 1.175)
Fasting plasma glucose		
Poor	Reference	
Intermediate	0.701	(0.363, 1.353)
Ideal	**0.436**	**(0.205, 0.927)**

LS7, Life's Simple 7; OR, odd ratio; CI, confidence interval.
Models were adjusted for sex, age, education, and cardiovascular disease.
Values in bold mean statistically significant ($p < 0.05$).

(MCI vs. dementia) may account for the discrepancy. In the Framingham Heart Study Offspring cohort, higher recent CVH scores were associated with less cognitive impairment and a lower 10-year risk of incident stroke, but there was no association with incident all-cause dementia or Alzheimer's disease. Higher remote CVH scores were all associated with a lower 10-year risk of incident stroke, dementia, and less cognitive impairment (Pase et al., 2016). Accordingly, our results remain robust when CVD is adjusted. These findings suggested that the LS7 components might contribute to the development of both CVD and cognitive decline simultaneously, and CVD is not a necessary mediating factor in the development of dementia but rather a concurrent outcome.

Although a significant association was observed for the LS7 overall or biological score with a decreased MCI risk, no significant association was found for the behavioral score. Several reasons may be involved. First, all the participants self-reported an ideal-level diet, and no participants were former smokers in our study. Due to a lack of diversity in the social demographic characteristics within the study population, it is difficult to identify the impact of behavioral dimensions. Second, the recall or comprehension bias of self-reported lifestyle may affect the results (Gardener et al., 2016). Third, the effects of behavior may already be present in the biological status. However, further research studies on a larger population are still needed to clarify the underlying reasons.

Fasting plasma glucose, which has been shown to influence the onset and progression of the many underlying pathologies associated with dementia (Biessels et al., 2006), was the only component that showed a significant association with MCI incidence, confirming that diabetes or poor fasting plasma glucose control in older age was a major risk factor accelerating cognitive decline and dementia (Yaffe et al., 2012; Biessels et al., 2014).

Mechanism studies have explained the effect of the plasma glucose level on brain function. Prolonged exposure to hyperglycemia would lead to abnormal cerebral capillaries that impair brain perfusion (Gispen and Biessels, 2000). Insulin, which would elevate insulin resistance, is actively carried across the blood–brain barrier (Banks, 2004) and activated via cerebral insulin receptors (Bondy and Cheng, 2004), affecting the energy homeostasis in the brain and interfering the learning and memory (Zhao and Alkon, 2001). Moreover, alterations of insulin and glucose homeostasis in the brain may influence amyloid metabolism by stimulating its secretion and blocking its breakdown (Craft and Watson, 2004).

It is uncertain why other individual components reported in studies of other populations were not significantly associated with MCI in this sample. In particular, the contentious "obesity paradox" pointed to the protective effects of high adiposity in later life, and high adiposity may also be harmful in the subsequent period, especially in the presence of other co-existing cardiovascular risk factors (Anstey et al., 2011; Qizilbash et al., 2015). Thus, the link between obesity and dementia risk still needs a thorough evaluation. For the unexpected results of individual components, we speculate that it is due to the participant characteristics reducing our capability to detect the impact of these components on cognitive function. For example, a large proportion of participants in our study reported never having smoked (88.2%) in their lifetime, and it was possible that smoking did not accurately capture the risk of MCI, resulting in discrepancy from a cross-sectional study in China (Jia et al., 2020).

Limitations

The cross-sectional design could not induce cause–effect relationship, and the small sample size restricted its capacity to be generalized. Selection bias may exist since the small sample size and older adults with cognitive impairment, especially those with psychological symptoms, may be less likely to participate in the study. A cohort study with a larger sample and longer follow-up is needed to confirm the reliability of the LS7 metric and its causality with MCI.

Implications

As risk factor management for dementia is typically handled by general practitioner providers in most countries, and LS7 consists of common primary care information, it would be a practical strategy to focus on educating and inspiring older adults to adhere to LS7 recommendations in order to maintain their cognitive health.

Conclusion

In conclusion, our study discovered a strong association between a higher LS7 score and optimal CVH status with a substantially attenuated risk of MCI. LS7 was able to reveal valuable information that was not apparent in the individual components, even in a small sample, suggesting that it captures several key risk factors for cognitive decline. LS7 could be an effective and convenient tool for medical staff to monitor and manage geriatric cognitive health in both research and clinical practice. Future research investigating whether interventions targeting LS7 components can prevent or reverse dementia is suggested.

Data availability statement

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

Ethics statement

The study protocol was approved by Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology (s906). The patients/participants provided their written informed consent to participate in this study.

Author contributions

JM and MY contributed to the conception and design of the study. YL, QY, and JC provided clinical knowledge support and constructive suggestions for the study. MY, XH, and JC collected and assessed the data. MY and XH analyzed and interpreted the data. DR provided critical guidance on data analysis. MY and YL drafted the manuscript. All authors contributed to the manuscript revision and approved the submitted version.

Funding

This study was supported by the Humanities and Social Sciences Foundation of the Ministry of Education of China (grant no. 22YJC630126), 2021–2022 Health Research Project of Hubei Provincial Health and Health Commission (grant no. WJ2021M105), and the Fundamental Research Funds for the Central Universities (grant no. YCJJ202201054).

Acknowledgments

The authors would like to acknowledge all of the older adults who participated in the study and the contributions of medical staff in Xinmin Community Health Center, Zhuanyang Street, Wuhan Economic and Technological Development Zone.

Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2023.1203920/full#supplementary-material

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frontiers | Frontiers in Neuroscience

TYPE Review
PUBLISHED 02 June 2023
DOI 10.3389/fnins.2023.1206948

OPEN ACCESS

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RECEIVED 16 April 2023
ACCEPTED 18 May 2023
PUBLISHED 02 June 2023

CITATION
Yang X and Tang Z (2023) The role of pyroptosis in cognitive impairment. *Front. Neurosci.* 17:1206948. doi: 10.3389/fnins.2023.1206948

The role of pyroptosis in cognitive impairment

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Cognitive impairment is a major global disease, manifests as a decline in cognitive functioning and endangers the health of the population worldwide. The incidence of cognitive impairment has increased rapidly with an increasingly aging population. Although the mechanisms of cognitive impairment have partly been elucidated with the development of molecular biological technology, treatment methods are very limited. As a unique form of programmed cell death, pyroptosis is highly pro-inflammatory and is closely associated with the incidence and progression of cognitive impairment. In this review, we discuss the molecular mechanisms of pyroptosis briefly and the research progress on the relationship between pyroptosis and cognitive impairment and its potential therapeutic values, to provide a reference for research in the field of cognitive impairment.

KEYWORDS

pyroptosis, cognitive impaiment, NLRP3 inflammasome, treatment, GSDMD

Introduction

Cognitive impairment is defined as a decline in cognitive functioning and endangers the health of the population especially elder people worldwide. The degree of cognitive impairment ranges from mild subjective cognitive impairment to severe dementia. Mild cognitive impairment (MCI) has a prevalence of approximately 6% in ages 60–64 and increases to approximately 25% in those ages 80–84 (Petersen et al., 2018). Approximately 5%–10% of people with MCI progress to dementia annually (Sanford, 2017). With an increasingly aging population, the incidence of cognitive impairment has increased rapidly. Although the mechanisms of cognitive impairment have partly been elucidated with the development of molecular biological technology, however, the tools and strategies for the treatment of cognitive impairment remained limited. To fully understand the neuropathological changes of cognitive impairment and develop effective therapeutic methods, there is still a long way to go.

The long-recognized modes of cell death are limited to apoptosis and necrosis. Apoptosis is mainly characterized by cell shriveling and the formation of apoptotic bodies, which are then rapidly engulfed by surrounding phagocytes without causing an inflammatory response. Necrosis was previously thought to be an unregulated and passive death process, but with further research, it has now been shown that some of the necrosis can be controlled and is called programmed necrosis (Tonnus et al., 2019), of which pyroptosis is one of the main forms. Recently increasing studies have revealed that pyroptosis played a significant role in cognitive impairment. This review summarized the molecular mechanisms of pyroptosis and focus on the function of pyroptosis involved in the pathogenesis and treatment of cognitive impairment-related diseases.

Molecular mechanisms of pyroptosis

Pyroptosis, a highly pro-inflammatory programmed cell death, was first observed in macrophages after a bacterial infection or treatment with bacterial toxins and was for a long time mistaken for a macrophage-specific cell death dependent on caspase-1, a pro-inflammatory protease cleaving interleukin 1β (IL-1β) (Thornberry et al., 1992). Subsequent studies revealed that intracytoplasmic pattern recognition receptors (PRRs) recognized exogenous pathogen-associated molecular patterns (PAMPs) or endogenous dangerous signaling to form inflammasomes that recruited and activated caspase-1, thus leading to pyroptosis (canonical pyroptosis pathway); murine caspase-11 and human caspase-4/5 could act directly as PRRs to recognize inflammasome assembled by polysaccharide-like lipid A and also result in pyroptosis (non-canonical pyroptosis pathway), which overturned the traditional concept of inflammasome (Fang et al., 2020). Recent studies have found that caspase-1 and caspase-11/4/5 both cleaved the common substrate gasdermin D (GSDMD) and led to pyroptosis (Kayagaki et al., 2015; Shi et al., 2015), gasdermin family proteins were identified as key effector molecules that mediate the onset of pyroptosis (Figure 1).

The canonical pyroptosis pathway was dependent on the activation of caspase-1, which exerted its effects via the inflammasome pathway. Inflammasome was first proposed in 2002 (Martinon et al., 2002) and was now defined as a class of multimeric protein complexes mainly composed of PRRs, apoptosis-associated speck-like protein containing CARD (ASC), and pro-caspase-1, to identify various irritating and damaging signals in natural immune responses and had a close relationship to the occurrence of cell death (Lamkanfi and Dixit, 2017). PRRs mainly included Toll-like receptors (TLRs), melanoma deficiency factor 2 (AIM2) and NOD-like receptors (NLRs), of which nucleotide-binding oligomerization domain-like receptor protein3 (NLRP3) got the most attention. PRRs could identify PAMPs or endogenous dangerous signaling to form inflammasome complex after two stages of priming and activation, which in turn activates its downstream caspase-1. Activated caspase-1 could cleave GSDMD to GSDMD-N terminal, forming pores in the cell membrane. Meanwhile, the pro-inflammatory factors pro-IL-1 and pro-IL-18 were also cleaved by activated caspase-1, transferred to mature IL-1β and IL-18, releasing from the cell membrane pores, thus inducing pyroptosis. Numerous studies have demonstrated that NLRP3/caspase-1 mediated pyroptosis signaling pathway played a crucial role and was the most common therapeutic target of cognitive impairment (Van Zeller et al., 2021; Li et al., 2022), any blockade of NLRP3/caspase-1 mediated pyroptosis may reverse the incidence or progression of cognitive impairment.

The non-canonical pyroptosis pathway was dependent on the activation of human caspase-4/-5 and homologous murine caspase-11 by intracellular lipopolysaccharides (LPS). LPS typically consisted of a hydrophobic domain known as lipid A (or endotoxin), a non-repeating "core" oligosaccharide, and a distal polysaccharide (or

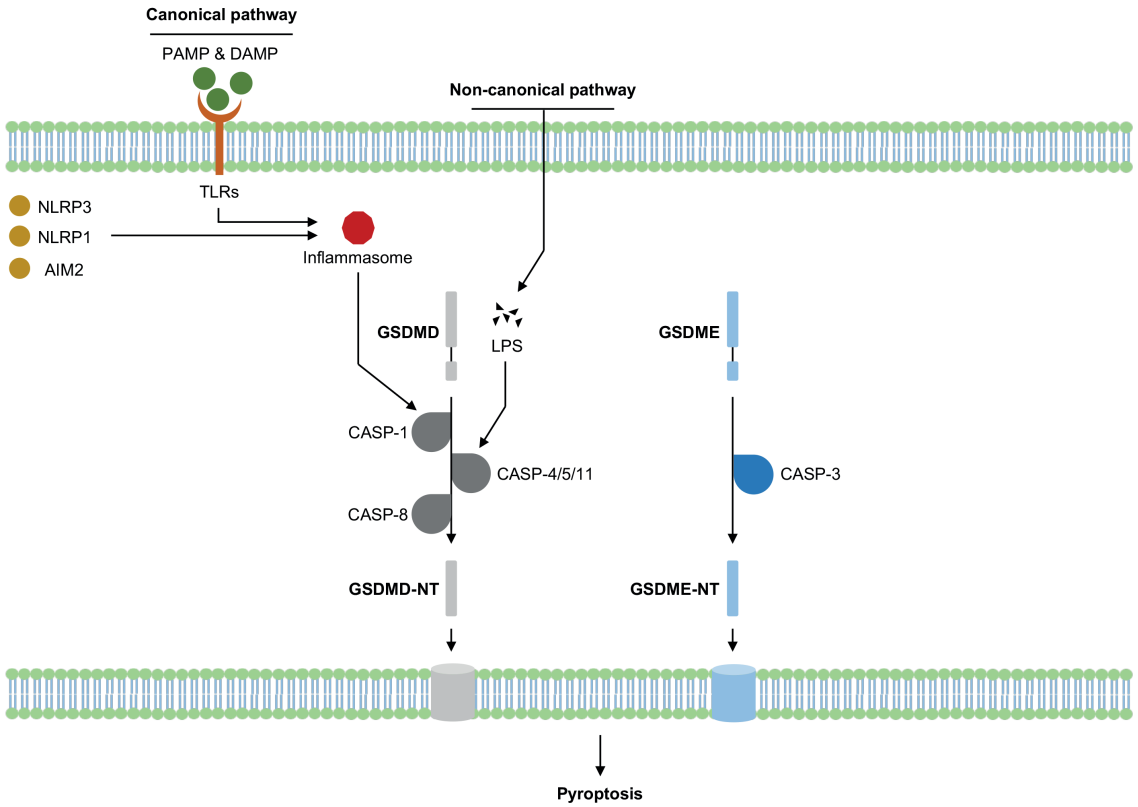

FIGURE 1
Summary of pyroptosis activation in cognitive impairment-related diseases. LPS, Lipopolysaccharide; CASP, Caspase; GZM, Granzyme; NT, N-terminal domain; PAMP, Pathogen-associated molecular patterns; DAMP, Damage-associated molecular patterns; TLRs, Toll-like receptors; NLRP3, nucleotide-binding oligomerization domain-like receptor protein 3; NLRP1, NLR family pyrin domain containing 1; AIM2, melanoma deficiency factor 2.

O-antigen) (Raetz and Whitfield, 2002). LPS could directly bind and activate caspase-4/-5/-11 protein to initiate pyroptosis (Zheng et al., 2021). Similar to the canonical pyroptosis pathway, activated caspase-4/-5/-11 cleaved GSDMD to GSDMD-N terminal, inducing pore formation in the cell membrane (Shi et al., 2017). During the process, LPS could also induce caspase-11-dependent cleavage of the pannexin-1 channel protein, activating the P2X purinoreceptor 7 (P2X7) receptor-dependent membrane pore opening and causing subsequent ATP release, K^+ efflux, osmotic imbalance, leading to cell swelling and membrane rupture, and eventually resulting in pyroptosis (Shi et al., 2015; Liu et al., 2016; He et al., 2023). Furthermore, released ATP and K^+ efflux through pannexin-1 transmembrane channel could activate NLRP3 inflammasome and IL-1β secretion, indicating that NLRP3 might be a crucial bridge between the canonical and non-canonical pyroptosis pathways (Karmakar et al., 2015; Yang et al., 2015; Karmakar et al., 2016).

GSDMD belonged to gasdermin family proteins and was primarily identified by two separate studies in 2015, Dixit et al. found that GSDMD played a key role in LPS-induced activation of the non-canonical inflammasome by screening chemically induced mouse mutants (Kayagaki et al., 2015), while Shao et al. performed a genome-wide screen of caspase-11 and caspase-1-induced pyroptosis pathways in cell lines, which revealed that GSDMD is the substrate of all inflammatory caspases and is the true executor of pyroptosis (Shi et al., 2015). Multiple caspases such as caspase-1/-4/-5/-8/-11 could cleave and activate GSDMD. Caspase-1 activated GSDMD through inflammasome complexes such as AIM2, NLRC4 or NLRP3 (Broz and Dixit, 2016). The activation of GSDMD by caspase-4 was reported to be regulated by interferon regulatory factor 2 (Benaoudia et al., 2019; Kayagaki et al., 2019). It was reported that caspase-8-dependent GSDMD cleavage relied on caspase-8 dimerization and autoprocessing (Demarco et al., 2020). LPS-triggered caspase-11-GSDMD signaling pathway was upregulated by IFN-γ and IFN-β (Brubaker et al., 2020; Zhang et al., 2020). Unlike GSDMD-mediated pyroptosis, gasdermin E (GSDME)-induced pyroptosis mainly relied on the activation of caspase-3. Traditionally caspase-3 is an apoptosis-related caspase, which could be activated under the treatment of TNF-α or chemotherapy drugs, inducing cell apoptosis. However, when GSDME existed, activated caspase-3 would cleave GSDME at the site of residue Asp270 and induce pyroptosis instead of apoptosis (Ouyang et al., 2023). The role of GSDMD and GSDME-mediated pyroptosis in cognitive impairment have been elucidated, but the mechanisms of other gasdermin family members such as GSDMA, GSDMB, GSDMC and DFNB59 in cognitive impairment remained unclear.

Pyroptosis and cognitive impairment

Alzheimer's disease

The most common neurodegenerative condition affecting the aged population is Alzheimer's disease (AD), which is characterized by a particular sequence of pathological alterations in the brain that cause neurodegeneration, loss of synaptic connections, progressive memory problems, and cognitive impairment (Masters et al., 2015). Unfortunately, despite a large number of studies on the mechanisms of AD, there were no approved therapies to halt or reverse its progression (Van Zeller et al., 2021). Recent studies elucidated the relationship between pyroptosis and AD, and some drugs targeting the pyroptosis pathway showed therapeutic potential.

Rui et al. (2021) detected the expression levels of NLRP3, caspase-1, GSDMD, and IL-1β and found all the above parameters were increased in the peripheral blood mononuclear cells (PBMCs) of amnestic mild cognitive impairment (aMCI) and AD patients, and IL-1β was positively associated with the disease, indicating the important role of pyroptosis in AD. Li et al. (2020) found that neuronal pyroptosis induced by the overexpression of NLRP3/caspase-1/GSDMD axis was the key cause of neuronal loss in AD, NLRP3 inhibitor MCC950 could inhibit neuronal pyroptosis by downregulating NLRP3/caspase-1/GSDMD axis, reduced the neurotoxicity of amyloid-$\beta_{1\text{-}42}$ ($A\beta_{1\text{-}42}$) *in vitro*, improved the spatial memory ability *in vivo*. NLRP3 inhibitor might be a potential therapeutic agent of AD. Tian et al. (2021) revealed that activated caspase-1 directly induced pyroptosis through NLRP3 and AIM2 activation in an AD mouse model induced by sevoflurane, caspase-1 small-molecule inhibitor VX-765 could significantly inhibit the pyroptosis pathway, suppress the release of IL-1β and IL-18 and downregulate tau phosphorylation, thus restoring neuron function of AD. Several studies focused on the ameliorative effects of traditional Chinese medicine in AD. Salidroside, the main pharmacological active ingredient isolated from *Rhodiola rosea L.* (Cai et al., 2021), Dendrobium nobile Lindl. Alkaloid (DNLA), the main active compound in *Dendrobium nobile Lindl* (Li et al., 2022), as well as Jiedu-Yizhi formula (Wang et al., 2022) were found to inhibit NLRP3-mediated or LPS-induced pyroptosis and improve AD. Li et al. (2021) revealed that Schisandrin, a representative lignan of *Schisandra chinensis Bail.*, could also inhibit Aβ-induced NLRP-1-mediated neuronal pyroptosis and ameliorate cognitive impairment of AD. Quinones in Chinese Medicine could potentially prevent AD via modulating the NLRP3 inflammasomes, adopt molecular docking study indicated that purpurin and rhein might be the most promising NLRP3 inhibitors, however, further study was required to ascertain the preventive effect (Chen et al., 2020). Bai et al. (2021) elucidated that N-salicyloyl tryptamine derivatives could restore Aβ-induced pyroptosis through NLRP3/caspase-1/GSDMD axis and ameliorate cognitive function. It was reported that upregulated RAGE–TXNIP axis or activated transient receptor potential vanilloid 4 (TRPV4) participated in causing pyroptosis and result in cognitive impairment in AD, which could be the potential therapeutic target through suppression of overactivated pyroptosis (Sbai et al., 2022; Guo et al., 2023).

Perioperative neurocognitive disorder

Perioperative neurocognitive disorder (PND) is one of the common complications during the perioperative period and is mainly manifested as cognitive impairment. PNDs include acute postoperative delirium and relatively long-lasting postoperative cognitive dysfunction (Li et al., 2022). Age, surgical trauma, and anesthetics are the main risk factors of PND, however, the mechanisms of PND remained unclear. Many studies have elucidated the important role of pyroptosis in the pathogenesis of PND and targeting pyroptosis could be an effective method for PND treatment.

It was reported that NLRP3 inflammasome-mediated pyroptosis directly led to cognitive impairment in PND mice model induced by

isoflurane, and NLRP3 inflammasome inhibitor MCC950 could inhibit overactivated pyroptosis and exert a neuroprotective effect, thus improving cognitive impairment (Fan et al., 2018). Zhou et al. demonstrated that pyroptosis, as well as the level of reactive oxygen species (ROS) was significantly upregulated in a postoperative cognitive dysfunction (POCD) mouse model induced by sevoflurane. Not only the pyroptosis inhibiter, necrosulfonamide (NSA), could improve cognitive impairment via suppressing pyroptosis, but also the ROS scavenger, N-acetylcysteine (NAC), could ameliorate POCD by reducing the level of ROS and pyroptosis through NLRP3 inflammasome pathway (Zhou et al., 2023). Caspase-1 inhibitor, VRT-043198, was reported to ameliorate PND in an aged mice model by inhibiting caspase-1-mediated pyroptosis (Tang et al., 2022). Zuo et al. (2020) revealed that elamipretide could also attenuate pyroptosis by inhibiting NLRP3/caspase-1 pathway and partly restore PND in aged mice. Que et al. (2020) demonstrated that isoflurane exposure resulted in cognitive dysfunction in aged rats, accompanied by decreased expression of DUSP14, and it was found that DUSP14 could regulate NLRP3-mediated pyroptosis, overexpression of DUSP14 inhibited pyroptosis and improved cognitive impairment, indicating that DUSP14 might be a new therapeutic target for POCD. Isoflurane induced hippocampal neuronal damage and cognitive impairment by upregulating SETD7 and activating pyroptosis in the hippocampus, knockdown of STED7 could inhibit the level of pyroptosis and the release of inflammatory cytokines, prevent hippocampus damage and improve POCD (Ma et al., 2022). Apart from NLRP3/caspase-1 axis, other pyroptosis pathways were revealed to be associated with PND. Wang et al. found that caspase-3 was activated in POCD, and activated caspase-3 could cleave gasdermin E (GSDME) to form GSDME-N terminal, forming pores in the cell membrane and inducing pyroptosis. Caspase-3 inhibitor Ac-DEVD-CHO (Ac-DC) could inhibit pyroptosis and improve cognitive impairment (Wang et al., 2023). NF-κB and HMGB1 induced pyroptosis were also elucidated in PND, NF-κB inhibitor or HMGB1 inhibitor treatment effectively improved PND by significantly inhibiting pyroptosis (Dai et al., 2021; Shan et al., 2023). Li et al. (2022) found that esketamine improved POCD in aged rats and alleviated the pyroptosis of astrocytes after LPS exposure, moreover, an underlying connection between STING/TBK1 signaling pathway and caspase-1-mediated pyroptosis was indicated, which required further research. MicroRNA-140-3p was found to improve POCD by repressing neuron pyroptosis via HTR2A/ERK/Nrf2 axis by targeting DNMT1 (Wu et al., 2022).

Sepsis-associated encephalopathy

Sepsis-associated encephalopathy (SAE) is a frequent complication that leads to long-term cognitive impairments and psychiatric diseases in sepsis patients and has a close association with increased morbidity and mortality. The potential mechanisms of SAE are complex, including endothelial dysfunction, damage to the blood–brain barrier, oxidative stress, etc. However, the molecular changes in SAE required further research. Accumulating evidence has indicated that pyroptosis may be the bridge between SAE and overactivated neuroinflammation, especially the NLRP3/caspase-1 pathway. NLRP3 inhibitor MCC950 and the caspase-1 inhibitor Ac-YVAD-CMK or VX765 were used for the treatment of SAE and the results were exhilarating. Administration of the above inhibitors could repress overactivated pyroptosis and the release of pro-inflammatory cytokines, restore the synapse plasticity and preserve long-term potential, thus improving cognitive dysfunction (Fu et al., 2019; Xu et al., 2019). It was mentioned that electroacupuncture could improve 7-day survival rates and cognitive function by downregulating NLRP3/caspase-1/GSDMD pyroptosis pathway in an SAE mouse model (Li et al., 2022). As the most important pyroptosis pathway, the activity of NLRP3/caspase-1 signaling pathway was mediated by various cell components or molecules. Zhou et al. found that p38 MAPK and ERK signaling pathways might regulate NLRP3/caspase-1 pathway, and the phosphorylation of p38 MAPK and ERK was positively correlated with NLRP3, caspase-1, and inflammatory factor levels in SAE. Downregulation of p38 MAPK and ERK led to suppression of pyroptosis, however, the direct connection between these two pathways needed deeper exploration (Zhou et al., 2019). Jing et al. revealed the importance of IRE1α/Xbp1s-Ca^{2+} signaling in endoplasmic reticulum (ER) stress, which was involved in NLRP3 inflammasome activation. IRE1α/Xbp1s pathway was activated, promoting the ER Ca^{2+} influx to the cytoplasm and inducing NLRP3 inflammasome-mediated pyroptosis. The selective inhibitor STF083010 targeting IRE1α/Xbp1s could partly restore the process, and improved cognitive function by attenuating microglial pyroptosis (Jing et al., 2022). Mitochondria-mediated pyroptosis was reported in SAE, mitochondria impairment was associated with cognitive dysfunction. The mitochondrial protectant dexpramipexole (DPX) could sustain mitochondrial function and inhibit NLRP3/caspase-1 pyroptosis pathway, thus ameliorating neuroinflammation and cognitive impairment in SAE (Zhang et al., 2023). Sevoflurane was reported to activate HMGB1-induced NLRP3/ASC inflammasome, induce pyroptosis, and impair cognitive function in PND (Shan et al., 2023), however, in SAE, sevoflurane could act as protective role. Chen et al. (2022) demonstrated that sevoflurane could improve cognitive dysfunction by inhibiting the NLRP3-dependent caspase-1/11-GSDMD pathway, in which SIRT1 played a key role. Yang et al. showed that cannabinoid type 2 receptor (CB2R) helped to protect neurons and promote survival in SAE patients. Furthermore, it has been proven that the CB2R-specific agonist HU308 could repress neuronal pyroptosis, attenuate brain tissue damage and improve cognitive impairment in SAE (Yang et al., 2022).

Cerebrovascular diseases

Cerebrovascular diseases are also key contributors to the overall burden of cognitive impairment and mainly include acute ischemia stroke and chronic cerebral hypoperfusion (CCH). An acute ischemic stroke occurs due to the sudden interruption or reduction of blood supply in part of the brain, and the process is often combined with pre-existing microvascular and neurodegenerative changes, which results in a series of pathological changes leading to cognitive impairment (Rost et al., 2021). CCH is caused by chronic reduction of cerebral blood flow, which is a common pathophysiological process in cerebral vascular diseases such as atherosclerosis or arteriosclerosis, leading to a state of prolonged ischemia and hypoxia in the brain tissue, finally results in progressive and persistent cognitive impairment (He et al., 2023). Although the mechanisms of cerebrovascular disease-induced cognitive

dysfunction have not been fully understood, it has been identified that pyroptosis was involved in the pathological process.

Kim et al. elucidated that AIM2 inflammasome, as well as caspase-1, IL-1β, IL-18, was significantly upregulated in the hippocampus and cortex in the mouse model of post-stroke cognitive impairment than in those of the sham group. AIM2 inflammasome-mediated pyroptosis could cause acute and chronic neuronal death after stroke, which might result in cognitive dysfunction. Moreover, knockout of AIM2 or inhibition of caspase-1 could improve cognitive function and partly reverse brain volume in the hippocampus compared to those in stroke mice (Kim et al., 2020). Furthermore, Kim et al. developed a miniaturized electronic device of photobiomodulation (PBM), consisting of packaged light-emitting diodes (LEDs) that incorporate a flexible substrate for *in vivo* brain PBM in a mouse model. The preventive and therapeutic effects of PBM affixed to the exposed skull of stroke mice model were evaluated, and the results showed that the PBM with 630 nm LED array could significantly attenuate the progression of cognitive impairment in the chronic poststroke phase via regulating AIM2 inflammasome activation and AIM2 inflammasome-mediated pyroptosis (Kim et al., 2022). It was reported that NLRP3/caspase-1-dependent pyroptosis participated in the cerebral ischemia/reperfusion injury and cognitive decline after focal cortical infarction, NLRP3 inhibitor and caspase-1 inhibitor could improve the symptoms, respectively (Sun et al., 2020; Dong et al., 2022). The antiepileptic drug valproic acid (VPA) was also reported to improve cerebral ischemia/reperfusion injury via modulating an apoptosis repressor with caspase recruitment domain (ARC)-mediated caspase-1-dependent pyroptosis pathway (Zhu et al., 2019).

The activation of AIM2 inflammasome contributed to the pathophysiology of chronic CCH-induced brain injury (Poh et al., 2021), and it was revealed and knockout of AIM2 attenuated pyroptosis in the cerebellum following CCH mainly by decreasing the production of proinflammatory cytokines (Poh et al., 2021). It was reported that curcumin and emodin could protect against CCH-induced cognitive dysfunction via inhibiting overactivated NLRP3-dependent pyroptosis (Zheng et al., 2021; Jiang et al., 2023). Chai et al. found that the level of legumain, a lysosomal cysteine protease, was significantly increased in the hippocampus of mice with CCH, considering the abnormal upregulation of legumain in mediating synaptic plasticity impairment and neuroinflammation, targeting legumain might be a potential therapy for CCH. Legumin knockout could partly restore synaptic plasticity and protect against cognitive impairment by decreasing the levels of inflammatory cytokines and the inflammasome complex and inhibiting pyroptosis (Chai et al., 2021). Interestingly, behavioral therapy also showed potential for the treatment of CCH-induced cognitive dysfunction. Poh et al. (2021) observed increased expression of inflammasome components and precursor IL-1β in the brain tissue following CCH, intermittent fasting (16 h food deprivation daily) could significantly reduce the expression levels of cleaved caspases-1/-8/-11 and maturation of both IL-1β and IL-18, inhibit proptosis and improve cognitive impairment, suggesting the therapeutic effect of non-pharmaceutical intervention.

Metabolic disorders

It has been well-recognized that metabolic disorders such as type 2 diabetes mellitus, obesity and cardiovascular diseases are associated with cognitive impairment (Zilliox et al., 2016; Sharma, 2021). Considerable molecular biological studies have elucidated the mechanisms of how diabetes and obesity/high-fat diet (HFD) caused cognitive impairment, among which pyroptosis played an important role.

Diabetes mellitus induced the risk and promoted the development of cognitive dysfunction mainly via the greater occurrence of small-/micro-vascular diseases or even stroke. Ward et al. found that diabetes could induce neuronal degeneration and blood–brain barrier disruption, thus impairing cognitive function. In the process amplified NLRP3 activation was observed, and NLRP3 inhibitor could ameliorate cognitive function and vascular integrity in a high-fat diet/streptozotocin-induced (HFD/STZ) diabetic male Wistar rat model with stroke. Although the role of pyroptosis was not deeply discussed, NLRP3 inhibitor showed therapeutic potential (Ward et al., 2019). Ruan et al. showed the effect of HECT domain E3 ubiquitin protein ligase 3 (HECTD3) in diabetes-related cognitive impairment. HECTD3 was upregulated, together with the increased levels of NLRP3/caspase-1/GSDMD pyroptosis pathway, in the hippocampus of STZ-induced diabetic rats and PC12 cells treated with high glucose medium. HECTD3 silencing could inhibit the activation of NLRP3 inflammasome, suppressed pyroptosis level and exerted a neuroprotective effect via MALT-mediated JNK signaling (Ruan et al., 2022). It was revealed that the P2X7-mediated NLRP1/Caspase-1 pyroptosis pathway, as well as apoptosis and oxidative stress, was overactivated in high glucose-induced hippocampal neuron injury. Naofucong, a compound preparation based on traditional Chinese medicine theory and modern pharmacology, was found to reduce both oxidative stress and pyroptosis by suppressing P2X7/NLRP1/caspase-1 pathway, finally improving cognitive impairment (Jing et al., 2021). Wang et al. elucidated the mechanism of how tetracyclic oxindole alkaloid isorhynchophylline (IRN) helped lessen diabetes-induced cognitive impairment. Spliced form of X-box binding protein 1 (sXBP1) played a crucial role in the process. IRN promoted sXBP1 translocation into the nucleus, and restored downstream high glucose-mediated impairment of insulin signaling, endoplasmic reticulum stress, and pyroptosis/apoptosis, thus improving cognitive dysfunction (Wang et al., 2023). Gestational diabetes mellitus (GDM) is defined as diabetes diagnosed for the first time during pregnancy and can lead to cognitive impairment in offspring. Liang et al. found that chemerin was significantly upregulated in the serum, placenta tissue, and umbilical cord blood of the diabetic mother, further study revealed that chemerin-induced diabetic pregnant disease via chemokine receptor-like 2 (CCRL2)-dependent enrichment of chemerin in the brain of offspring, which led to macrophage recruitment, activation of NLRP3/caspase-1 mediated pyroptosis, resulting in cognitive impairment. Chemerin exerted effects via chemerin receptor 23 (ChemR23), therefore targeting CCRL2 and ChemR23 could be effective for treating cognitive dysfunction in offspring of GDM (Liang et al., 2019).

Compared with cardiovascular diseases and diabetes mellitus, cognitive impairment is easy to be ignored in patients with obesity (Wang et al., 2017; Zhang et al., 2020). It is important to uncover the relationship between obesity/HFD and cognitive impairment. Sui et al. reported that under HFD conditions, neuronal pyroptosis was significantly increased, tau protein was hyperphosphorylated, Nrf-2/HO-1 signaling pathway was activated. Exogenous IGF-1 could improve cognitive impairment in a C57BL/6 J mice model fed with HFD by reversing the activity of the above signaling (Sui et al., 2021).

MicroRNAs also showed potential in treating obesity/HFD-related cognitive impairment. Wang et al. found that HFD caused cognitive impairment following neuronal pyroptosis and a decrease of IGF-1/GSK3β signaling pathway in the midbrain and hippocampus tissues. Inhibition of miR-129 by miR-129 antagomir could attenuate NLRP3/caspase-1 mediated pyroptosis and improve cognitive impairment by activating IGF-1/GSK3β signaling pathway via directly targeting IGF-1 (Wang et al., 2021). Yang et al. used BV2 cells treated with palmitic acid to establish an *in vitro* model of HFD, the results showed TLR4/MyD88/NF-κB p65 signaling, together with NLRP3 expression, was upregulated in palmitic acid-treated BV2 cells. miR-124 could target TLR4/MyD88/NF-κB p65/NLRP3 signaling and reduce its activity, showing a protective effect against HFD-induced neuronal injury (Yang et al., 2022).

Discussion and perspectives

Although the effects and mechanisms of pyroptosis in cognitive impairment are not fully understood, numerous pieces of evidence showed that the various pyroptosis signaling pathway participated in the incidence and progression of cognitive dysfunction induced by different causes. Pyroptosis was regulated by canonical, non-canonical and gasdermin-dependent signaling pathways, forming a complex regulation network. The levels of pyroptosis signaling pathway were significantly upregulated in cognitive impairment, together with the release of large amounts of inflammatory substances such as IL-1β and IL-18, resulting in a cascade of inflammatory reactions, which could be harmful to brain tissues. Targeting and downregulation of the pyroptosis signaling pathway was an effective method to improve cognitive impairment, NLRP3 inhibitor and caspase-1 inhibitor were the most common agents to repress the activation of pyroptosis. Apart from the therapeutic methods/agents directly targeting the pyroptosis signaling pathway, different approaches have been also taken for the treatment of cognitive impairment (Table 1). Photobiomodulation (PBM) with 630 nm LED array affixed to the exposed skull of stroke mice model could significantly attenuate the progression of cognitive impairment in the chronic poststroke phase via regulating AIM2 inflammasome activation and AIM2 inflammasome-mediated pyroptosis (Kim et al., 2022). Electroacupuncture was also reported to improve 7-day survival rates and cognitive function by downregulating NLRP3/caspase-1/GSDMD pyroptosis pathway in an SAE mouse model (Li et al., 2022). Behavioral therapy such as intermittent fasting could also significantly inhibit overactivated proptosis and improve cognitive impairment (Poh et al., 2021). These attempts suggest the therapeutic effect of the non-pharmaceutical intervention and broaden the way to develop new therapy methods. The pathological changes of cognitive impairment were accompanied by the activation of the components of pyroptosis pathway, indicating the detection of pyroptosis components could be an early diagnostic biomarker. Therefore, pyroptosis played a crucial role in cognitive dysfunction, further research would be remarkably helpful for the prevention and protection of cognitive impairment.

Recent studies also focused on the relationship between mutation of gasdermin genes and specific diseases. Ruan et al. (2018) analyzed the structure of the GSDMA3 membrane pore with the help of cryo-electron microscopy and partly revealed mechanisms of how the cleavage of GSDMA3 formed membrane pores and the mechanisms of autoinhibition. Due to a loss of autoinhibition, disease-related mutations of GSDMA3 and its N terminal alone could initiate pyroptosis and had a close association with spontaneous alopecia and hyperkeratosis (Ding et al., 2016). Single nucleotide polymorphisms (SNPs) in GSDMA and GSDMB were reported to be related to childhood asthma and to a lesser extent to adult asthma (Zheng et al., 2020). Mutations of GSDME and DFNB59 could both induce deafness, but the mechanisms were different. GSDME mutations resulted in its overexpression and led to pyroptosis in HeLa cells (Wang et al., 2017), while DFNB59 mutations exerted function in a non-pyroptosis way (Delmaghani et al., 2006). Xia et al. (2021) reported the cryo-electron microscopy structures of the pore of GSDMD, elucidating the process of GSDMD-dependent membrane pore formation and GSDMD-mediated release of IL-1β. Liu et al. (2019) revealed the mechanisms of autoinhibition, lipid binding and oligomerization of GSDMD-N-terminal in virtue of the crystal structures. These studies of molecular structure gave an explanation for the actions of a number of mutant gasdermin family members (Ruan et al., 2018). However, the association between mutation of gasdermin genes and cognitive impairment required future exploration.

Given the unknown mechanisms of cognitive impairment, we are beginning to understand the molecular biological/pathological functions of cognitive impairment and pyroptosis. Further research towards elucidating new mechanisms of the pyroptosis signaling pathway will deepen our comprehension of cognitive impairment, and provide new ideas for developing more potent methods.

Author contributions

XY carried out the primary literature search, drafted, and revised the manuscript. ZT contributed to the drafting and revising of the manuscript. All authors contributed to the article and approved the submitted version.

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 DW declared a past co-authorship with the author ZT to the handling editor.

Publisher's note

TABLE 1 Summary of potential agents/methods targeting pyroptosis to treat cognitive impairment.

Disease	Agents/methods	Targets	Model	Ref
Alzheimer's disease (AD)/ amnestic mild cognitive impairment (aMCI)	–	NLRP3/Caspase-1/GSDMD axis	5xFAD mice	Rui et al. (2021)
	Salidroside	NLRP3 inflammasome	AD mouse model induced by Aβ1-42 and D-galactose (D-gal)/$AlCl_3$, respectively	Cai et al. (2021)
	Jiedu-Yizhi formula	NLRP3/Caspase-1/GSDMD axis and LPS/ Caspase-11/GSDMD pyroptosis pathways	AD rat model induced by Aβ25–35	Wang et al. (2022)
	VX765	NLRP3/Caspase-1/GSDMD axis and AIM2 activation	AD mouse model induced by sevoflurane	Tian et al. (2021)
	HC067047 or knockdown of hippocampal TRPV4	Canonical and noncanonical pyroptosis	A mouse model induced by systemic administration of lipopolysaccharide (LPS)	Guo et al. (2023)
	Verapamil/TXNIP silencing	RAGE-TXNIP axis/NLRP3 inflammasome	5xFAD mice	Sbai et al. (2022)
	Dendrobium Nobile Lindl. Alkaloid	NLRP3-Mediated Pyroptosis	AD mouse model induced by hippocampus injection of LPS	Li et al. (2022)
	Quinones	NLRP3 inflammasome	–	Chen et al. (2020)
	Schisandrin	NLRP1 inflammasome	APP/SP1 double transgenic mice	Li et al. (2021)
	N-salicyloyl tryptamine	NLRP3/Caspase-1/GSDMD axis	AD rat model induced by Aβ25–35	Bai et al. (2021)
	MCC950	NLRP3 inflammasome	SAMP8 mice	Li et al. (2020)
Postoperative cognitive dysfunction (POCD)/ Perioperative Neurocognitive Disorders (PND)	Necrosulfonamide (NSA) and N-acetylcysteine (NAC)	NLRP3/Caspase-1 pathway	–	Zhou et al. (2023)
	Overexpression of DUSP14	NLRP3/Caspase-1 Pathway	A POCD aged rat model induced by isoflurane	Que et al. (2020)
	Esketamine	STING/TBK1 pathway/Caspase-1-mediated pyroptosis	A POCD aged rat model induced by sevoflurane	Li et al. (2022)
	Knockdown of SETD7	NLRP3 inflammasome	A POCD mouse model induced by isoflurane	Ma et al. (2022)
	Silencing of PINK1 and/or Ac-DEVD-CHO	Caspase-3/GSDME-Dependent Pyroptosis	A POCD rat model induced by isoflurane	Wang et al. (2023)
	microRNA-140-3p	DNMT1 mediated HTR2A/ERK/Nrf2 axis	A POCD rat model induced by sevoflurane	Wu et al. (2022)
	Elamipretide	NLRP3/Caspase-1 Pathway	A PND mouse model induced by isoflurane	Zuo et al. (2020)
	VRT-043198	NGF and BNDF expression	An aged abdominal exploratory laparotomy (AEL) mouse model of PND	Tang et al. (2022)
	MCC950	NLRP3 inflammasome	A POCD mouse model induced by isoflurane	Fan et al. (2018)
	BAY11-7082	NF-κB-mediated pyroptosis	SD rat pups at postnatal day 6 received sevoflurane	Dai et al. (2021)
	Glycyrrhizin	HMGB1-mediated NLRP3/ASC inflammasome	Pregnant rats on gestational day 20 received sevoflurane	Shan et al. (2023)
Sepsis-Associated Encephalopathy (SAE)	MCC950 & Ac-YVAD-CMK	NLRP3/Caspase-1 pathway	A mouse model of SAE induced by cecal ligation and puncture (CLP)	Fu et al. (2019)
	VX765	NLRP3/Caspase-1 pathway	A mouse model of SAE induced by CLP	Xu et al. (2019)
	Erbin	IRE1α/Xbp1s-Ca2+ axis/NLRP3 inflammasome	A mouse model of SAE induced by CLP	Jing et al. (2022)
	Dexpramipexole	Mitochondria-mediated NLRP3/caspase-1 pyroptosis	A mouse model of SAE induced by peripheral administration of lipopolysaccharide (LPS)	Zhang et al. (2023)
	Sevoflurane	Inflammatory-pyroptotic signaling (NLRP3, caspase 1/11, GSDMD, TLR4 and TRIF)	A mouse model of SAE induced by CLP	Chen et al. (2022)
	HU308	Neuronal pyroptosis	A mouse model of SAE induced by CLP	Yang et al. (2022)
	Electroacupuncture	NLRP3/Caspase-1 Pathway	A mouse model of SAE induced by CLP	Li et al. (2022)
	Recombinant club cell protein(rCC16) and/ or U46619	NLRP3/Caspase-1 Pathway	A rat model of SAE induced by CLP	Zhou et al. (2019)
Chronic post-stroke cognitive impairment (PSCI)	Ac-YVAD-CMK	AIM2 inflammasome	Middle cerebral artery occlusion (MCAO)/ reperfusion-induced PSCI mouse model	Kim et al. (2020)
Cognitive decline after focal cortical infarction	VX765	NLRP3-dependent pyroptosis	Distal middle cerebral artery occlusion (dMCAO) rat model	Dong et al. (2022)
Cerebral ischemia/reperfusion injury	CY-09	Caspase-1/GSDMD-dependent pyroptosis	A focal cerebral ischemia mouse model accomplished by the endovascular MCAO	Sun et al. (2020)
Ischemic stroke	Photobiomodulation	AIM2 inflammasome	Photothrombotic cortical ischemia mouse model induced by photothrombosis of the cortical microvessels	Kim et al. (2022)
	Valproic acid (VPA)	Caspased-1/NLRP1 and NLRP3 inflammasome	Ischemia/reperfusion (I/R) mouse model	Zhu et al. (2019)

(Continued)

TABLE 1 (Continued)

Disease	Agents/methods	Targets	Model	Ref
Chronic cerebral hypoperfusion (CCH)/ vascular dementia/vascular cognitive impairment (VCI)	Curcumin	NLRP3-dependent pyroptosis	A rat model of diabetes mellitus and CCH	Zheng et al. (2021)
	Knockout of legumain	Pyroptosis	Right unilateral common carotid artery occlusion (rUCCAO) rat model	Chai et al. (2021)
	Emodin	NLRP3 inflammasome-mediated pyroptosis	BV2 cells/HT22 cells	Jiang et al. (2023)
	AIM2 knockout	AIM2 inflammasome	Bilateral common carotid artery stenosis (BCAS) mouse model	Poh et al. (2021)
	AIM2 knockout	AIM2 inflammasome	Bilateral common carotid artery stenosis (BCAS) mouse model	Poh et al. (2021)
	Intermittent fasting (IF)	Inflammasome-associated apoptotic and pyroptotic death	Bilateral common carotid artery stenosis (BCAS) mouse model	Poh et al. (2021)
High-fat diet (HFD)-induced cognitive impairment	miR-129 antagomir	IGF-1/GSK3β Signaling Pathway	A rat model fed with HFD	Wang et al. (2021)
	miR-124	TLR4/MyD88/NF-κB p65/NLRP3 Signaling Pathway	BV2 cells treated with palmitic acid	Yang et al. (2022)
	Exogenous IGF-1	NLRP3/Caspase-1 Pathway	A mouse model fed with HFD	Sui et al. (2021)
Diabetes-associated cognitive decline	–	NLRP3 inflammasome	A diabetic rat model induced by streptozotocin (STZ)	Ruan et al. (2022)
	Naofucong	P2X7/NLRP1/Caspase-1 Pathway	HT22 cells treated with high glucose medium	Jing et al. (2021)
	Isorhynchophylline	Spliced form of X-box binding protein 1 (sXBP1)/pyroptosis	A diabetic mouse model induced by STZ	Wang et al. (2023)
Cognitive disorders of offspring from mothers with diabetes in pregnancy	Chemerin	NLRP3/Caspase-1 pathway	A diabetic pregnant mouse model induced by STZ	Liang et al. (2019)
Post-stroke cognitive impairment in diabetes	MCC950	NLRP3 inflammasome	A diabetic rat model induced by HFD/STZ, stoke rat model induced by 90-min mechanical middle cerebral artery occlusion (MCAO) surgery	Ward et al. (2019)

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frontiers | Frontiers in Aging Neuroscience

TYPE Original Research
PUBLISHED 22 June 2023
DOI 10.3389/fnagi.2023.1214748

OPEN ACCESS

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RECEIVED 30 April 2023
ACCEPTED 05 June 2023
PUBLISHED 22 June 2023

CITATION
You Y, Chen Y, Chen X, Wei M, Yin J, Zhang Q and Cao Q (2023) Threshold effects of the relationship between physical exercise and cognitive function in the short-sleep elder population.
Front. Aging Neurosci. 15:1214748.
doi: 10.3389/fnagi.2023.1214748

Threshold effects of the relationship between physical exercise and cognitive function in the short-sleep elder population

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Background: It has been demonstrated that elderly people's cognitive capacities can be improved with exercise, and short sleep is linked to cognitive decline. However, the impact of physical exercise on cognitive performance in seniors who do not get enough sleep is largely unknown. This makes it an intriguing subject to explore further.

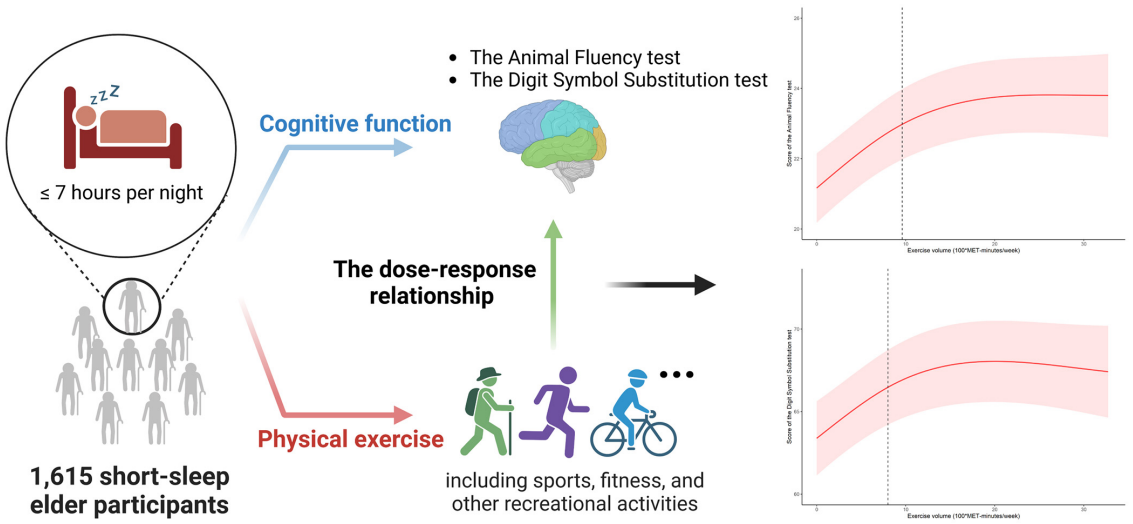
Methods: This study consisted of elders (over 60 years old) who participated throughout the National Health and Nutrition Examination Survey's 2011–2014 cycle (NHANES). Weighted linear regression model and restricted cubic splines analysis were performed to evaluate the association between physical exercise and cognitive function. In the end, 1,615 samples were scrutinized and the total number of weighted respondents was 28,607,569.

Results: Results showed that in the Animal Fluency test and the Digit Symbol Substitution test, a positive association was found between physical exercise volume and scores in the fully adjusted model. A two-piecewise linear regression model was then applied to explore the threshold effect of exercise on cognitive performance. Before 960 and 800 MET-minutes/week, there were consistent positive relationship between exercise and scores of the Animal Fluency test [ß (95% CI): 0.233 (0.154, 0.312), $p < 0.001$] and Digit Symbol Substitution test [β (95% CI): 0.555 (0.332, 0.778), $p < 0.001$], respectively. However, there was a saturation effect where physical exercise volume reached the two inflection points.

Conclusion: According to our research, the benefit of exercise did not always expand with the exercise volume increment under the short-sleep condition, which challenged existing knowledge. The short-sleep elder group could maintain cognitive performance with no more than 800 MET-minutes/week of physical exercise. Verification of these findings requires further biological investigations.

KEYWORDS

cognitive function, physical exercise, short-sleep, elder population, NHANES, threshold effect



GRAPHICAL ABSTRACT
Study design and main findings.

1. Introduction

Aging leads to cognitive decline such as progressive impairment in memory, judgment, language, and attention, among other cognitive domains (Morley, 2018). In United States, there was an increase in the prevalence of cognitive impairment among women from 18.7% in 1996 to 21.2% in 2014 and among men from 17.6% in 1996 to 21.0% in 2014 (Hale et al., 2020). It was determined from results analyzing 160 studies in a meta-analysis that dementia occurred at a pooled incidence of 17.2 per 1,000 person in a year in elder population aged 60 years or older (Fiest et al., 2016). A decline in cognitive abilities, especially cognitive impairments and their associated diseases, can have a profound effect on an individual, his or her family, and society in general (Wubker et al., 2015; Connors et al., 2019). Sleep factors, with unusual sleep patterns (i.e., short-sleep), poor sleep quality, and sleep disorder (e.g., insomnia) were associated with occurrence of cognitive impairment in the elderly.

In modern society, short-sleep in the elder population has become increasingly common. Sleeplessness and disturbed sleep appear to increase as people age, along with a decrease in good quality nocturnal sleep (Ohayon et al., 2004; Basner et al., 2007). In addition, plentiful evidence has shown that inadequate sleep had negative consequences on cognitive function (Hu et al., 2017; Xu et al., 2021; You et al., 2023c). One cross-sectional study using the UK Biobank data reported that short-sleep (<7 h) was associated with a significant decline in cognitive abilities in the elderly (Kyle et al., 2017). Over a 3-year follow-up, another population-based analysis of adults over 50 found that individuals who complained for sleep issues suffered accelerated cognitive deterioration than those who didn't (Jelicic et al., 2002). Given the significant breadth and impact of insufficient sleep on cognition among elders, there was an urgent need to find effective and practical solutions to these problems.

Studies have found that regular exercise and physical activity was an effective strategy to mitigate the cognitive decline in the elder group (Espeland et al., 2017; Dominguez et al., 2021). Physical exercise can improve memory, focus, and concentration (Chirles et al., 2017), as well as reduce the risk of neurological diseases (Rolland et al., 2008), cardiovascular diseases (Fletcher et al., 2005), diabetes (Sampath Kumar et al., 2019), and osteoarthritis (You et al., 2021b), which were all common among senior citizens. Furthermore, regular exercise has been demonstrated to improve overall mental health (Deslandes et al., 2009; You et al., 2021c), reduce stress (Stubbs et al., 2017), and improve sleep disturbance (You et al., 2023a), which can all have a positive effect on cognitive function. Hence, regular exercise is a simple and effective way to maintain cognitive health, decrease the prevalence of certain diseases, and elevate living standards for elderly people.

However, the effects of physical exercise on cognition in the elderly were not consistent. An epidemiological study showed that neither global nor domain-specific cognitive function improved with moderate-intensity physical exercise programs after 24 months (Sink et al., 2015). Contrarily, a single exercise session had no impact on cognition and even raised perceptions of stress (Hopkins et al., 2012). It is possible that these inconsistent findings are due to different study designs and confounding factors, particularly when the impact of sleep on elderly people is considered. Elderly people's cognitive abilities can be improved through exercise, while short sleep is associated with cognitive decline. To sum up, it is not only crucial but also interesting to explore the relationship between physical exercise and cognitive function under short-sleep conditions. Additionally, the evidence from large population-based studies is limited.

To the best of our knowledge, there was limited prior evidence that specifically examined whether physical exercise affected cognitive function in the community of elder groups with short-sleep conditions. In this study, by using a general sample from the National Health and Nutrition Examination Survey (NHANES), we aimed to: (1) examine the relationship between physical exercise and cognitive function in the short-sleep elder population; and (2) quantify its dose-response form and further assess the relationship by threshold analysis.

2. Materials and methods

2.1. Design and participants

Study data were from the National Health and Nutrition Examination Survey (NHANES), a comprehensive population-based survey intended to gather information about civilians in the United States (US). A multistage probability sampling design was applied to derive a typical selection of non-institutionalized households through the NHANES, which has been collected on approximately 10,000 people every two years since 1999. A research procedure of NHANES was approved by the Institutional Review Board (IRB) of the National Center for Health Statistics (NCHS), with written informed consent obtained.

Based on two cycles of "continuous NHANES" (2011/2012, 2013/2014), a total of 3,632 participants were initially included after excluding those less than 60 years old (n = 16,198). In addition, participants who slept less than 7 h were included in this study, leaving 2,126 samples for finally analysis. Subsequently, eligible participants needed to have complete data on cognitive tests. This resulted in an analytical sample of 1,833 survey participants. Finally, participants without covariates data were excluded from the analysis, leaving 1,615 samples for finally analysis (see **Figure 1**).

2.2. Exposure measurement

Self-reported sleep length was collected on usual weekdays or workdays. In NHANES year cycle 2011–2014, participants were asked about their routine sleep hours: "How much sleep do you get (hours)?" Referring to previous literature (Su et al., 2021), short-sleep duration was defined as ≤7 h per night. The Physical Activity Questionnaire was used to gather data on the exposure variable, physical exercise, during home interviews. Physical exercise was defined as leisure time physical activity (including sports, fitness, and other recreational activities), as opposed to work-related physical activities (which included paid and unpaid jobs, household chores, and yard work).

The metabolic equivalent of task (MET) for the specified activity was multiplied by the participants' reported weekly exercise time. To determine the MET-minutes per week, we used moderate and vigorous physical exercise (MVPE) measures. The Physical Activity Guidelines for Americans (PAGA) weighting mechanism was employed in the MVPE approach, where 2 min of moderate activity equated to 1 min of vigorous exercise (Ainsworth et al., 2000). Subsequently, the standard MET value of each activity was then multiplied by the overall amount of MVPE minutes per week to determine the MET-minutes per week. This method of quantifying physical exercise volume was also employed in earlier papers (You et al., 2022). Each level of exercise corresponded to a predetermined MET score, depending on whether reported as moderate (4 MET) or vigorous intensity (8 MET). Since the cumulative effects of a single exercise event may not be accurately reflected by a shift of 1 MET, exercise volume was described in terms of 100 MET as a unit of measurement (100*MET-min/week) in this study. In view of the fact that there was limited recommended physical activity guide for the elderly with short-sleep, the physical exercise volume was then categorized into three quantiles, none (<1 MET-min/week), low (from 1 to 360 MET-min/week), and moderate to vigorous (≥360 MET-min/week) for further analysis.

2.3. Cognitive function modules

The Animal Fluency test and the Digit Symbol Substitution test (DSST) were used to measure cognitive function in the NHANES. These assessments were conducted in a household interview or at a Mobile Examination Center (MEC). In the Animal Fluency test, which measured categorical verbal fluency and executive function, participants were instructed to name as many animals as they could in a minute. Processing speed, sustained attention, and working memory were evaluated using the Wechsler Adult Intelligence Scale (WAIS III) performance module called the DSST. This examination was administered using a paper form with a key located on top containing nine symbols and digits. A total of 133 symbols were displayed followed by numbers, and participants were asked to determine what each symbol represented in 2 min. Higher scores indicated greater cognitive function across all tests. The score was calculated as the total number of accurate matches. Detailed information about paradigm of the two cognitive tests was described in the **Supplementary material**.

2.4. Covariate assessment

Referring to the previous literature (Huang et al., 2021; You et al., 2023b), age, gender, race (non-Hispanic white, non-Hispanic black, Mexican American, and other races), marital status (never married, married or living with partner, widowed, divorced, or separated), family poverty income ratio [low income (<1), middle income (1,3), and high income (>3)], and educational attainment (below high school, high school, and college or above) were all extracted from the demographic questionnaire. Additionally, the questionnaires for smoking cigarettes and drinking alcohol were used to gather information about smoking status and alcohol intake status. According to the questionnaire replies, the status of alcohol use was divided into three categories: non-drinker, moderate alcohol use, and heavy alcohol use. Smoking status was classified as never, former, and current. Moreover, we evaluated the individuals' chronic diseases (Wang et al., 2023). Participants were deemed to have diabetes mellitus (DM) if they met the following criteria: (1) A doctor has diagnosed you with diabetes; (2) HbA1c (%) > 6.5; (3) fasting glucose (mmol/l) ≥ 7.0; and (4) random blood glucose (mmol/l) ≥ 11.1; (5) 2-h OGTT Blood Glucose (mmol/l) ≥ 11.1; (6) use of insulin or diabetes drugs. Self-reported congestive heart failure, coronary heart disease, angina, heart attack, or stroke were attributed to cardiovascular disease (CVD). Detailed covariate information was available at http://www.cdc.gov/nchs/nhanes/.

2.5. Statistical analyses

To comply with the NHANES protocol, all data were combined into a single dataset and analyzed using the masked variance

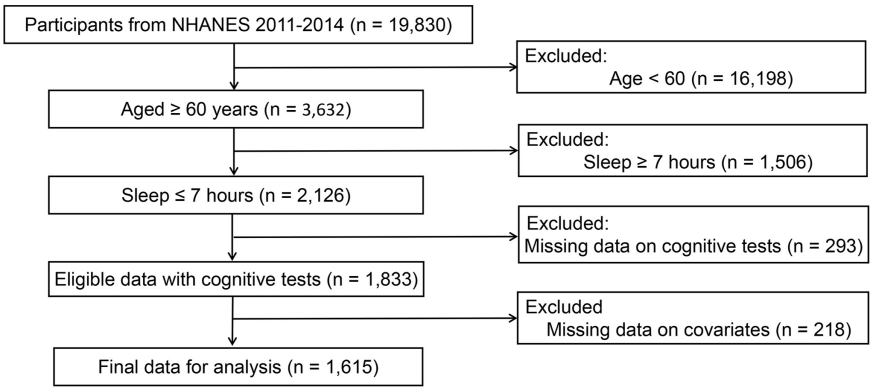


FIGURE 1
Flowchart depicting the selection strategy.

and weighting procedure. Using the weights from the Mobile Examination Center interviews, 4 years' worth of survey data from NHANES 2011 to 2014 were combined to address non-response, non-coverage, and unequal probabilities of selection. This strategy was consistent with the weight method of prior researches (Shen et al., 2019; You et al., 2022). The merged weights were calculated as $WT_{11-14} = (1/2) * WTMEC2YR_{11-12} + (1/2) * WTMEC2YR_{13-14}$, where WTMEC2YRs were variables from NHANES 2011–2014. In this study, we employed both multivariate adjusted and unadjusted models: Model 0 was adjusted for no covariates; Model 1 was adjusted for age, sex, race; Model 2 was adjusted for age, sex, race, marital status, education, poverty status, body mass index, smokers, alcohol drinkers, diabetes mellitus, and cardiovascular diseases.

Weighted linear regression model was used to investigate the association between physical exercise and test results for cognitive function. To explore the threshold impact and take into account any confounders, we constructed a model of two-piecewise linear regression. The threshold level of physical exercise (100 * MET-minutes/week) was determined using a recurrence method, which includes identifying the inflection point along a predefined interval and selecting the most likely inflection point. Using the log-likelihood ratio test, the two-piecewise linear regression model was compared to the one-line linear regression model. Simultaneously, the non-linear relationship was further evaluated using the restricted cubic spline (optimal knots = 3). Stratified analyses were conducted to explore the influence of covariates on the relationship between physical exercise and cognitive function. The R Foundation's software[1] was used for all statistical analyses, and a p value of 0.05 or less was regarded as statistically significant.

3. Results

In the final analysis, 1,615 participants aged 60 or older were included, and represented for a weighted population of 28,607,569. Table 1 displays the sociodemographic data of the study subjects. Study participants were an average of 68.79 years old, 47.17% of whom were male. The mean sleep length of all participants was 6.29 h per day. In addition, the average physical activity among total participants was 595 MET-minutes/week. For the cognitive function assessment, the mean score of the Animal Fluency test (reflecting verbal fluency and executive function) and the score of the Digit Symbol Substitution test (reflecting processing speed, sustained attention, and working memory) was 18.54 and 53.55, respectively.

Physical exercise and cognitive function test results were analyzed using a weighted linear regression model. As for the Animal Fluency test, when physical exercise was assessed as a continuous variable, Table 2 reveals that higher exercise volume was associated with better performance [Model 0, β (95% CI): 0.115 (0.085,0.144), $p < 0.001$; Model 1, β (95% CI): 0.099 (0.071, 0.128), $p < 0.001$; Model 2, β (95% CI): 0.077 (0.048, 0.106), $p < 0.001$]. Exercise was also associated with this outcome when assessed as a category variable. In the fully adjusted Model 2, taking the none exercise group as the reference, moderate to vigorous volume was positively associated with the Animal Fluency test scores [β (95% CI): 1.946 (1.126, 2.765), $p < 0.001$]. However, no significant association was identified in the low level physical exercise group. According to Supplementary Table 1, stratified analysis revealed that these associations were consistent across subgroups.

When it comes to the Digit Symbol Substitution test, similar findings are also identified in Table 2. Results showed that higher exercise volume was associated with higher scores of the Digit Symbol Substitution test when exercise volume was assessed as a continuous variable [Model 0, β (95% CI): 0.263 (0.152, 0.375), $p < 0.001$; Model 1, β (95% CI): 0.224 (0.119, 0.328), $p < 0.001$; Model 2, β (95% CI): 0.077 (0.048, 0.106), $p = 0.038$]. Also, this association persisted when exercise was assessed as a category variable. In the fully adjusted Model 2, using the reference group of those with no exercise, moderate to vigorous volume was positively associated with the Digit Symbol Substitution test performance [β (95% CI): 3.707 (1.325, 6.090), $p = 0.006$] in the Model 2. Additionally, a stratified analysis showed that these associations were consistent for subgroups with different demographic characteristics, as detailed in Supplementary Table 2.

An analysis of the log-likelihood ratio was performed to compare the one-line (non-segmented) model to the segmented regression model, and our results indicated a threshold existed. As for the Animal Fluency test (Table 3), based on a two-piecewise

1 http://www.R-project.org

linear regression model, we calculated that the inflection point was 960 MET-minutes/week. As seen on the left side of the inflection point, the β (95% CI) and *p*-value were 0.233 (0.154, 0.312) and < 0.001, respectively. On the right side of the inflection point, we found no significant association between physical exercise and cognitive test's score, with β (95% CI) and *p*-value of 0.013 (−0.027, 0.053) and 0.522. Similar results are also found in the Digit Symbol Substitution test (Table 4). The score of the test was positively correlated with physical exercise until it bottomed out at 800 MET-minutes/week [β (95% CI): 0.555 (0.332, 0.778), $p < 0.001$]. However, when the physical exercise volume was higher than 800, such association seemed to saturate [β (95% CI): −0.044 (−0.136, 0.048), $p = 0.349$]. In Figure 2, using restricted cubic splines, we flexibly modeled and visualized the relationship between cognitive performance and physical exercise volume among short-sleep elders. When exercise volume reached 9.6 and 8 (100*MET-minutes/week), there was a saturation effect where the effects of physical exercise on the Animal Fluency test and Digit Symbol Substitution test plateaued.

TABLE 1 Demographic characteristics of study participants in NHANES.

Variable	(%/Mean)*
Age	
<65	36.42
[65, 72)	32.34
≥72	31.24
Sex	
Male	47.17
Female	52.83
Race/ethnicity	
Non-hispanic white	76.99
Non-hispanic black	9.32
Mexican American	3.68
Other race/ethnicity	10.01
Marital status	
Never married	4.63
Married/living with partner	64.90
Widowed/divorced	30.47
Education	
Below high school	5.65
High school	30.62
College or above	63.72
Poverty income ratio	
<1	9.47
[1,3)	37.11
≥3	53.42
BMI (kg/m^2)	
<25	26.77
[25, 30)	34.41
≥30	38.82
Smokers	
Never smoker	50.96
Former smoker	37.24
Current smoker	11.80
Alcohol drinkers	
Non-drinker	36.11
Moderate alcohol use	57.68
High alcohol use	6.21
Diabetes mellitus	
No	68.81
Yes	31.19
Cardiovascular diseases	
No	79.42
Yes	20.58
Physical exercise (100*MET-minutes/week)	5.95 ± 0.48
Sleep duration (hours/day)	6.29 ± 0.03
Score of the Animal Fluency test	18.54 ± 0.26
Score of the Digit Symbol Substitution test	53.55 ± 0.67

*Weighted percentage for category variables and weighted Mean ± SE for continuous variables.
NHANES, National Health and Nutrition Examination Survey; BMI, body mass index; MET, metabolic equivalent of task.

4. Discussion

In this population-based study, physical exercise volume was found to be positively associated with the cognitive function in the short-sleep elders. Additionally, exercise and cognitive performance were found to be non-linearly correlated. The relationship was stated as follows: the scores of cognitive tests rose substantially with the expanded level of exercise, but reached a plateau after exercise volume at 960 MET-minutes/week for the Animal Fluency test and 800 MET-minutes/week for the Digit Symbol Substitution test. Our study detected that physical exercise had a threshold effect on cognitive function in short-sleep elders.

Our study identified a positive association between physical exercise volume and cognitive function in elderly individuals who get short amounts of sleep, which was consistent with a prior meta-analytic study in the aging population (Colcombe and Kramer, 2003; Lam et al., 2018). In several population studies (Spirduso and Clifford, 1978; Emery and Gatz, 1990), it was also verified that older high-fit individuals performed cognitive tests better than older low-fit individuals. While the mechanism of this association was not yet understood, it was clear that, in addition to improving cognitive function, exercise has been linked to increased expression of brain chemicals such as molecular mediators and growth factors represented by brain-derived neurotrophic factor (BDNF). Animal studies showed that exercise induces BDNF in the brain, most robustly in the hippocampal region (Cotman et al.,

TABLE 2 Associations between physical exercise and cognitive function in the short-sleep elder population.

	Model 0[a]		Model 1[b]		Model 2[c]	
	β (95% CI)	*p*-value	β (95% CI)	*p*-value	β (95% CI)	*p*-value
Score of the Animal Fluency test						
Physical exercise (100*MET-minutes/week)	0.115 (0.085,0.144)	< 0.001	0.099 (0.071, 0.128)	< 0.001	0.077 (0.048, 0.106)	< 0.001
Physical exercise (as category)						
None	Reference		Reference		Reference	
Low	0.503 (−1.247,2.253)	0.561	0.294 (−1.227, 1.815)	0.694	0.160 (−1.308, 1.629)	0.813
Moderate to vigorous	2.746 (1.847,3.645)	< 0.001	2.445 (1.596, 3.295)	< 0.001	1.946 (1.126, 2.765)	< 0.001
Score of the Digit Symbol Substitution test						
Physical exercise (100*MET-minutes/week)	0.263 (0.152, 0.375)	< 0.001	0.224 (0.119, 0.328)	< 0.001	0.077 (0.048, 0.106)	0.038
Physical exercise (as category)						
None	Reference		Reference		Reference	
Low	3.478 (−1.368, 8.325)	0.153	3.191 (−0.880, 7.262)	0.119	1.249 (−2.238, 4.736)	0.443
Moderate to vigorous	7.979 (4.952,11.007)	< 0.001	6.684 (4.244, 9.123)	< 0.001	3.707 (1.325, 6.090)	0.006

CI, confidence interval.
[a]Model 0, no covariates were adjusted.
[b]Model 1, age, sex, race were adjusted.
[c]Model 2, age, sex, race, marital status, education, poverty status, body mass index, smokers, alcohol drinkers, diabetes mellitus, and cardiovascular diseases were adjusted.

TABLE 3 Threshold effect analysis of the relationship between physical exercise and score of the Animal Fluency test in the short-sleep elders (based on Model 2).

	β (95% CI)
One-line linear regression model	0.077 (0.051, 0.103)
Two-piecewise linear regression model	
Exercise < 9.6 (100*MET-minutes/week)	0.233 (0.154, 0.312)
Exercise ≥ 9.6 (100*MET-minutes/week)	0.013 (−0.027, 0.053)
Log-likelihood ratio test	

Age, sex, race, marital status, education, poverty status, body mass index, smokers, alcohol drinkers, diabetes mellitus, and cardiovascular diseases were adjusted.

TABLE 4 Threshold effect analysis of the relationship between physical exercise and score of the Digit Symbol Substitution test in the short-sleep elders (based on Model 2).

	β (95% CI)
One-line linear regression model	0.099 (0.037, 0.163)
Two-piecewise linear regression model	
Exercise < 8.0 (100*MET-minutes/week)	0.555 (0.332, 0.778)
Exercise ≥ 8.0 (100*MET-minutes/week)	−0.044 (−0.136, 0.048)
Log-likelihood ratio test	

Age, sex, race, marital status, education, poverty status, body mass index, smokers, alcohol drinkers, diabetes mellitus, and cardiovascular diseases were adjusted.

2007). Neuronal cells' survival, differentiation, migration, dendritic arborization, synaptogenesis, and plasticity were all influenced by BDNF (Greenberg et al., 2009). This neurotrophin's molecular mechanism has been explored in a recent study that FNDC5, which was previously identified as a muscle protein induced by exercise, was elevated in the brain and might lead to better cognitive ability (Wrann et al., 2013). There was also a study that explored these effects from the molecular perspective that the benefits of exercise were attributed to the control of communications between BDNF, p-CREB, and NMDAR signaling, which was closely related to the brain function of spatial learning and memory (Wu et al., 2020).

From the dose-response investigation of the relation between exercise and cognitive function in short-sleep elders was performed, our study found that there was a threshold effect of exercise in this special group. The 2018 Physical Activity Guidelines indicated that there was still much to learn regarding how much physical exercise is necessary to enhance cognitive abilities (Erickson et al., 2019), and there lacked strong evidence that whether physical activity was always effective in improving the cognition, especially in short-sleep aged adults. Physical exercise appeared to have a threshold effect (no more than 800 MET-minutes/week) on cognitive function in short-sleep elders, with an increase in cognitive function observed when exercise volume was kept within such a level (800 MET-minutes/week volume exercise was equal to perform 200-min moderate intensity exercise or 100-minutes vigorous intensity exercise per week). This was a novel finding, considering that WHO Guidelines 2020 recommended elders to exercise for 150–300 min each week at a moderate level (WHO, 2020).

Consistent with our results, researchers using cohort data from the China Health and Retirement Longitudinal Study also discovered that moderate and mild physical exercise was linked to higher cognitive functioning, as opposed to vigorous exercise (Wu et al., 2021). Obviously, sleep plays an important role in cognitive function and lacking sleep may induce disorders of brain hormones and chemicals during daily executive activities. Moderate level exercise has been proposed to activate the reticulum system's arousal mechanism, thus improving various cognitive functions (Dietrich and Audiffren, 2011). Excessive exercise might, however, result in the prefrontal cortex being disengaged from higher-order functions due to greater activation of the premotor cortex and supplementary motor area. It was also found that vigorous exercise

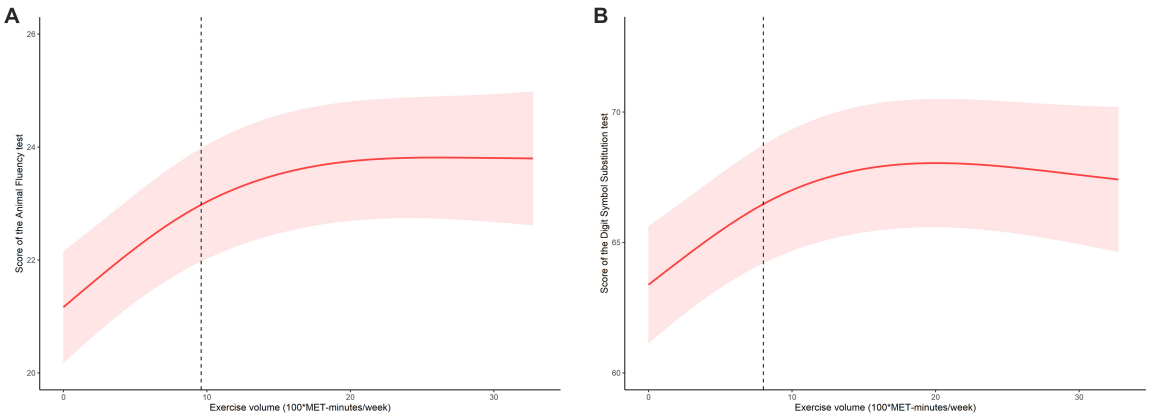


FIGURE 2
The dose-response relationship between exercise volume with the score of the Animal Fluency test **(A)** and score of the Digit Symbol Substitution test **(B)** in the short-sleep elders.

might be difficult for beginners and elders with concomitant diseases, and could lead to feelings of incompetence, failure, and low self-esteem (You et al., 2021a). Hence, exercise should be regulated, taking into account the individual's sleep habits and duration, to ensure the most beneficial effect on cognitive function.

The strengths of this study included that we used the study samples from a nationwide population. To our awareness, this was the initial research to examine the dose-response relationship between physical exercise and cognitive function in the specific short-sleep aged population. Exercise volume and cognitive performance associations were analyzed using adjusted weighted regression in consideration of the complex multistage sampling design of NHANES. In addition, threshold analysis was performed in order to quantify the dose-response form of the association. We also used the stratified analysis to further verify these results in consideration of confounding factors, including sociodemographic characteristics, BMI, smoking and alcohol drinking status, as well as chronic diseases.

It was also important to note that this study had the following limitations. Firstly, due to the NHANES' cross-sectional design, the causal or temporal relationship among these associations was still questionable in the elderly short-sleep population. There was also an assumption that elders with cognitive decline or impairment would unable to perform high volume of exercise activities. Secondly, in spite of the fact that we adjusted for possible confounders, residual confounding effects (i.e., biological and genetic factors) could still bias our results. Thirdly, the measurement of physical exercise was assessed by self-report questionnaires in NHANES design, which tended to be imprecise compared with objectively measured test such as the accelerometer (Barros et al., 2021). Moreover, the results of this study were only applicable to elderly people with short sleep, and additional research is needed in order to better understand sleep patterns and the effects of age. Lastly, it is unknown whether the pandemic or other public health emergencies will alter these associations. Research on the biological mechanisms of exercise and COVID-19 is therefore necessary to shed light on this population's cognition (Gonzales et al., 2022).

5. Conclusion

Utilizing the NHANES data, we assessed short-sleep older adults' physical exercise and cognitive function in this study. Physical exercise showed positive associations with performance on a test of Animal Fluency and a test of Digit Symbol Substitution. In addition, a dose-response-based analysis detected the threshold effect in the short-sleep elders, and performing no more than 800 MET-minutes/week exercise was positively associated with cognitive abilities. However, the underlying molecular mechanisms of such association remain unknown. Future research is needed to better understand the relationship between physical exercise and cognitive function in this population, as well as the potential mechanisms.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://wwwn.cdc.gov/nchs/nhanes/Default.aspx.

Author contributions

YY, YC, and XC designed the study and wrote the original draft manuscript. YY, YC, XC, MW, and JY reviewed and edited the revised version of manuscript, collected, analyzed, and interpreted the data. QZ and QC critically administrated, reviewed, and approved the manuscript. All authors read and approved the final manuscript.

Acknowledgments

The authors appreciate the time and effort given by participants during the data collection phase of the National Health and Nutrition Examination Survey (NHANES) project.

Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2023.1214748/full#supplementary-material

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frontiers | Frontiers in Neuroscience

TYPE Original Research
PUBLISHED 05 July 2023
DOI 10.3389/fnins.2023.1189590

OPEN ACCESS

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RECEIVED 19 March 2023
ACCEPTED 19 June 2023
PUBLISHED 05 July 2023

CITATION
Liu J, Lin T, Liu G, Dong X and Min R (2023) Risk factors for agitation in home-cared older adults with dementia: evidence from 640 elders in East China.
Front. Neurosci. 17:1189590.
doi: 10.3389/fnins.2023.1189590

Risk factors for agitation in home-cared older adults with dementia: evidence from 640 elders in East China

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Background: Agitation is common among older adults with dementia, negatively affecting their quality of life and their caregivers'. Since home care remains the dominant approach for older adults, this study investigates the risk factors for agitation in older adults with dementia in China.

Methods: We perform a cross-sectional study of home-cared older adults with dementia in Ningbo, China, using 2020 data. We use a self-made questionnaire to investigate the risks of agitated behavior and its related factors. We perform descriptive, univariate, and regression analyses.

Findings: We address 640 older Chinese adults; 42.8% of the sample exhibits one or more agitated behaviors. We find that basic health issues, such as activities of daily living (ADL), family support issues, such as Zarit Burden Interview (ZBI) scale and Family APGAR Questionnaire (APGAR), and behavioral awareness issues, such as fall and scald, significantly influence the occurrence of agitation behaviors (p<0.05). Older adults with severe ADL disorder (b=6.835, β=0.196, p<0.001), ZBI score of 67.00–88.0 (b=10.212, β=0.248, p=0.005), severe APGAR disorder (b=3.699, β=0.100, p=0.012) and a history of fall (b=9.311, β=0.199, P=<0.001) or scald (b=9.288, β=0.125, p=0.002) are more likely to exhibit agitated behaviors.

Interpretation: Agitated behavior in home-cared older adults with dementia are diverse and related to mental state, family support, and behavioral awareness issues. Caregivers, often family members, should be attentive to the needs of dementia patients and take active and effective measures to improve their quality of life. They should be aware of the causes and triggers of agitated behavior and take steps to reduce its occurrence.

KEYWORDS

agitation, elderly adults, dementia, home-cared, Cohen-Mansfield agitation inventory

1. Introduction

Dementia is a leading cause of disability in people older than 65 in China (Li et al., 2015; Charlson et al., 2016; Feigin et al., 2019). More than 55 million people live with dementia worldwide, and the number is expected to reach 78 million by 2030 (2022). In China, the incidence rate of dementia in older adults aged 60–69 years is 2.9%, and it reaches 31.9% in those

over 90 years old (Jia et al., 2020). With the aging of the Chinese population, the number of elderly patients with dementia has increased (Wang et al., 2019). According to the latest statistics, in 2019, over 15.33 million Chinese people had dementia, and the number is expected to reach 45.33 million by 2050 (Nichols et al., 2022). Along with cognitive and functional decline, roughly five out of every six patients, including those who are home-cared, exhibit behavioral and psychological symptoms in dementia (BPSD) (Ismail et al., 2016). In addition, within 2 years of dementia diagnosis, 20% of those who were initially asymptomatic will develop symptoms, while 50–80% of those with significant symptoms will stay agitated for several months (Hendriks et al., 2015). Furthermore, at least 50% of older adults with dementia have severe BPSD on a monthly (Ryu et al., 2005). Agitated behavior is one of the most prevalent and difficult BPSD, causing feelings of helplessness and distress in families and formal caregivers (Givens et al., 2015), as well as being a strong predictor of poor quality of life (Wetzels et al., 2010).

Agitated behavior is defined as inappropriate verbal, vocal, or motor activity and encompasses physical and verbal aggression (Cohen-Mansfield and Billig, 1986). Among those with moderate or severe dementia, approximately 50% of patients experience behavioral symptoms every month, and 70–90% exhibit at least one or more behavioral symptoms during onset, the most frequent being physical non-agitated behavior (Seitz et al., 2010). A family survey has reported that the incidence of dementia agitation exceeds 50% (Hamel et al., 1990). The recurring hospitalization of the elderly with dementia is mostly due to the emergence of agitation behavior, which places a great load on both the elderly and their caregivers (Wolf et al., 2018; Yilmaz and Aşiret, 2021). When the agitated behavior of older adults with dementia is severe, it may lead to violent and aggressive behavior, threatening the safety of themselves and their caregivers. In addition, since almost all dementia patients rely on others for care during their illness, especially family caregivers (non-professional caregivers) (Liu et al., 2017), exploring factors related to agitated behavior in dementia patients is critical for the safety of older people with dementia and their caregivers.

Individual factors, human nature, and the physical environment have a cumulative influence on the onset and progression of agitation in the elderly with dementia. Understanding these influencing factors can assist caregivers in avoiding as much inducement and aggravation factors as feasible in order to effectively prevent the occurrence and development of agitation behavior. According to the existing research, the main six factors that cause agitation in older people with dementia are as follows: (1) Basic demographic factors: Cohen-Mansfield and Marx (1992) discovered a higher incidence of speech agitation in women compared to males, whereas Schreiner found no gender difference (Schreiner, 2001). For older adults with dementia receiving nursing home care, married older adults showed more aggressive behavior than unmarried e older adults (Cohen-Mansfield and Marx, 1992). In addition, other studies have shown a positive correlation between age and verbal arousal (Pelletier and Landreville, 2007). (2) Disease-related factors: dementia type and disease severity are also significant determinants of agitation. Most studies indicate that the severity of the disease and the degree to which cognitive function is impaired correlates with the severity of the agitated behavior of the older adults with dementia, particularly the physical aggressive, physical non-aggressive, and verbal aggressive behaviors (Robitaille et al., 2015). (3) Mental and psychological factors: BPSD include behavioral symptoms such as agitation, emotional symptoms such as depression and anxiety, and mental symptoms such as hallucinations and delusions, among which behavioral symptoms are often accompanied by emotional symptoms and mental symptoms (Bessey and Walaszek, 2019). Studies have shown that the severity of mental symptoms in older adults with dementia is positively correlated with the severity of aggressive behavior (Volicer et al., 2012). (4) Social and cultural environment factors: the social participation of older adults with dementia and the surrounding cultural environment are also important factors affecting agitation behavior. Lack of activity and communication disorder can lead to aggressive behavior (Talerico et al., 2002; Kong, 2005). (5) Physical environment factors: the physical environment around the older adults with dementia is another important dimension of the factors affecting agitation behavior (Kong, 2005). It is critical to maintain a stable, quiet, and pleasant atmosphere, as well as adequate stimuli, in order for older adults with dementia to feel at ease and familiar, which is critical for controlling agitation behavior. Understanding these influencing factors can assist caregivers in avoiding as much inducement and aggravation factors as feasible in order to effectively prevent the occurrence and development of agitation behavior. Furthermore, the majority of current studies focus on the agitation behavior of older adults with dementia in nursing homes, with few investigations on home-cared older adults with dementia. However, the statistics released by Alzheimer's Disease International indicate that over 70% of older adults with dementia live at home (2022). Hence, the factors related to agitated behavior of dementia patients, especially those resorting to family support, should be explored. Reducing the occurrence of agitated behavior and improving the living conditions of patients with dementia are of utmost importance.

As the disease progresses, the majority of adults with dementia require care at home from family members (Van Den Wijngaart et al., 2007). Therefore, emotional support and life care from family members play a significant role in the occurrence of agitation in adults with dementia. This study investigated home-cared older adults with dementia and influencing factors of their aggressive behavior, which is crucial for reducing the incidence of dementia patients and improving the older adults' healthy life quality.

2. Materials and methods

2.1. Study design

This study conducted a cross-sectional analysis of data collected from three communities in Ningbo City, Zhejiang Province, in 2020 to investigate the risk factors for agitation in home-cared older adults with dementia. All participants provided informed consent before the questionnaire. The local ethics committee approved this study. The study protocol and content were approved by the Research Ethics Committee of the Ningbo College of Health Sciences (NBWY-2019-012).

2.2. Participant

Inclusion criteria: a. being older than 60 as per the local population census; b. conforming to the Diagnostic and Statistical Manual of

Mental Disorders, Fifth Edition (DSM-V) dementia diagnoses and being confirmed by clinicians; c. receiving home care; and d. willing to respond to the questionnaires.

Exclusion criteria: a. being under 60 years of age according to the local population census; b. Clinical Dementia Score (CDR) =0 or 0.5; c. receiving nursing home care or other non-home care.

2.3. Sampling

The sample size was calculated according to the survey sample size estimation formula for the current survey rate (Supplementary material). We removed questionnaire with missing age and sex, and missing CMAI score values of more than 10%. Finally, a total of 640 valid questionnaires were retained (Figure 1).

2.4. Study indicators

This study was conducted using a self-administered questionnaire based on a maturity scale. The questionnaire included three parts: the situation of older adults, assessment of agitation behavior, and potential risk factors (literature-learned). Specific questionnaire contents and indicators are in the (Supplementary material). The Cronbach's α of the questionnaire is 0.888, whereas the Kaiser–Meyer–Olkin (KMO) was 0.911.

2.4.1. Evaluation of agitation behavior

The Cohen Mansfield Agitation Inventory (CMAI) was used to evaluate agitation behavior of older adults with dementia. The CMAI has four dimensions and 29 items. Physical agitated behavior (12 items), physical non-agitated behavior (nine items), verbal agitated behavior (four items), and verbal non-agitated behavior (four items) (Cohen-Mansfield, 1986; Cohen-Mansfield et al., 1989; Lin et al., 2007). We rated the answers using a seven-point Likert Scale. The total score for agitated behavior ranged from 29 to 203 points; a total score ≥ 39 points indicated the existence of agitated behavior. The higher the score, the more severe the agitated behavior (Husebo et al., 2014). If at least two types of agitated behavior scored four points or above, or at least three scored three points or above, or at least four of scored two points or above, the behavior was considered agitated (Katz et al., 1963; Rabinowitz et al., 2005). The Cronbach's α for the CMAI is 0.931, whereas the Kaiser–Meyer–Olkin (KMO) was 0.931.

2.4.2. Basic health issues

We collected basic demographic information, including gender, age, marital status, education level of older adults, types of dementia and the number of chronic diseases.

Then, we used the activities of daily living (ADL) scale to evaluate the health status of participants. ADL has 10 items. Each item was rated as one to four, respectively. In line with the Barthel index score, more than 60 points represent good ability, 41–60 points denote moderate dysfunction and ≥ 40 points indicate severe dysfunction (Katz et al., 1963). The Cronbach's α for the ADL is 0.925, whereas the Kaiser–Meyer–Olkin (KMO) was 0.865.

2.4.3. Family support issues

Family support issues include number of children, education level of the caregiver, age of the caregiver and the caregiver's knowledge of dementia.

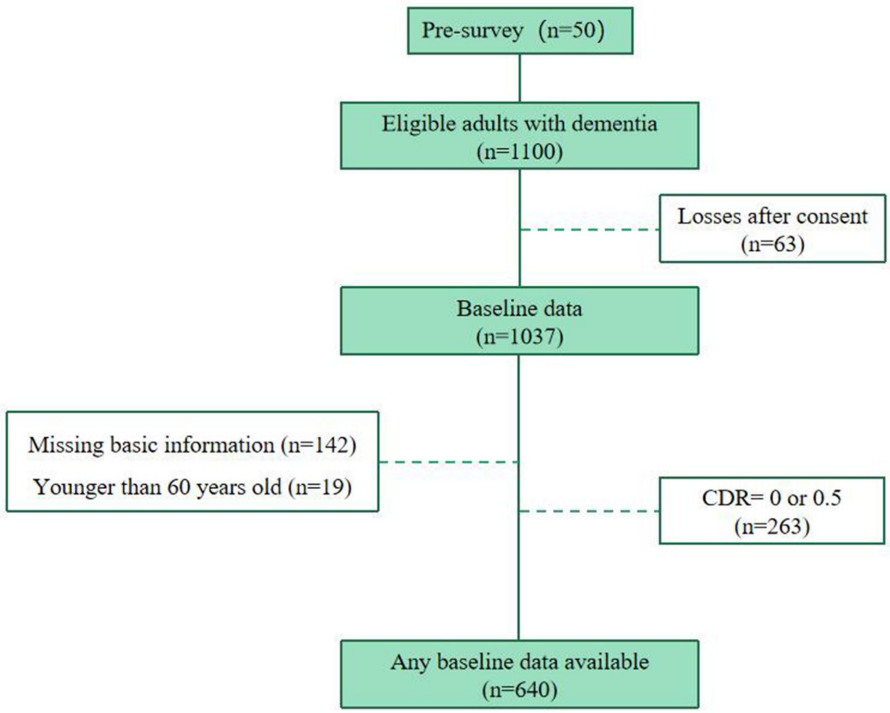

FIGURE 1
Baseline flow diagram of recruited older adults with dementia.

We used the Zarit Burden Interview (ZBI) scale to assess caregivers' feelings regarding the burden of caring for older adults with dementia at home. ZBI has four dimensions: caregiver health, mental state, and economic and social life. We considered 22 items, and each scored from zero to four points; a score of 21–40 and 41–60 points indicate no or mild burden and moderate or heavy burden, respectively (Zarit et al., 1980). The Cronbach's α for the ZBI is 0.953, whereas the Kaiser–Meyer–Olkin (KMO) was 0.949.

Besides, we used the Family APGAR Questionnaire (APGAR) to measure the subjective satisfaction of older adults to family functions. The Family APGAR Questionnaire has five items and three possible responses (2, 1, 0) to each item. The total scores may range from 0 to 10 (low to high satisfaction with family function) (Smilkstein et al., 1982). The Cronbach's α for the APGAR is 0.945, whereas the Kaiser–Meyer–Olkin (KMO) was 0.879.

2.4.4. Behavioral awareness issues

We used the University of Washington Clinical Dementia Score (CDR) to assess the severity of Alzheimer's disease (AD). The CDR is constructed from a semi-structured interview with the patient and a suitable informant and assesses impairment in each of six cognitive categories (Memory, Orientation, Judgment and Problem Solving, Community Affairs, Home and Hobbies, and Personal Care) using a five-point scale (Morris, 1993). From the six individual category ratings, clinical scoring rules determine the global CDR, with CDR 1, 2, or 3 indicating mild, moderate, or severe dementia (Morris, 1993). The Cronbach's α for the CDR is 0.935, whereas the Kaiser–Meyer–Olkin (KMO) was 0.899.

In addition, we measured whether the elderly had fallen, aspirated, scalded and fallen out of bed in the last 3 months.

2.5. Statistical methods

We used SPSS 27.0 software for statistical description and data analysis. We employed the Mann–Whitney U tests and Kruskal-Wallis H tests to determine whether each variable affected the risk of agitation in home-cared older adults with dementia ($p < 0.05$). After identifying the relevant factors as independent variables, we employed the CMAI score as the dependent variable. We used a multiple linear model to evaluate correlations with agitation ($p < 0.05$). We set the test's significance level at $\alpha = 0.05$ (Miller and Ulrich, 2019).

3. Results

3.1. Occurrence of four types of agitated behavior among home-cared older adults with dementia

In this study, 33.3% home-cared older adults had mild dementia, 29.7% had moderate dementia, and 37% had severe dementia (Table 1). We measure the risk of four types of agitated behavior in older adults with dementia using CMAI. The incidence of physical non-agitated behavior is the highest (37.0%), followed by physical agitated behavior (20.9%), verbal non-agitated behavior (13.0%), and verbal agitated behavior (10.5%). Moreover, as shown in Figure 2, approximately one-fourth of older adults with dementia exhibited two or more types of agitation simultaneously.

3.2. Associated factors of agitated behavior risk among home-cared older adults with dementia

The results of the one-factor analysis (Table 1) show that, in terms of the basic health issues, age, level of education, ADL of home-cared older adults with dementia were associated to the occurrence of agitation behavior ($p < 0.05$) (Table 1). In terms of the family support issues, ZBI, the education level of caregivers, the age of caregivers and APGAR were associated with agitated behavior ($p < 0.05$) (Table 1). Furthermore, in terms of the behavioral awareness issues, home-cared older adults with dementia who had fallen, aspirated, scalded, and fallen out of bed in the last 3 months were likely to have agitated behavior ($p < 0.05$) (Table 1).

3.3. Regression analysis of factors related to agitated behavior risk among home-cared older adults with dementia

We employed the basic health issues, family support issues and behavioral awareness issues as independent variable, and the CMAI score as dependent variable. We used a multiple linear model to evaluate correlations.

The regression analysis results (Table 2) show that, in terms of the basic health issues, the home-cared older adults with mild ADL disorder ($b = 5.197$, $\beta = 0.140$, $p = 0.007$), moderate ADL disorder ($b = 11.087$, $\beta = 0.228$, $p < 0.001$), and severe ADL disorder ($b = 6.835$, $\beta = 0.196$, $p < 0.001$) were more likely to exhibit agitated behavior than the older adults with dementia who received better home care with ADL. Moreover, older adults with a high school education ($b = -4.719$, $\beta = -0.129$, $p = 0.004$) were less likely to exhibit agitated behavior than the illiterate.

Then, in terms of the family support issues, home-cared older adults with ZBI score of 67.00–88.0 ($b = 10.212$, $\beta = 0.248$, $p = 0.005$) were more likely to exhibit agitated behavior than those with a ZBI score of 22.0 or lower. Additionally, older adults with moderate ($b = 3.827$, $\beta = 0.088$, $p = 0.018$) or severe family dysfunction ($b = 3.699$, $\beta = 0.100$, $p = 0.012$) were more likely to exhibit agitated behavior than those with healthy family function.

Furthermore, in terms of the behavioral awareness issues, older adults with dementia who had fallen ($b = 9.311$, $\beta = 0.199$, $P = <0.001$) or scalded ($b = 9.288$, $\beta = 0.125$, $p = 0.002$) in the past 3 months were more likely to have agitated behavior.

4. Discussion

After a multi analysis of home-cared older adults with dementia in Ningbo, China, we found that among the 640 elders, 37% have severe dementia, 37% show physical non-agitated behavior, and almost 1/4 exhibit two or more types of agitation simultaneously. The results of this study indicates that the basic health issues, family support issues and behavioral awareness issues of home-cared older

TABLE 1 One-factor analysis of risk factors associated with agitated behavior.

Variable		N (%)	Median	Test statistic	*p*-value
Basic health issues					
Gender	Males	297 (46.4%)	36.0 (29.0 ~ 50.0)	51497.500	0.808*
	Females	343 (53.6%)	35.0 (30.0 ~ 49.0)		
Age (in years)	60–74	204 (31.9%)	38.0 (31.0 ~ 53.0)	16.613	**<0.001**+
	75–89	361 (56.4%)	35.0 (29.0 ~ 48.0)		
	Above 90	75 (11.7%)	33.0 (29.0 ~ 40.0)		
Marital status	Married	308 (48.4%)	35.0 (29.0 ~ 48.5)	0.945	0.331*
	Single	328 (51.6%)	36.0 (30.0 ~ 50.0)		
Educational level of the elderly	Illiteracy	174 (27.2%)	39.0 (31.0 ~ 55.0)	15.180	**0.002**+
	Primary	247 (38.6%)	36.0 (29.0 ~ 51.0)		
	Middle	197 (30.8%)	33.0 (29.0 ~ 42.0)		
	University and above	22 (3.4%)	35.5 (29.0 ~ 51.0)		
Types of dementia	Alzheimer's disease	391 (71.2%)	35.0 (29.0 ~ 51.0)	6.245	0.100+
	Vascular dementia	33 (6.0%)	38.0 (30.0 ~ 57.0)		
	Mixed dementia	68 (12.4%)	39.5 (31.5 ~ 51.5)		
	Others	57 (10.4%)	33.0 (29.0 ~ 43.0)		
Number of chronic diseases	No	119 (18.7%)	33.0 (29.0 ~ 44.0)	7.341	0.025+
	A type	173 (27.1%)	36.0 (30.0 ~ 52.0)		
	Various kinds	346 (54.2%)	36.0 (30.0 ~ 50.0)		
Activities of daily living	Very mild	103 (16.1%)	29.0 (29.0 ~ 32.0)	93.348	**<0.001**+
	Mild	189 (29.6%)	37.0 (32.0 ~ 50.0)		
	Moderate	97 (15.2%)	43.0 (34.0 ~ 57.0)		
	Severe	250 (39.1%)	37.0 (29.0 ~ 53.0)		
Family support issues					
Number of children	0	60 (9.6%)	37.5 (32.0 ~ 51.0)	8.656	0.034+
	1	145 (23.2%)	33.0 (29.0 ~ 46.0)		
	2	207 (33.1%)	35.0 (29.0 ~ 49.0)		
	Above3	214 (34.2%)	37.0 (30.0 ~ 53.0)		
Zarit burden interview	≤22.00	19 (3.0%)	29.0 (29.0 ~ 35.0)	65.740	**<0.001**+
	23.00–44.00	176 (27.5)	32.0 (29.0 ~ 39.0)		
	45.00–66.00	283 (44.3%)	36.0 (30.0 ~ 46.0)		
	67.00–88.00	145 (22.7%)	49.0 (31.0 ~ 61.0)		
	Above89.00	16 (2.5%)	48.0 (32.0 ~ 72.5)		
Educational level of the caregivers	Illiteracy	39 (6.3%)	41.0 (30.0 ~ 60.0)	13.695	**0.003**+
	Primary	220 (35.4%)	35.0 (29.0 ~ 46.5)		
	Middle	285 (45.8%)	37.0 (29.0 ~ 43.0)		
	University and above	78 (12.5%)	33.0 (29.0 ~ 43.0)		
Age of the caregivers	Under 44	115 (18.1%)	35.0 (29.0 ~ 45.0)	21.792	**<0.001**+
	45–59	274 (43.2%)	37.0 (31.0 ~ 53.0)		
	60–74	159 (25.1%)	36.0 (30.0 ~ 53.0)		
	Above 75	86 (13.6%)	31.0 (29.0 ~ 43.0)		

(Continued)

TABLE 1 (Continued)

Variable		N (%)	Median	Test statistic	*p*-value
Caregiver knowledge	Not understood	166 (27.0%)	33.5 (30.0 ~ 51.0)	1.721	0.423+
	General	248 (38.8%)	35.0 (29.0 ~ 49.0)		
	See	201 (31.4%)	39.0 (30.0 ~ 50.0)		
APGAR	Mild	317 (50.2%)	32.0 (29.0 ~ 41.0)	66.282	**<0.001**+
	Moderate	119 (18.8%)	38.0 (31.0 ~ 48.0)		
	Severe	196 (31.0%)	43.0 (34.0 ~ 56.0)		
Behavioral awareness issues					
Clinical dementia rating	Mild	213 (33.3%)	35.0 (29.0 ~ 47.0)	3.658	0.161+
	Moderate	190 (29.7%)	34.0 (29.0 ~ 50.0)		
	Severe	237 (37.0%)	37.0 (31.0 ~ 50.0)		
Fall	No	534 (83.7%)	34.0 (29.0 ~ 45.0)	42501.500	**<0.001***
	Yes	104 (16.3%)	53.0 (41.0 ~ 65.0)		
Aspiration	No	549 (88.7%)	34.0 (29.0 ~ 46.00)	27261.500	**<0.001***
	Yes	70 (11.3%)	52.5 (38.0 ~ 61.0)		
Scald	No	575 (94.3%)	35.0 (29.0 ~ 47.0)	15848.000	**<0.001***
	Yes	35 (5.7%)	58.0 (46.0 ~ 73.0)		
Falling out of the bed	No	569 (93.3)	35.0 (29.0 ~ 47.0)	18446.000	**<0.001***
	Yes	41 (6.7%)	58.0 (44.0 ~ 72.0)		

Data are expressed as median (interquartile range). *P*-value < 0.05 indicates stat. *Mann-Whitney *U*-tests; +Kruskal-Wallis H tests. Bold values are statistically significant.

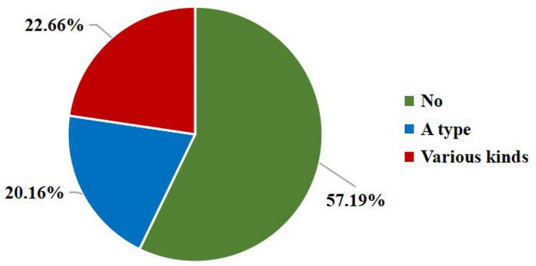

FIGURE 2
The occurrence of four types of agitated behavior in the older adults with dementia.

adults with dementia have an impact on the occurrence of their agitated behavior. Further analysis of these influencing factors is of great significance for the study of home care for the older adults with dementia.

4.1. Analysis of the current situation in home-cared older adults with dementia

This study indicated that home-cared older adults with dementia were slightly more likely to exhibit two or more agitated behaviors (22.7%) than to exhibit only one agitated behavior (20.2%). In addition, among the four agitated behavior, the incidence of physical non-agitated behavior was the highest (37.0%), followed by physical agitated behavior (20.9%), which may be owing to the fact that family caregivers are more likely to observe volatile, transient, and minor behaviors, such as physical non-agitated behaviors such as repetitive movements and verbal non-agitated behaviors such as repetitive sentences, than professional nursing staff, such as nurses, who contribute attention to behaviors that affect nursing work or daily management, such as physical agitated behaviors (Dukas, 2020).

Physical non-agitated behavior is associated with the older adults' incapacity to express their needs or lead a monotonous lifestyle, reflecting the older adults' need for social opportunities or physical exercise (Altunöz et al., 2015). Verbal non-agitated behavior is linked with the caregiver providing care without communicating with the patient, and repeated sentences or inquiries had been most prevalent, consistent with memory loss in patients with cognitive dysfunction (Isaac et al., 2021). Therefore, family caregivers of home-cared older adults with dementia should pay more attention to the social requirements and mutual communication of older adults.

4.2. The impact of basic health issues on agitated behavior in home-cared older adults with dementia

Due to memory, learning, thinking, spirit, and other aspects of the disorder, older adults with dementia frequently lose the ability to care for themselves. Previous studies have shown that the occurrence and persistence of agitation behavior in dementia patients is significantly related to the decline of daily living ability (Beck et al., 1998). In this study, we used the ADL scale to assess the daily living ability of older adults, and the results of multiple regression also showed that the lower

TABLE 2 Multiple disorderly regression of the risk factors associated with agitated behavior.

Variable	Unstandardized coefficients	Standardized coefficients	*P*-value
Basic health issues			
75–89 years old of the elderly	−4.127 ± 1.360	−0.120	**0.003**
Above 90 years old of the elderly	−9.272 ± 2.169	−0.175	**<0.001**
Activities of daily living = 2.00	5.197 ± 1.912	0.140	**0.007**
Activities of daily living = 3.00	11.087 ± 2.258	0.228	**<0.001**
Activities of daily living = 4.00	6.835 ± 1.897	0.196	**<0.001**
Primary school education level of the elderly	−3.019 ± 1.545	−0.087	0.051
Middle school education level of the elderly	−4.719 ± 1.647	−0.129	**0.004**
University and above education level of the elderly	−0.597 ± 3.407	−0.006	0.861
Family support issues			
Zarit burden interview = 23.00–44.00	−0.409 ± 3.402	−0.011	0.905
Zarit burden interview = 45.00–66.00	2.666 ± 3.402	0.078	0.434
Zarit burden interview = 67.00–88.00	10.212 ± 3.591	0.248	**0.005**
Zarit burden interview = Above89.00	8.577 ± 5.089	0.077	0.092
Primary school education level of the caregiver	−1.306 ± 2.394	−0.037	0.586
Middle school education level of the caregiver	1.909 ± 2.390	−0.056	0.425
University and above education level of the caregiver	−3.071 ± 2.885	0.060	0.288
45–59 years old of the caregiver	−0.0.071 ± 1.662	−0.002	0.966
60–74 years old of the caregiver	0.942 ± 1.786	0.025	0.598
Above 75 years old of the caregiver	−2.867 ± 2.541	−0.045	0.260
Moderate family dysfunction	3.827 ± 1.617	0.088	**0.018**
Severe family dysfunction	3.699 ± 1.476	0.100	**0.012**
Behavioral awareness issues			
Fall	9.311 ± 1.960	0.199	**<0.001**
Aspiration	−1.095 ± 2.208	−0.496	0.620
Scald	9.288 ± 3.042	0.125	**0.002**
Falling out of the bed	4.266 ± 3.092	0.061	0.168

Bold values are statistically significant.

the ADL of home-cared dementia patients, the higher the agitation score. The possible reason is that home-cared older adults with dementia who are better at daily living have more opportunities to interact with others and engage in physical activity, but the loss of daily living abilities makes it difficult for older adults to comprehend environmental stimulation, causing agitation (Lin et al., 2009). This finding reveals that as the disease progresses, home-cared older adults with dementia will require increasing assistance with activities of daily living, caregivers should communicate with the older adults with more patience and actively engage them in necessary physical activity and socialization.

4.3. The effects of ZBI and APGAR on agitated behavior in home-cared older adults with dementia

In China, due to the inequalities of the current medical security system and the impact of traditional family culture, home-based care has always played an essential role. In this study, about 50.1% of home-care providers for older adults with dementia are their spouses and children. When older adults with dementia reside with their families, family interventions (particularly family caregivers) can influence the disease's progression or improvement to some extent. As the primary healthcare provider for older adults, family caregivers are responsible for providing a variety of nursing and support services. Long-term and intensive care will bring great burden to caregivers (Xiao et al., 2014). Previous research has demonstrated that the living conditions, care-giving abilities, and physical and mental health of caregivers have a direct impact on the quality of life and prognosis of older adults with dementia (Norton et al., 2013; Park et al., 2015). In this study, we use ZBI to assess the burden of care-giving across four dimensions: health, mental state, economic difficulties, and social life. The results indicated that dementia patients with a ZBI greater than 67 are more likely to exhibit agitated behavior than those with a ZBI of less than 23. Family can provide practical support for the elderly, but an increase in family burden will have a negative effect on the progression of dementia in the elderly. Continuous support and assistance for family caregivers can reduce

care-giving stress and improve their quality of life, as well as improve the health of older adults.

Additionally, for home-cares, daily life support is essential, but emotional support from family members should also be considered. In the context of the Chinese family pension, family is the primary or even sole focus of the social activity of older adults in their homes. The reactions of family caregivers to the emotions of the elderly, as well as how they interact with one another, have a significant impact on the emotional fluctuations of the elderly. In this research, we find that compared to older adults with well APGAR, those with moderate or severe APGAR were more likely to exhibit agitated behavior. Previous studies have also found that almost all variables of family dynamics (family satisfaction) are significantly associated with all variables of mental health for caregivers, for example, caregivers' mental health is stronger when their family functions well (Sutter et al., 2014). As a result, family caretakers should pay more attention to methods and encouragement when interacting with the elderly. For example, when the elderly desire to participate in new activities or develop, family members should give their full approval and support.

4.4. Fall and scald are more likely to trigger agitated behavior in home-cared older adults with dementia

This study showed that older adults with dementia who had fallen or scalded in the last 3 months are more likely to have agitated behavior, which is probably because the patient's physical injury will affect the patient's mental state, and then cause the occurrence of provocative behavior. For example, approximately 5–15% of the elderly will sustain brain injuries, soft tissue contusions, dislocations, and other similar injuries as a result of falls (Katz et al., 2004). Furthermore, older adults with a high risk of falls and scalds have sequelae such as mobility disorders induced by some cerebrovascular diseases, which will also contribute to the occurrence of agitated behavior. Previous studies have also shown that there is a correlation between agitated behavior and the occurrence of falls in dementia patients (Katz et al., 2004; Dong et al., 2022). As a result, during the care process, we must also attach importance to avoid the occurrence of high-risk behavior that will harm the older adults' physical health. For instance, the caregivers should inspect the indoor furniture and lighting every week, increase the bar and lighting in the indoor area where the older adults frequently engage in activities to reduce the risk of falls, adjust the height and placement of the kettle to reduce the risk of scalds, and more. Additionally, the older adults with dementia should avoid going to crowded locations and being outside when it is raining or snowing.

4.5. Limitations and prospects

Some limitations can be pointed from this study. Firstly, our study is a cross-sectional study and only surveyed in one city, which makes the representativeness of the sample may be insufficient. Secondly, we have only explored basic health issues, family support issues, behavioral awareness issues, and there is insufficient research on the living environment of dementia patients.

As we know, agitated behaviors are diverse and closely related to mental state, family support and caregivers' burden. The results of this study, demonstrating that the occurrence of agitated behavior is related to the ADL, ZBI, APGAR. For the home-cared older adults with dementia, their caregivers, such as relatives and adult children, should pay attention to the company of older adults with dementia, the causes and rules of dementia older adults' anxiety behaviors, and take active and effective coping ways to improve the quality of life of older adults with dementia.

Data availability statement

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

Author contributions

RM planned the study and the overall analysis method. JL and TL substantially contributed to acquisition and interpretation of data and writing of the manuscript. GL and XD contributed to data analysis and data collation. All authors contributed to the article and approved the submitted version.

Funding

This study was supported by the Fundamental Research funds for the Central Universities (HUST:2020kfyXJJS057) and the Natural Science Foundation of Zhejiang Province (LQ20H260006).

Acknowledgments

We would like to thank Editage (www.editage.co.kr) for English language editing.

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/fnins.2023.1189590/full#supplementary-material

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frontiers | Frontiers in Neuroscience

TYPE Review
PUBLISHED 05 July 2023
DOI 10.3389/fnins.2023.1206491

OPEN ACCESS

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RECEIVED 15 April 2023
ACCEPTED 12 June 2023
PUBLISHED 05 July 2023

CITATION
Yu S-j, Tang H-l, Li W-h, Bin C-l, Liu Z, Tang Z-h and Liang J-h (2023) Donepezil combined with traditional Chinese medicine has promising efficacy on mild cognitive impairment: a systematic review and meta-analysis.
Front. Neurosci. 17:1206491.
doi: 10.3389/fnins.2023.1206491

Donepezil combined with traditional Chinese medicine has promising efficacy on mild cognitive impairment: a systematic review and meta-analysis

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Objective: Prior research has shown mixed results regarding the effectiveness of combining donepezil and traditional Chinese medicine (TCM) to treat mild cognitive impairment (MCI). In light of this, our study aims to examine the efficacy and safety of this treatment approach for patients with MCI.

Methods: We conducted a comprehensive search of various databases, including Medline (*via* PubMed), Cochrane, Embase, Web of Science, Chinese National Knowledge Infrastructure, Chinese Biomedical Literature Database, Chinese Scientific Journal Database, and Wanfang Database from their inception to November 16, 2022. The selection of studies, risk of bias assessment, and data extraction were carried out independently by two authors. The statistical analysis was performed using STATA.

Results: Our meta-analysis included a total of 35 studies with 2,833 patients, published between 2008 and 2022, with intervention durations ranging from 4 weeks to 12 months. However, most of the studies had a high risk of detection bias. Our findings indicated that the combination of donepezil and TCM significantly improved the Montreal Cognitive Assessment (MoCA) score (weighted mean difference [WMD] = 2.79, 95% confidence interval [CI]: 1.82 to 3.75) and the Barthel Index score (WMD = 9.20, 95% CI: 5.39 to 13.00) compared to donepezil alone. However, subgroup analyses showed that the MoCA score did not increase significantly in patients with MCI resulting from cerebrovascular disease (WMD = 1.47, 95% CI: −0.02 to 2.96).

Conclusion: The combination of donepezil and TCM may have a more positive effect on cognitive function and activities of daily living in patients with MCI compared to the use of donepezil alone. However, due to the limited quality of the studies included in our analysis, these findings should be interpreted with caution.

KEYWORDS

mild cognitive impairment, traditional Chinese medicine, donepezil, meta-analysis, systematic review

1. Introduction

Mild cognitive impairment (MCI) is a cognitive state that falls between normal aging and early dementia (Petersen, 2004). It is characterized by cognitive deficits in at least one domain accompanied by a slight decline in instrumental activities of daily living (Petersen et al., 2018). Along with this, MCI also causes decreased living quality, depression, and avoidant coping strategies like withdrawal from social engagement. These features are major indicators of MCI (Anderson, 2019). The prevalence of MCI tends to rise with age, ranging from 6.7% in individuals aged 60 to 65 to 25.2% in those aged 80 to 84 (Petersen et al., 2018). Furthermore, individuals with MCI have a higher risk of developing dementia compared to their age-matched healthy counterparts (Petersen, 2004; Petersen et al., 2018). A recent meta-analysis of epidemiological studies has revealed that the prevalence of MCI among the Chinese population aged 50 and above is 15.4% (Deng et al., 2021). With the global population aging rapidly, many countries, including China, are facing the challenge of MCI. By 2040, the number of senior citizens in China is projected to reach 402 million, accounting for approximately 28% of the population (Lancet, 2022). Therefore, it is crucial to prioritize interventions for MCI in order to improve the quality of life for patients, reduce the incidence of dementia, and alleviate the economic and medical burdens on society.

The demand for pharmacotherapy among patients with MCI and their families has increased significantly (Tricco et al., 2013). Donepezil, a commonly used Western medicine (WM) for improving cognition in MCI clinical research, has been found to have limited effects on cognitive function in patients with MCI and is associated with more adverse events (AEs), according to a recent meta-analysis (Zhang X. et al., 2022). Research on finding new treatments for patients with MCI has become a popular topic in recent times. In recent years, traditional Chinese medicine (TCM) has gained significant attention in treating MCI due to its better efficacy and fewer AEs (Pei et al., 2020). Modern studies have shown that TCM has multiple benefits in improving cognitive function, including regulating the central cholinergic system, reducing hippocampal oxidative stress, and protecting cerebral blood vessels (Pei et al., 2020). From an integrated WM and TCM perspective, we believe that the combination of donepezil and TCM may provide greater benefits in treating patients with MCI than donepezil alone. Research (Di et al., 2017) has shown that combining donepezil with *Ginkgo Biloba* extract tablets effectively improved cognitive function in patients with MCI and delayed the progression to Alzheimer's disease (AD) when compared to donepezil alone. Similarly, another study (Shou et al., 2022) has found that combining donepezil with modified Shenghui decoction was superior to using donepezil alone in improving cognitive function and daily activities in patients with MCI. Several trials have suggested that the combination of donepezil and TCM may be more effective than donepezil alone in treating patients with MCI. However, the results of these trials are still controversial and inconclusive (Liu et al., 2008; Dong, 2015; Luo, 2019; Yang, 2021). Currently, there is no high-quality summary of the efficacy and safety of this combination therapy. This highlights the need for further research in this area. Previous meta-analyses investigating TCM on patients with MCI have had limitations that need to be addressed. First, previous studies on the efficacy of TCM on patients with MCI had methodological flaws that may have affected their results. For instance, some studies included participants with different conditions such as patients with MCI and dementia (Yang et al., 2016), or age-associated memory impairment (May et al., 2009). Additionally, other studies had diverse comparators including placebos, no intervention, and other therapies (Liang et al., 2022). These deficiencies were caused by the lack of strict eligibility criteria which resulted in high heterogeneity among the included studies and concealed the true efficacy of TCM on patients with MCI. Second, previous studies have mainly focused on the effects of TCM on cognitive function in patients with MCI, with limited attention given to other outcomes such as activities of daily living (Dong et al., 2019; Wang W. et al., 2021). This incomplete investigation of result indicators can hinder clinicians from fully understanding the effects of TCM on patients with MCI, thereby limiting their ability to make informed clinical decisions. Third, previous studies had limited published trials and participants (Wang W. et al., 2021) which may affect the reliability of their results. With the recent increase in relevant research (Li et al., 2022; Shou et al., 2022), it is necessary to update evidence. Therefore, we will use the meta-analysis method to quantify the efficacy and safety of donepezil combined with TCM on patients with MCI, guided by the theory of WM and TCM. This will provide more advanced, objective, and reliable evidence-based medical evidence for clinical decision-making and policy development. Due to the limitations of previous research on TCM in treating patients with MCI, we will conduct an extensive search, formulate rigorous inclusion criteria, and perform a more comprehensive and in-depth exploration.

2. Methods

Our study adhered to the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; Page et al., 2021) and the Cochrane Handbook for Systematic Reviews of Interventions (Cumpston et al., 2019). As all data analyzed were from previous studies, ethical approval and patient consent were not required.

2.1. Literature search

To assess the effectiveness and safety of donepezil combined with TCM in treating patients with MCI, an extensive search was conducted in eight electronic databases: Medline (*via* PubMed), Cochrane, Embase, Web of Science, Chinese National Knowledge Infrastructure, Chinese Biomedical Literature Database, Chinese Scientific Journal Database, and Wanfang Database. The search included studies published from the inception of these databases until November 16, 2022 and only randomized controlled trials (RCTs) were considered. To broaden the search, we used a combination of Medical Subject Headings (MeSH) and free text terms, merged using Boolean logical operators as detailed below: "cognitive dysfunction," "mild cognitive impairment," "traditional Chinese medicine," "Chinese patent medicine," "donepezil," and "randomized controlled trial." The search strategies used are presented in detail in Supplementary Table 1. To ensure comprehensive coverage, we conducted additional searches for relevant studies using various sources, including similar systematic reviews and meta-analyses, grey literature such as noncommercial

dissertations and government documents, and relevant journals such as Frontiers in Neuroscience, Nature Neuroscience, Chinese Journal of Neurology and Chinese Journal of Nervous and Mental Diseases, as well as major conferences.

2.2. Eligibility criteria and literature screen

Eligibility criteria were developed based on the PICOS principle (participants, interventions, comparators, outcomes, and study design).

1) Participants: The inclusion criteria for the studies were limited to participants diagnosed with MCI, whereas studies involving other forms of cognitive dysfunction, such as dementia, were excluded from the analysis.
2) Interventions: The studies considered in this analysis involved the use of donepezil in combination with TCM, specifically Chinese herbal compounds, Chinese patent medicine, single Chinese herbs, and their extracts. The TCM was administered in various forms such as decoction, granule, tablet, capsule, powder, or injection. Studies that solely employed TCM or donepezil in conjunction with non-pharmacological therapies like acupuncture were excluded from this analysis.
3) Comparators: For the purpose of our study, we only considered cases where the control group received a comparable dosage of donepezil. We did not include studies where the control group received no intervention, a placebo, or other medications.
4) Outcomes: This study included primary outcomes related to clinical effectiveness (CE), cognitive assessment tools such as the Mini-mental State Examination (MMSE; Folstein et al., 1975) and the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005). Additionally, secondary outcomes were measured using the TCM syndrome scale (TCMSS; Zhuang et al., 2022), the Barthel Index (BI; Mahoney and Barthel, 1965), and AEs.
5) Study design: Our study encompassed all forms of RCTs without limitations on language, region, or publication date. However, we excluded review articles, meta-analyses, case reports, and observational studies from our analysis.

The literature screening process was conducted by two independent authors, with any disagreements resolved by the corresponding author. All studies were managed and screened using EndNote (Version 20.2). Duplicate papers were removed initially, followed by the elimination of irrelevant files through title and abstract browsing. Full-text screening was then conducted on the remaining documents to identify eligible studies.

2.3. Data extraction

Based on the Cochrane data extraction criteria (Cumpston et al., 2019), two authors separately extracted key data from the studies, including (1) basic information such as lead author, publication date, region of the trial, etc.; (2) patient characteristics like age, gender, disease course, etc.; (3) treatment methods: the experimental and control groups; (4) literature quality: collect the relevant content based on the Cochrane Risk of Bias (ROB) tool (Cumpston et al., 2019); (5) outcomes: the number of CE and AEs as well as the pre- and post-treatment scores of the MMSE, MoCA, TCMSS, and BI. Any discrepancies were resolved through discussion.

2.4. Quality assessment

To evaluate the quality of the studies, the ROB tool (Cumpston et al., 2019) was employed, which consisted of the following seven items: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias. The level of bias risk for each item was graded as low, unclear or high. For selection bias, we scrutinized the study's method for generating random sequences and the rigorous assignment of patients with MCI based on random numbers. We also examined whether the study used blind methods for researchers, participants, and evaluators to minimize performance and detection biases. Additionally, we evaluated whether the study had a significant amount of missing data, only reported favorable outcomes, or had other factors that could affect results. The ROB figures were generated using Review Manager (Version 5.4), and two authors independently evaluated the ROB of the included studies. Any discrepancies were settled by the corresponding author.

2.5. Statistical analyses

In accordance with the Cochrane Collaboration Handbook (Cumpston et al., 2019), we conducted a conventional paired meta-analysis of the included studies. To calculate the pooled effect size for the dichotomous variable, we utilized relative risk (RR) and 95% confidence interval (CI) while for a continuous variable, we employed weighted mean difference (WMD) and 95% CI. We assessed heterogeneity among the studies using the Cochran Q-test and I^2 statistic (Cumpston et al., 2019). If the p-value was greater than 0.1 for the Q-test and the I^2 statistic was less than 50%, indicating acceptable heterogeneity, we reported the fixed effect model. Otherwise, we reported the random effect model (Higgins and Thompson, 2002; Higgins et al., 2003). To account for potential publication bias, we evaluated the funnel plot for asymmetry and the p value of less than 0.05 (Egger et al., 1997, 2003). To investigate the impact of various factors on results and possible sources of heterogeneity, we divided the data into seven subgroups before conducting statistical analyses. These subgroups were based on intervention duration ($<$ 24 weeks vs. $\geq$ 24 weeks), region (developed vs. undeveloped), publication year ($\leq$ 2018 vs. $>$ 2018), total sample size ($<$ 100 vs. $\geq$ 100), male to female ratio ($\geq$ 1 vs. $<$ 1), pathogenesis (MCI caused by Parkinson's disease [MCI-PD] vs. MCI resulting from cerebrovascular disease [MCI-CVD] vs. MCI due to vascular risk factors [MCI-VRF]), and disease course ($\leq$ 2 years vs. $>$ 2 years). To ensure the reliability of our results, we conducted sensitivity analyses by excluding one study at a time. The statistical analyses were carried out using STATA (Version 14.0).

3. Results

3.1. Literature selection and characteristics of the included studies

In this study, we collected 1,150 papers, out of which 1,140 were from target databases and 10 were manually retrieved. After eliminating 197 duplicates and 802 irrelevant articles based on title and abstract screening, we reviewed the full text of the remaining 151 articles. Of these, 116 studies were excluded because they were mixed with other types of cognitive dysfunction (76 items), only used TCM or donepezil combined with acupuncture as interventions (38 items), or lacked appropriate outcomes (2 items). Finally, we included 35 RCTs in our review (Liu et al., 2008; Yang et al., 2011; Li and Zhou, 2014; Shen, 2014; Wang et al., 2014; Ye and Feng, 2014; Dong, 2015; Guan et al., 2015; Liu, 2015; Liu and Liu, 2015; Su et al., 2015; Xie and Chen, 2015; Yu, 2016; Di et al., 2017; Gao et al., 2017; He et al., 2017; Gu, 2018; Wang et al., 2018; Luo, 2019; Qian, 2019; Yang, 2019; Gan et al., 2020; Han, 2020; Li and Wang, 2020; Liu, 2020; Zhang, 2020; Wang X. et al., 2021; Yang, 2021; Zhang et al., 2021; Zhou and Du, 2021; Li, 2022; Li et al., 2022; Shou et al., 2022; Wen, 2022; Zhi, 2022). The study selection process is detailed in Figure 1. All RCTs were conducted in China between 2008 and 2022, with a total of 2,833 participants enrolled. The mean age of participants ranged from 51.17 (3.98) to 80.05 (3.40) years, with a lower proportion of female patients (44.18%) than male patients (55.82%; one study was not reported). The number of participants in each study ranged from 30 to 126 and the intervention duration varied from 4 weeks to 12 months. Table 1 provides a summary of the characteristics of the included studies.

3.2. Quality of the included studies

This study examines the quality of various studies on random sequence generation, and most studies had low risk except for high risk study conducted by Zhang (2020). Allocation concealment was unclear risk across all studies, while performance bias was mostly unclear risk except for one (Xie and Chen, 2015) high risk. Detection bias was mostly high risk, with only one (Yang, 2021) study judged as low risk. Attrition bias risk was low in all studies, and reporting bias was mostly low risk, except for one high risk study (Yang et al., 2011). The majority of trials had low risk when considering other bias, except for five high risk studies (Shen, 2014; Ye and Feng, 2014; Liu, 2015; Liu and Liu, 2015; Yu, 2016). Figure 2 and Supplementary Figure 1 provide detailed quality assessment results.

3.3. Primary outcomes

The effectiveness of combining donepezil with TCM on CE was evaluated in 21 studies involving 1,708 participants (Wang et al., 2014; Dong, 2015; Guan et al., 2015; Liu, 2015; Xie and Chen, 2015; Di et al., 2017; Gao et al., 2017; He et al., 2017; Luo, 2019; Qian, 2019; Yang, 2019; Han, 2020; Li and Wang, 2020; Liu, 2020; Wang X. et al., 2021; Zhang et al., 2021; Li, 2022; Li et al., 2022; Shou et al., 2022; Wen, 2022; Zhi, 2022). The results showed that donepezil combined with TCM significantly increased CE compared to donepezil alone (RR = 1.15, 95% CI: 1.06 to 1.25, $p > 0.999$, $I^2 = 0.00\%$, fixed model; as shown in Table 2). However, the asymmetrical funnel plot (refer to Figure 3) and Egger's test ($p < 0.05$) suggested potential publication bias.

The cognitive function of 2,539 participants was assessed in 31 studies using the MMSE (Liu et al., 2008; Yang et al., 2011; Li and Zhou, 2014; Shen, 2014; Wang et al., 2014; Ye and Feng, 2014; Dong, 2015; Guan et al., 2015; Liu, 2015; Liu and Liu, 2015; Xie and Chen, 2015; Yu, 2016; Di et al., 2017; Gao et al., 2017; He et al., 2017; Gu, 2018; Wang et al., 2018; Luo, 2019; Qian, 2019; Yang, 2019; Han, 2020; Li and Wang, 2020; Liu, 2020; Zhang, 2020; Yang, 2021; Zhang et al., 2021; Zhou and Du, 2021; Li, 2022; Li et al., 2022; Wen, 2022; Zhi, 2022). The results showed that donepezil combined with TCM was more effective than donepezil in promoting cognitive function recovery (WMD = 2.33, 95% CI: 1.90 to 2.76, $p < 0.001$, $I^2 = 91.40\%$, random model; as shown in Table 2). The symmetrical funnel plot (refer to Figure 3) and Egger's test ($p > 0.05$) indicated no apparent publication bias.

In 21 studies involving 1,735 participants, cognitive function was evaluated using the MoCA (Yang et al., 2011; Li and Zhou, 2014; Guan et al., 2015; Su et al., 2015; Xie and Chen, 2015; Yu, 2016; Gao et al., 2017; Luo, 2019; Qian, 2019; Yang, 2019; Gan et al., 2020; Liu, 2020; Zhang, 2020; Yang, 2021; Zhang et al., 2021; Zhou and Du, 2021; Li, 2022; Li et al., 2022; Shou et al., 2022; Wen, 2022; Zhi, 2022). Results indicated that the combination of donepezil and TCM led to a significant improvement in cognition when compared to donepezil alone (WMD = 2.79, 95% CI: 1.82 to 3.75, $p < 0.001$, $I^2 = 96.00\%$, random model; as shown in Table 2). However, the asymmetrical funnel plot (refer to Figure 3) and Egger's test ($p < 0.05$) suggested the possibility of publication bias.

3.4. Secondary outcomes

In 11 trials involving 777 participants, the efficacy of TCMSS was studied (He et al., 2017; Gu, 2018; Luo, 2019; Qian, 2019; Han, 2020; Liu, 2020; Wang X. et al., 2021; Yang, 2021; Zhang et al., 2021; Li et al., 2022; Zhi, 2022). The results indicated that the combination of donepezil and TCM was effective in alleviating symptoms of Chinese medicine as compared to donepezil alone (WMD = −3.01, 95% CI: −3.79 to −2.23, $p < 0.001$, $I^2 = 81.10\%$, random model; as shown in Table 2). Although the funnel plot showed asymmetry (refer to Supplementary Figure 2), the Egger's test ($p > 0.05$) indicated no significant publication bias.

In 7 trials involving 594 participants, the BI was utilized to assess activities of daily living (Dong, 2015; Xie and Chen, 2015; Yu, 2016; Liu, 2020; Zhang, 2020; Yang, 2021; Shou et al., 2022). Our study found that when donepezil was combined with TCM, it significantly improved activities of daily living compared to donepezil alone (WMD = 9.20, 95% CI: 5.39 to 13.00, $p < 0.001$, $I^2 = 83.40\%$, random model; as shown in Table 2). However, potential publication bias was suggested by the asymmetry of the funnel plot (refer to Supplementary Figure 2) and confirmed by the Egger's test ($p < 0.05$).

In 16 trials involving 1,201 participants (Liu et al., 2008; Yang et al., 2011; Shen, 2014; Di et al., 2017; Gao et al., 2017; He et al., 2017; Gu, 2018; Luo, 2019; Qian, 2019; Yang, 2019; Gan et al., 2020; Zhang, 2020; Wang X. et al., 2021; Zhou and Du, 2021; Li et al., 2022; Wen, 2022), it was reported that the combination of donepezil and TCM did not significantly reduce the incidence of AEs compared to donepezil alone (RR = 0.86, 95% CI: 0.62 to 1.19, P = 0.844, I2 = 0.00%, fixed model; as

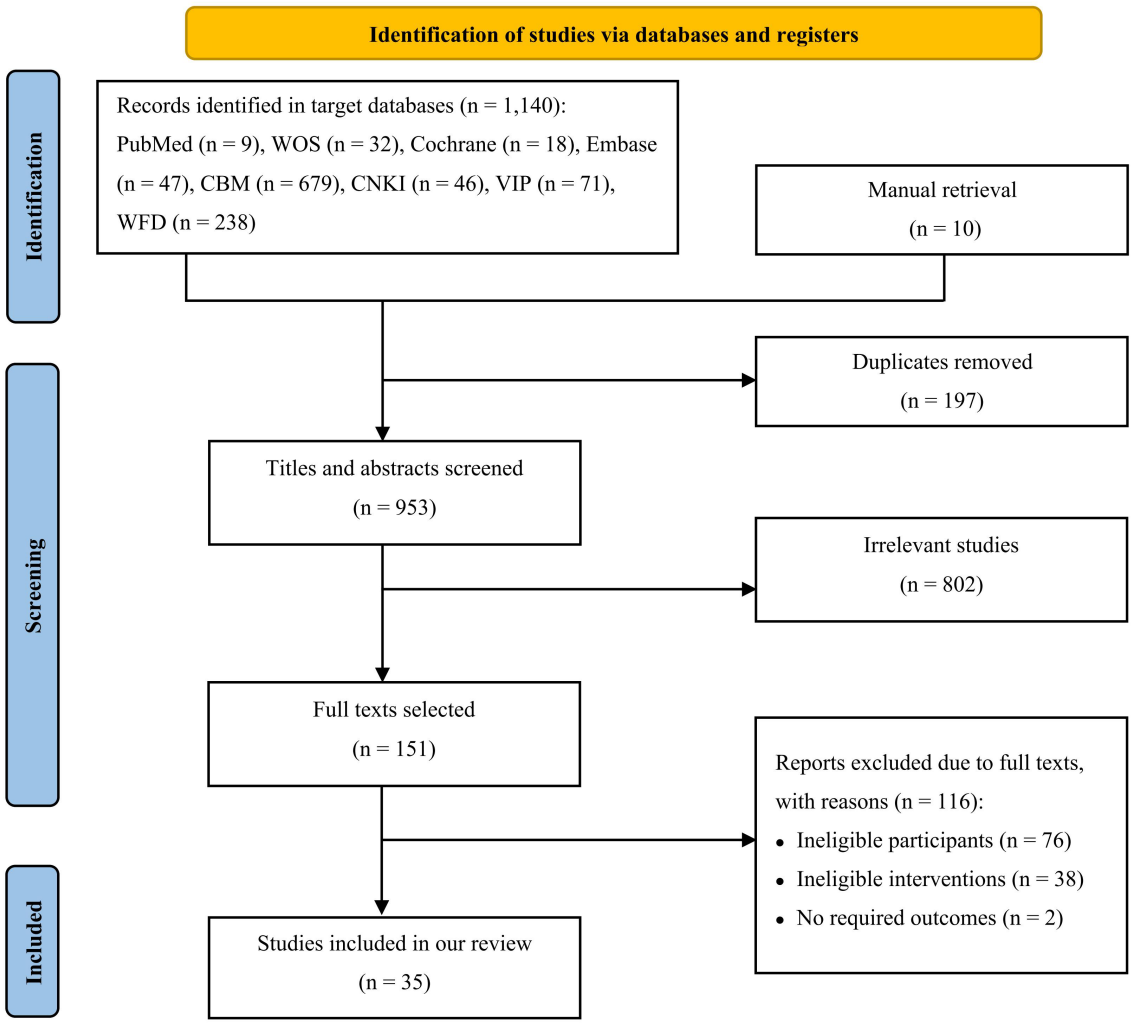

FIGURE 1
Flowchart of literature selection (CBM: Chinese Biomedical Literature Database; CNKI: Chinese National Knowledge Infrastructure; VIP: Chinese Scientific Journal Database; WFD: Wanfang Database; WOS: Web of Science).

shown in Table 2). The funnel plot (refer to Supplementary Figure 2) and Egger's test ($p > 0.05$) both indicated no evidence of publication bias.

3.5. Subgroup analyses and sensitivity analyses

Subgroup analyses of primary outcomes were conducted and the results showed that the majority of subgroups had consistent results. There was no significant difference observed between each subitem within the subgroup. However, in subgroup analyses of CE, studies with an intervention duration <24 weeks (RR = 1.15, 95% CI: 1.05 to 1.26, $p > 0.999$, $I^2 = 0.00\%$, fixed model), a total sample size <100 (RR = 1.17, 95% CI: 1.05 to 1.29, $p > 0.999$, $I^2 = 0.00\%$, fixed model), and a male to female ratio ≥ 1 (RR = 1.15, 95% CI: 1.06 to 1.25, $p > 0.999$, $I^2 = 0.00\%$, fixed model) showed a significant improvement in CE compared to studies with an intervention duration ≥24 weeks (RR = 1.15, 95% CI: 0.95 to 1.40, $p = 0.975$, $I^2 = 0.00\%$, fixed model), or more, a total sample size ≥100 (RR = 1.13, 95% CI: 0.98 to 1.30, $p = 0.998$, $I^2 = 0.00\%$, fixed model), or more, a male to female ratio < 1 (RR = 1.17, 95% CI: 0.88 to 1.54, $p = 0.846$, $I^2 = 0.00\%$, fixed model). In subgroup analyses of MoCA, it was observed that studies with disease course >2 years (WMD = 1.95, 95% CI: 1.28 to 2.63, $p = 0.388$, $I^2 = 0.80\%$, random model) had less heterogeneity compared to studies with disease course ≤2 years (WMD = 2.46, 95% CI: 0.30 to 4.61, $p < 0.001$, $I^2 = 94.60\%$, random model). In addition, the MoCA score showed a significant increase in patients with MCI-PD (WMD = 3.39, 95% CI: 2.02 to 4.76, $p < 0.001$, $I^2 = 91.50\%$, random model) and MCI-VRF (WMD = 3.14, 95% CI: 0.79 to 5.49, $p < 0.001$, $I^2 = 93.60\%$, random model), but not in those with MCI-CVD (WMD = 1.47, 95% CI: −0.02 to 2.96, $p = 0.003$, $I^2 = 82.70\%$, random model), when studies were classified by pathogenesis. Table 2 lists the detailed subgroup analyses. The sensitivity analyses suggested that all findings were robust.

4. Discussion

This study is the first to systematically review and analyze the effectiveness and safety of combining donepezil and TCM for patients

TABLE 1 Characteristics of the included studies.

Publications	Sample size		Age (mean±SD/range)		Proportion of male (%)	Intervention duration	Outcomes
	EG	CG	EG	CG			
Yang et al. (2011)	33	32	65.50 ± 10.90	63.50 ± 8.90	60.29%	60 days	②③⑥
Gu (2018)	35	35	68.40 ± 3.50	69.20 ± 3.70	55.71%	12 weeks	②④⑥
Han (2020)	41	43	56.77 ± 4.67	67.63 ± 3.86	46.43%	12 weeks	①②④⑥
Gao et al. (2017)	60	60	62.40 ± 5.95	62.08 ± 5.92	58.33%	6 months	①②③⑥
Xie and Chen (2015)	30	30	59.12 ± 16.76	60.15 ± 14.68	58.33%	60 days	①②③③
Zhang (2020)	63	50	63.70 ± 6.50	63.10 ± 7.30	48.67%	8 weeks	②③⑤⑥
Guan et al. (2015)	52	52	59.00 ± 5.70	60.00 ± 5.20	59.62%	3 months	①②③
Gan et al. (2020)	26	26	57.00 ± 3.40	58.00 ± 2.60	59.62%	12 weeks	②⑥
Wang et al. (2014)	40	32	55.60 ± 4.52	51.17 ± 3.98	59.72%	12 weeks	①②
Yang (2021)	25	34	67.68 ± 10.98	64.50 ± 12.23	59.32%	2 months	②③④⑤⑥
Li and Wang (2020)	30	30	61.50 ± 11.50	62.30 ± 7.80	56.67%	4 weeks	①②
Li and Zhou (2014)	34	34	57.36 ± 9.48	58.46 ± 9.18	57.35%	180 days	②③
Zhi (2022)	30	30	64.70 ± 6.99	63.87 ± 8.05	48.33%	60 days	①②③④⑥
Zhang et al. (2021)	46	45	63.28 ± 10.36	65.47 ± 10.29	52.75%	12 weeks	①②③④⑥
Shou et al. (2022)	41	41	67.90 ± 7.61	68.03 ± 7.77	65.85%	12 weeks	①③⑤
Di et al. (2017)	33	33	71.40 ± 8.80	70.80 ± 8.40	42.42%	12 months	①②⑥
Liu (2015)	50	50	71.05 ± 6.83	72.32 ± 5.30	56.00%	9 months	①②
Liu (2020)	43	43	69.01 ± 3.35	68.36 ± 3.54	50.00%	2 months	①②③④⑤
Liu and Liu (2015)	60	60	64.50 ± 3.00	65.20 ± 3.30	54.17%	9 months	②
Dong (2015)	57	57	66.20 ± 2.60	65.40 ± 2.50	57.89%	60 days	①②⑤
Liu et al. (2008)	16	14	64.92 ± 9.15	67.76 ± 9.13	50.00%	16 weeks	②⑥
Li et al. (2022)	32	32	59.03 ± 7.15	60.06 ± 6.58	67.19%	8 weeks	①②③④⑥
He et al. (2017)	40	40	72.32 ± 5.30	71.05 ± 6.83	56.25%	8 weeks	①②④⑥
Yu (2016)	40	40	NR	NR	NR	2 months	②③⑤
Ye and Feng (2014)	40	36	58–75		51.32%	12 weeks	②⑥
Luo (2019)	30	30	68.20 ± 29.26	66.97 ± 10.51	55.00%	3 months	①②③④⑥
Li et al. (2022)	63	63	62.73 ± 5.12	61.46 ± 6.17	53.17%	8 weeks	①②③⑥
Shen (2014)	38	38	70.32 ± 4.57		65.79%	3 months	②⑥
Su et al. (2015)	50	50	53.50 ± 8.50	51.80 ± 9.60	56.00%	56 days	③
Wang et al. (2018)	45	45	71.20 ± 4.60	70.20 ± 4.20	50.00%	3 months	②
Zhou and Du (2021)	63	63	65.80 ± 2.60	63.90 ± 2.30	53.97%	12 weeks	②③⑥
Wen (2022)	38	38	79.58 ± 4.18	80.05 ± 3.40	68.42%	8 weeks	①②③⑥
Yang (2019)	40	40	64.72 ± 7.55	63.48 ± 7.32	55.00%	12 weeks	①②③⑥
Wang X. et al. (2021)	30	30	68.83 ± 5.50	68.53 ± 5.29	55.00%	3 months	①④⑥
Qian (2019)	31	32	66.13 ± 5.51	67.59 ± 5.30	58.73%	12 weeks	①②③④⑥

CG, control group; EG, experimental group; NR, no reported; Outcomes (① CE, clinical effectiveness; ② MMSE, Mini-mental State Examination; ③ MoCA, Montreal Cognitive Assessment; ④ TCMSS, traditional Chinese medicine syndrome scale; ⑤ BI, Barthel Index; ⑥ AEs, adverse events); SD, standard deviation.

with MCI. An extensive literature search was conducted based on eight electronic databases and manual retrieval, ultimately identifying 35 studies with a total of 2,833 participants. Our results showed that combing donepezil and TCM significantly improved cognitive function and daily activities compared to donepezil alone. In addition, patients with MCI-PD and MCI-VRF showed a significant improvement in cognitive function, but this benefit was not observed in patients with MCI-CVD.

The results of our efficacy study revealed that the combination of donepezil and TCM led to a significant improvement in MMSE, MoCA, and BI scores compared to donepezil alone. This suggests that the combined treatment may be more effective in enhancing cognitive function and daily activities. Our findings align with previous meta-analyses conducted on the use of WM combined with TCM or TCM alone for patients with MCI. A meta-analysis of 21 RCTs demonstrated that the combination of WM and *Ginkgo Biloba* was more effective in

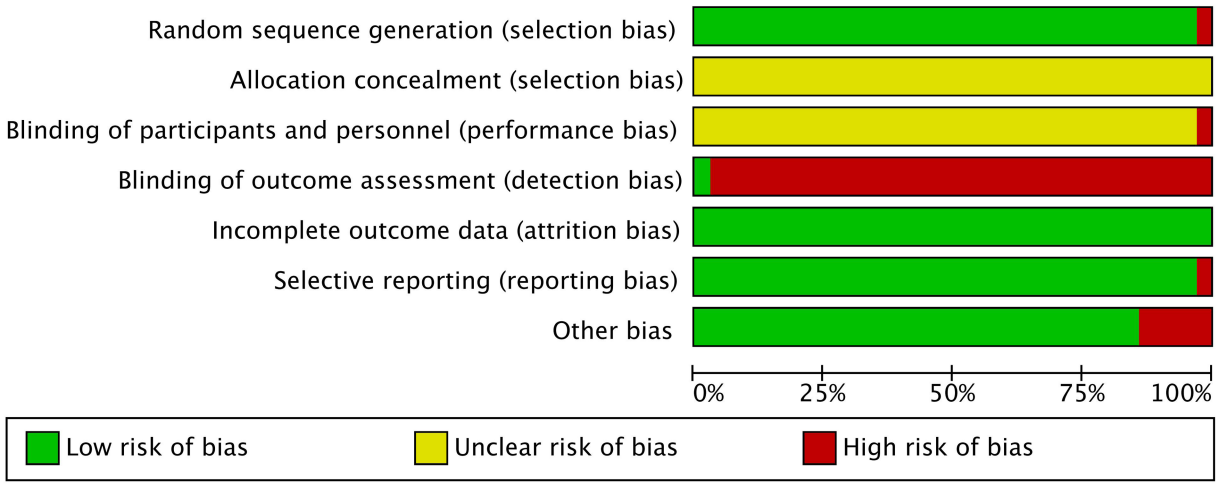

FIGURE 2
Risk of bias for summary quality (Each item presented as percentages).

improving cognitive function than WM alone (Yang et al., 2016). Another meta-analysis with 1,683 patients with MCI found that TCM significantly improved cognitive function and activities of daily living compared to no intervention and a placebo (Liang et al., 2022). Numerous scholars have conducted in-depth research to explore the intrinsic mechanism of TCM in cognition and have observed remarkable benefits. One such study (Zhang H. et al., 2022) observed that the Guilingji capsule increased serum levels of acetylcholine (Ach) while decreasing serum levels of acetylcholinesterase (AchE), homocysteine (Hcy), and high-sensitivity C-reactive protein (hs-CRP) in patients with MCI. This suggests that the mechanism for improving cognition may be related to regulating the cholinergic system and suppressing inflammation. According to a study (Han et al., 2014), Qingnao Yizhi granules were found to be effective in increasing serum levels of superoxide dismutase (SOD) and decreasing serum levels of malondialdehyde (MDA) and AchE in patients with MCI. This suggests that the Qingnao Yizhi granules may enhance cognitive function by scavenging free radicals, inhibiting brain tissue peroxidation, and promoting brain cell metabolism. Additionally, the study (Huang et al., 2022) found that serum levels of uric acid (UA) and SOD were significantly positively correlated with the MoCA score, indicating a potential relationship between these factors and cognitive function in patients with MCI. Research has shown that the steroid-enriched fraction of *Achyranthes bidentata* Blume can reduce oxidative stress and neuroinflammatory response in the cortical and hippocampal regions by modulating the MAPKs/NF-κB signaling pathway, leading to improved cognitive function (Lin et al., 2019). In addition, senegenin can exhibit anti-inflammatory, antioxidant, anti-apoptotic, and neurotrophic activity by regulating various pathways such as MAPK/NF-κB, Nrf2/HO-1, PI3K/Akt, and ROS/Ca^{2+}. These findings suggest that senegenin has neuroprotective effects (Chen et al., 2022).

The safety of combining donepezil with TCM is a crucial consideration. Our results found no significant difference in safety between donepezil combined with TCM and donepezil alone. During the intervention, a small number of participants in both groups experienced AEs, such as gastrointestinal symptoms, sleep disturbances, fatigue, dizziness, and muscle cramps. Most of these AEs were mild in intensity and consistent with those reported in previous studies on donepezil (Zhang X. et al., 2022). Previous studies have shown that TCM is relatively safe and there was no significant difference in AEs between TCM and a placebo (Zhang et al., 2019). In this review, we focused on the AEs caused by donepezil and investigated the correlation between the safety of donepezil and dosage forms, doses, and intervention durations. Firstly, our findings suggest that donepezil transdermal patches have less gastrointestinal harm compared to oral administration. The most common AEs reported among the studies included gastrointestinal symptoms, such as nausea, vomiting, diarrhea, constipation, gastric distention, and decreased appetite. One study (Larkin, 2022) suggested that donepezil transdermal patches could reduce gastrointestinal damage and frequency of administration compared to the oral route, improving medication compliance and alleviating AEs. However, all participants in previous studies took donepezil orally. Therefore, more large sample sizes, multi-center, and high-quality RCTs should be conducted in the future to validate the safety of donepezil transdermal patches combined with TCM for patients with MCI. According to studies, donepezil is safer in smaller doses. In fact, patients who took 10 mg/day had a higher risk of AEs and early withdrawal from the trial compared to those who received 5 mg/day (Birks and Harvey, 2018). On the other hand, another study (Battle et al., 2021) found no significant difference in AEs between 5 mg/day of donepezil and a placebo. Based on the above conclusions, it is believed that donepezil at a dose of 5 mg/day is relatively safe for patients with MCI. To minimize harm, we recommend titration administration starting at 5 mg/day of donepezil for 4 weeks before increasing to the necessary 10 mg/day dose (Homma et al., 2016). Additionally, a 3-year study (Winblad et al., 2006) demonstrated a decrease in the incidence of donepezil-related AEs over time. Therefore, we concluded that long-term intervention with donepezil is well-tolerated and early AEs can be managed by adjusting the dosage forms and doses.

In subgroup analyses of pathogenesis, our results showed that patients with MCI-PD and MCI-VRF experienced a significant increase in both the MoCA and MMSE scores, while patients with MCI-CVD only showed a significant enhancement in the MMSE score. Although both scales are commonly used scales to assess

TABLE 2 Outcomes and subgroup analyses based on primary outcomes.

Meta-analyses variables	Number of studies	Number of patients		Pooled effect sizes	Heterogeneity	
		EG	CG		*p*	I^2 (%)
Dichotomous variables				RR (95% CI)		
CE	21	857	851	1.15 (1.06 to 1.25)	> 0.999	0.00%
AEs	16	608	593	0.86 (0.62 to 1.19)	0.844	0.00%
Continuous variables				WMD (95% CI)		
MMSE	31	1,278	1,261	2.33 (1.90 to 2.76)	< 0.001	91.40%
MoCA	21	870	865	2.79 (1.82 to 3.75)	< 0.001	96.00%
TCMSS	11	383	394	−3.01 (−3.79 to −2.23)	< 0.001	81.10%
BI	7	299	295	9.20 (5.39 to 13.00)	< 0.001	83.40%
Subgroup analyses based on CE				RR (95% CI)		
Intervention duration						
Overall	21	857	851	1.15 (1.06 to 1.25)	> 0.999	0.00%
< 24 weeks	18	714	708	1.15 (1.05 to 1.26)	> 0.999	0.00%
≥ 24 weeks	3	143	143	1.15 (0.95 to 1.40)	0.975	0.00%
Region						
Overall	21	857	851	1.15 (1.06 to 1.25)	> 0.999	0.00%
Developed	8	320	320	1.18 (1.03 to 1.36)	0.999	0.00%
Undeveloped	13	537	531	1.14 (1.03 to 1.26)	> 0.999	0.00%
Publication year						
Overall	21	857	851	1.15 (1.06 to 1.25)	> 0.999	0.00%
≤ 2018	8	362	354	1.15 (1.01 to 1.30)	> 0.999	0.00%
> 2018	13	495	497	1.16 (1.04 to 1.29)	> 0.999	0.00%
Total sample size						
Overall	21	857	851	1.15 (1.06 to 1.25)	> 0.999	0.00%
< 100	16	575	569	1.17 (1.05 to 1.29)	> 0.999	0.00%
≥ 100	5	282	282	1.13 (0.98 to 1.30)	0.998	0.00%
Male to female ratio						
Overall	21	857	851	1.15 (1.06 to 1.25)	> 0.999	0.00%
≥ 1	19	783	775	1.15 (1.06 to 1.25)	> 0.999	0.00%
< 1	2	74	76	1.17 (0.88 to 1.54)	0.846	0.00%
Pathogenesis						
Overall	11	472	465	1.14 (1.02 to 1.28)	> 0.999	0.00%
MCI-PD	4	154	153	1.15 (0.95 to 1.39)	0.953	0.00%
MCI-CVD	4	163	157	1.17 (0.96 to 1.42)	0.984	0.00%
MCI-VRF	3	155	155	1.12 (0.93 to 1.34)	0.979	0.00%
Disease course						
Overall	11	462	463	1.15 (1.03 to 1.29)	> 0.999	0.00%
≤ 2 years	6	263	265	1.14 (0.99 to 1.33)	> 0.999	0.00%
> 2 years	5	199	198	1.16 (0.98 to 1.37)	0.999	0.00%
Subgroup analyses based on MMSE				WMD (95% CI)		
Intervention duration						
Overall	31	1,278	1,261	2.33 (1.90 to 2.76)	< 0.001	91.40%
< 24 weeks	26	1,041	1,024	2.16 (1.70 to 2.62)	< 0.001	91.00%
≥ 24 weeks	5	237	237	3.33 (1.64 to 5.02)	< 0.001	93.10%

(Continued)

TABLE 2 (Continued)

Meta-analyses variables	Number of studies	Number of patients		Pooled effect sizes	Heterogeneity	
		EG	CG		*p*	I^2 (%)
Region						
Overall	29	1,210	1,194	2.39 (1.95 to 2.83)	< 0.001	91.30%
Developed	11	461	461	2.33 (1.76 to 2.90)	< 0.001	88.50%
Undeveloped	18	749	733	2.50 (1.81 to 3.19)	< 0.001	89.10%
Publication year						
Overall	31	1,278	1,261	2.33 (1.90 to 2.76)	< 0.001	91.40%
≤ 2018	17	703	688	2.40 (1.74 to 3.07)	< 0.001	90.20%
> 2018	14	575	573	2.26 (1.64 to 2.88)	< 0.001	88.70%
Total sample size						
Overall	31	1,278	1,261	2.33 (1.90 to 2.76)	< 0.001	91.40%
< 100	23	810	806	1.74 (1.29 to 2.18)	< 0.001	80.50%
≥ 100	8	468	455	3.77 (3.18 to 4.36)	< 0.001	81.30%
Male to female ratio						
Overall	30	1,238	1,221	2.30 (1.86 to 2.74)	< 0.001	91.60%
≥ 1	27	1,101	1,095	2.32 (1.85 to 2.78)	< 0.001	90.90%
< 1	3	137	126	2.12 (0.91 to 3.34)	< 0.001	87.90%
Pathogenesis						
Overall	15	673	649	2.54 (2.01 to 3.06)	< 0.001	87.40%
MCI-PD	5	217	216	2.78 (2.20 to 3.35)	0.079	52.20%
MCI-CVD	6	266	243	1.91 (0.73 to 3.09)	< 0.001	94.30%
MCI-VRF	4	190	190	3.22 (1.86 to 4.59)	0.002	80.50%
Disease course						
Overall	14	628	616	2.78 (2.22 to 3.34)	< 0.001	83.80%
≤ 2 years	8	357	359	2.63 (1.84 to 3.42)	< 0.001	89.80%
> 2 years	6	271	257	3.00 (2.15 to 3.84)	0.045	55.90%
Subgroup analyses based on MoCA				WMD (95% CI)		
Intervention duration						
Overall	21	870	865	2.79 (1.82 to 3.75)	< 0.001	96.00%
< 24 weeks	19	776	771	2.50 (1.54 to 3.46)	< 0.001	95.70%
≥ 24 weeks	2	94	94	5.47 (3.09 to 7.85)	0.007	86.30%
Region						
Overall	20	837	833	2.88 (1.87 to 3.88)	< 0.001	96.20%
Developed	10	393	393	2.50 (0.93 to 4.06)	< 0.001	97.70%
Undeveloped	10	444	440	3.22 (2.12 to 4.32)	< 0.001	87.50%
Publication year						
Overall	21	870	865	2.79 (1.82 to 3.75)	< 0.001	96.00%
≤ 2018	7	299	298	3.35 (1.33 to 5.37)	< 0.001	96.50%
> 2018	14	571	567	2.54 (1.65 to 3.43)	< 0.001	90.80%
Total sample size						
Overall	21	870	865	2.79 (1.82 to 3.75)	< 0.001	96.00%
< 100	15	519	527	2.30 (1.78 to 2.81)	< 0.001	64.70%
≥ 100	6	351	338	4.07 (1.52 to 6.62)	< 0.001	98.90%

(Continued)

TABLE 2 (Continued)

Meta-analyses variables	Number of studies	Number of patients		Pooled effect sizes	Heterogeneity	
		EG	CG		*p*	I^2 (%)
Male to female ratio						
Overall	20	830	825	2.78 (1.79 to 3.78)	< 0.001	96.20%
≥ 1	19	767	775	2.76 (1.74 to 3.79)	< 0.001	96.40%
< 1	1	63	50	3.19 (1.24 to 5.14)	/	/
Pathogenesis						
Overall	12	531	518	2.86 (1.42 to 4.30)	< 0.001	97.60%
MCI-PD	5	218	218	3.39 (2.02 to 4.76)	< 0.001	91.50%
MCI-CVD	3	145	132	1.47 (−0.02 to 2.96)	0.003	82.70%
MCI-VRF	4	168	168	3.14 (0.79 to 5.49)	< 0.001	93.60%
Disease course						
Overall	8	341	327	2.23 (1.05 to 3.42)	< 0.001	90.40%
≤ 2 years	4	159	159	2.46 (0.30 to 4.61)	< 0.001	94.60%
> 2 years	4	182	168	1.95 (1.28 to 2.63)	0.388	0.80%

AEs, adverse events; BI, Barthel Index; CE, clinical effectiveness; CG, control group; CI, confidence interval; EG, experimental group; MCI-PD, mild cognitive impairment caused by Parkinson's disease; MCI-CVD, mild cognitive impairment resulting from cerebrovascular disease; MCI-VRF, mild cognitive impairment due to vascular risk factors; MMSE, Mini-mental State Examination; MoCA, Montreal Cognitive Assessment; RR, relative risk; TCMSS, traditional Chinese medicine syndrome scale; WMD, weighted mean difference.

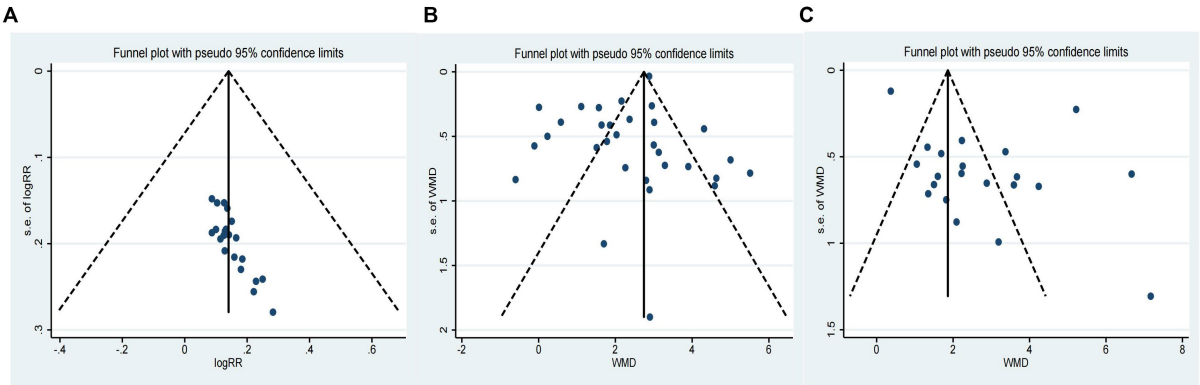

FIGURE 3
Funnel plot of primary outcomes [**(A)**: Funnel plot of CE; **(B)** Funnel plot of MMSE; **(C)** Funnel plot of MoCA].

cognitive function, the MoCA is more sensitive for patients with MCI (Liang et al., 2023). Therefore, we concluded that the combination of donepezil and TCM can improve cognitive function in patients with MCI-PD and MCI-VRF, but the benefit may be limited in patients with MCI-CVD. A previous study (Liang et al., 2022) has a significant positive effect on the MoCA score in patients with vascular-MCI. To further explore this, we subdivided the vascular-MCI into two subtypes: MCI-VRF and MCI-CVD. This was done because MCI-VRF which does not show visible cerebrovascular lesions on conventional imaging may be an early stage before MCI-CVD (Jia et al., 2014). Our findings confirmed that patients with MCI-VRF showed a significant cognitive improvement compared to patients with MCI-CVD, highlighting the importance of early intervention.

4.1. Strengths and limitations

Previous studies on the combination of donepezil and TCM for patients with MCI were limited by small sample sizes and single-center studies, which hindered the generalizability of their conclusions to clinical practice. In contrast, our study provides a comprehensive analysis of previous data, which quantifies the efficacy and safety of this combination. This strengthens the evidence-based medical evidence available for clinical practice and policy development. Following the PICOS principle, we established strict criteria for inclusion and exclusion to maintain consistency among the studies. This approach improves the reliability and validity of our findings. In contrast to earlier studies, we explored a broader range of outcome measures (CE, MMSE, MoCA, TCMSS, BI, and AEs), which provides a comprehensive

understanding of the advantages of combining donepezil with TCM in patients with MCI. Seven subgroups were created based on disease characteristics to investigate the impact of different factors on primary outcomes and potential sources of heterogeneity. Our study delved deeper than previous studies and revealed that patients with MCI-VRF experienced more significant cognitive improvement than those with MCI-VRF. We recommend conducting more high-quality RCTs in the future to confirm this discovery. Given that MCI-VRF is an earlier manifestation of MCI-CVD, early intervention may offer greater opportunities for patients with MCI. This has significant implications for clinical science decision-making and policy-making. To address the limited number of RCTs in previous studies, we performed an extensive search of larger electronic databases and supplemented manual retrieval to obtain more eligible literature. As a result, our study was performed on larger total sample sizes, making our findings more reliable than previous conclusions.

This study has some limitations that need to be taken into account when interpreting the results. Firstly, most of the studies included in this review had a high risk of detection bias, which could affect the precision of the findings and consequently the overall quality of our study. Secondly, although we did not include participants with diverse backgrounds, heterogeneity remained high. However, we believe that this heterogeneity may be objective and inevitable due to the population with MCI being in a transitional state between normal aging and early dementia. Therefore, caution should be exercised when interpreting the results of this study.

5. Conclusion

According to our study, the combination of donepezil and TCM may have a greater positive impact on cognitive function and daily activities compared to using donepezil alone. However, there was no significant difference in terms of safety. To strengthen our findings and provide more reliable evidence-based medical evidence, it is recommended that more high-quality RCTs be conducted in the future.

Author contributions

S-jY served as principal author and had full access to all the data in the study, takes responsibility for the accuracy of the data analysis, and the integrity of the data. J-hL and Z-hT contributed to the conception and design. ZL, H-lT, and S-jY contributed to data acquisition and interpretation. S-jY and C-lB contributed to the draft of the manuscript. J-hL, Z-hT, and W-hL contributed to revise of the article and final approval. All authors contributed to the article and approved the submitted version.

Funding

This research was supported by the National Natural Science Foundation of China (No. 81873204) and the Sichuan Science and Technology Program (Nos. 2021YFS0040 and 2022ZYD0075).

Acknowledgments

The authors affirm that the work submitted for publication is original and has not been published other than as an abstract or preprint in any language or format and has not been submitted elsewhere for print or electronic publication consideration. The authors affirm that each person listed as the author participated in the work in a substantive manner, in accordance with ICMJE authorship guidelines, and is prepared to take public responsibility for it. All authors consent to the investigation of any improprieties that may be alleged regarding the work.

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/fnins.2023.1206491/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Risk of bias for individual quality.

SUPPLEMENTARY FIGURE 2
Funnel plot of secondary outcomes.

SUPPLEMENTARY FIGURE 3
Flowchart of method implementation.

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frontiers | Frontiers in Neuroscience

TYPE Review
PUBLISHED 04 August 2023
DOI 10.3389/fnins.2023.1221990

OPEN ACCESS

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RECEIVED 13 May 2023
ACCEPTED 13 July 2023
PUBLISHED 04 August 2023

CITATION
Cai X-y, Qian G-p, Wang F, Zhang M-y, Da Y-j and Liang J-h (2023) Association between sedentary behavior and risk of cognitive decline or mild cognitive impairment among the elderly: a systematic review and meta-analysis. *Front. Neurosci.* 17:1221990. doi: 10.3389/fnins.2023.1221990

Association between sedentary behavior and risk of cognitive decline or mild cognitive impairment among the elderly: a systematic review and meta-analysis

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Background: Existing evidence on the association between sedentary behavior (SB) and cognitive function remains inconclusive. Therefore, this study investigated the association between SB and the risk of cognitive decline (CD) or mild cognitive impairment (MCI) in the elderly.

Methods: A comprehensive search was independently conducted by two researchers (XC and GQ) in seven electronic databases, including Medline (via PubMed), China Biology Medicine, Embase, Web of Science, China National Knowledge Infrastructure, Wanfang database, and VIP database for Chinese technical periodicals, covering studies published from the inception of database to June 2023. Studies that investigated the relationship between SB and the risk of CD or MCI in the elderly were included. The quality of the literature was assessed using the Newcastle–Ottawa Scale (NOS) and the Agency for Healthcare Research and Quality (AHRQ) assessment tools. The combined effect size analysis, subgroup analysis, and publication bias assessment were performed using STATA 14.0.

Results: A total of 13 cross-sectional and 6 cohort studies involving 81,791 individuals were included, comprising 17 high-quality studies and 2 medium-quality studies. We found that SB was significantly associated with an increased risk of CD [odds ratio (OR) = 1.69, 95% confidence intervals (CI): 1.47–1.94] or MCI (OR = 1.34, 95% CI: 1.14–1.56) among the elderly. Subgroup analysis stratified according to comorbidity, lifestyle, family structure, publication year, and region showed statistical differences between groups, and the consistency of the results revealed the sources of the heterogeneity.

Conclusion: This meta-analysis showed that SB is positively associated with the risk of CD or MCI in the elderly, providing a higher level of evidence for the promotion of healthy behaviors by clinicians and health policymakers. Due to the number and quality of the included articles, more high-quality longitudinal studies are needed to further confirm our findings.

KEYWORDS

sedentary behavior, cognitive decline, mild cognitive impairment, elderly, meta-analysis

Introduction

Cognitive decline (CD) refers to the measurable deterioration observed in various domains of cognitive function, including memory, language, and reasoning (Chun et al., 2021). It represents the preclinical stage of the Alzheimer's disease (AD) continuum, with ∼7% of CD per year progressing to mild cognitive impairment (MCI) (Mazzeo et al., 2019). MCI is a state of cognitive impairment between normal aging and dementia (Albert et al., 2011). MCI refers to significant memory deterioration and mild impairment in other domains of cognitive function that do not yet meet the diagnostic criteria for dementia (Langa and Levine, 2014). The incidence of MCI is 20.8%, and ∼10–20% of MCI progresses to AD annually (Jia et al., 2020). Cognitive impairment is irreversible, and there are no effective pharmacological or interventional treatments for the condition (Rojas-Fernandez and Cameron, 2012; Yu et al., 2023). Therefore, understanding the risk factors of CD and MCI could enhance the prevention of AD (Petersen et al., 2018).

In 2017, the members of the Sedentary Behavior Research Network (SBRN) defined SB as all activities with ≤1.5 metabolic equivalents (METs) of energy expenditure, such as sitting or lying down (Tremblay et al., 2017). SB is common in the elderly and is an independent risk factor for certain diseases (Keadle et al., 2017). Numerous studies have shown that SB is associated with elevated risks of all-cause mortality, cardiovascular mortality, cancer mortality, and the incidence of type 2 diabetes in the elderly population (Bull et al., 2020; Liang et al., 2022). Recently, there has been growing interest in the relationship between SB and cognitive function (Poulin et al., 2016), but issues that have been raised by previous studies remain to be resolved. First, the available evidence remains controversial. For instance, some studies have shown that SB is associated with lower cognitive function and is independently associated with a significantly higher risk of dementia (Falck et al., 2017; Yan et al., 2020). However, two other studies showed that there was no association between SB and cognitive function over time (Kesse-Guyot et al., 2012; Hamer and Stamatakis, 2014). Possible explanations for these differences are that these studies, published over a decade ago, were not appropriately designed, the 2-year follow-up may not have been sufficient to detect longitudinal changes, and SB was self-reported and less objective. Second, previous systematic reviews were based on qualitative studies that had limitations in terms of sample size, population diversity, and the inclusion of individuals with underlying medical conditions (Falck et al., 2017). Thus, further research is needed to improve the quality of evidence and its applicability. Overall, differences in exposures, small sample sizes, short follow-up periods, self-reported SB measures, and uneven quality of review articles often lead to conflicting findings (Hamer and Stamatakis, 2014; Falck et al., 2017). As a result, there is a need to combine and summarize data on the relationship between SB and the risk of CD or MCI to obtain more robust evidence. Thus, we performed a systematic review and meta-analysis of relevant published studies to assess this relationship.

Methods

This meta-analysis was conducted following the guidelines of Meta-analysis of Observational Studies in Epidemiology (MOOSE) and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (Stroup et al., 2000; Page et al., 2021). Ethical approval was not required because the study was based on previously published articles. In addition, the authors had no conflicts of interest.

Search strategies and study selection

The reviewed databases included Medline (via PubMed), China Biology Medicine, Embase, Web of Science, China National Knowledge Infrastructure, Wanfang database, and VIP database for Chinese technical periodicals. They were systematically searched to identify relevant articles published from inception to 11 June 2023. The search was performed using a combination of free words and theme words. Search strategies were developed using Boolean logical operators and truncates. The main search terms included "cognitive dysfunctions," "mild cognitive impairment," "cognitive decline," "cognition," "sedentary behavior," "sedentary lifestyle," "physical inactivity," and "sedentary time" (see Supplementary material 1 for detailed search strategies). Moreover, articles included in the literature of the relevant systematic review and meta-analysis studies were also searched. This was supplemented by a manual search of conference articles or gray literature to identify references cited in the included literature. When full text was not available, the authors' or corresponding authors' email addresses or other contact details were sought to request full-text access. Two researchers (XC and GQ) independently performed a comprehensive literature search and exported the identified articles to Endnote X9 software (Thompson ISI Research Soft, Philadelphia, USA). After eliminating duplicates manually and electronically with the software, initial screening was performed by reading the titles and abstracts of the articles to exclude irrelevant articles. Next, full-text screening of the articles was conducted, and articles that did not meet the inclusion criteria were removed. In case of discrepancies in the selection of the articles, a senior expert of the research group was consulted to reach a consensus.

Inclusion and exclusion criteria

Literature inclusion was based on the population, intervention, comparison, outcome, and study design (PICOS) principles of evidence-based medicine (Liberati et al., 2009). The inclusion criteria were as follows: (1) Mean age or age range of the participants ≥ 60 years [The United Nations (UN) defines elderly individuals as those aged 60 years and above (United Nations, 2019)] and CD or MCI patients with undiagnosed dementia. Diagnostic criteria were based on elements from

the National Institute of Aging Alzheimer's Association (NIA-AA), the Diagnostic and Statistical Manual of Mental Disorders (DSM), and Petersen's criteria (Montine et al., 2012; Battle, 2013; Petersen et al., 2018); (2) articles were cross-sectional, cohort, and case–control studies, without language restrictions; (3) outcome indicators including CD or MCI, according to the Mini-Mental State Examination (MMSE), the scores ranged from 0 to 30. The boundary values of CD and MCI were divided according to educational level: illiteracy $\leq$ 17 points, primary school $\leq$ 20 points, and junior high school and above $\leq$ 24 points) (Folstein et al., 1975); Montreal Cognitive Assessment (MoCA) (Dong et al., 2012); and Ascertain Dementia 8 (AD 8) (Galvin et al., 2005); and (4) the exposure indicator was SB or physical inactivity. The exclusion criteria were as follows: (1) randomized controlled trials, literature reviews, abstracts, repeatedly published literature, and animal studies literature; (2) studies with incomplete data on outcome indicators; (3) low-quality articles with flaws in the study design; and (4) articles that combined other interventions and did not adjust for confounding factors.

Data extraction and quality assessment

Two researchers (XC and GQ) extracted data from the included studies separately, and disagreements were resolved by consensus or consultation with a third researcher. Data extracted from the articles included the year of publication, type of study, follow-up period, region, age, sex ratio, sample size, exposure characteristics, and outcome indicators. In addition, when there were several studies in the same article, the data were extracted separately, and in the case of incomplete data, the authors were contacted to request the complete data. Quality assessment of the included studies was conducted using the Newcastle–Ottawa Scale (NOS) and the Agency for Healthcare Research and Quality (AHRQ) (Rostom et al., 2004; Stang, 2010). Specifically, the quality of cohort and case–control studies was assessed using the NOS scale, focusing on three main aspects: sample selection, comparability, and outcomes or exposure, with a total score of 9. A score of one point was assigned for each of the following criteria: consistency of the study with the exposure, selection of the control from the same population, adequate representation of the population, absence of pre-study occurrence of the disease under investigation, and objective ascertainment of exposure. One point each was deducted if the study involved two distinct groups, namely individuals with medical histories requiring further investigation, or recorded the exposure factors through self-reporting. Moreover, two points were assigned in cases of good comparability of studies and correction of important factors. In addition, three points were allocated in cases where outcomes were assessed, follow-up was appropriate, or exposure and response rates were assessed. Points were deducted for failure to mention response rates, missed visits, or short follow-up periods. Scores ranging from 0 to 3 were categorized as low quality, scores from 4 to 6 were considered moderate quality, and scores from 7 to 9 were classified as high quality. For cross-sectional studies, the AHRQ scale was used for quality assessment. It contained 11 items, with a response of "yes," "no," and "unclear." A score ranging from 0 to 3 was classified as low quality, scores from 4 to 7 were considered moderate quality, and scores from 8 to 11 were categorized as high quality. Disagreements on the quality of the literature were resolved by consensus or consultation with another experienced researcher.

Statistical analyses

Meta-analysis was performed using STATA 14.0 software. The combined odds ratios (OR) and 95% confidence intervals (CI) were used to evaluate the relationship between SB and the risk of CD or MCI in the elderly, with a *P*- value of $\leq$0.05 representing statistically significant differences across the two groups. The existence of heterogeneity among studies was assessed using the I^2 test. If the *P*-value is $>$0.1 and $I^2 \leq 50\%$, indicating low heterogeneity among the studies, the fixed effects model was used for the analysis. On the other hand, if the *P*-value is $\leq$0.1 and $I^2 > 50\%$, indicating significant heterogeneity between studies, the random effects model was used for analysis. To address studies with a high level of heterogeneity, subgroup analysis was conducted by dividing the variables into two groups. The sources of heterogeneity were explored based on the following factors: the period of follow-up ($\geq$3 vs. $<$3 years), region (developed countries vs. developing or undeveloped countries), sample size ($\geq$1,000 vs. $<$1,000), year of publication ($\geq$2017 vs. $<$2017), length of SB exposure ($\geq$5 vs. $<$5 h/day), complications (yes vs. no), lifestyle (adjusted vs. unadjusted smoking, drinking, sleeping, various activity behaviors, and healthy eating), comorbidity (adjusted vs. unadjusted depression, anxiety, obesity, diabetes, stroke, hypertension, medications, medical history, and rheumatic disease), and family structure (adjusted vs. unadjusted marital status, residential status, and living alone). In addition, statistical significance was evaluated by testing for differences across the effect sizes of each subgroup using a 95% CI. Egger's test was used to evaluate publication bias in the included studies, and a *P*-value of $>$0.05 hypothetically indicated that there was no publication bias.

Results

Literature selection

A total of 9,713 relevant articles were retrieved from each database, and 1,699 duplicate articles were removed. After the initial screening of titles and abstracts, 7,782 articles were excluded, and 232 were selected for full-text screening. Furthermore, 213 articles did not meet the criteria and were excluded. Finally, 19 articles (13 cross-sectional and six cohort studies) were included (Ferreira et al., 2010; Dogra and Stathokostas, 2012; Lee et al., 2013; Gillum et al., 2015; Lara et al., 2016; Paulo et al., 2016; Brunner et al., 2017; Gomes et al., 2017; Ku et al., 2017a,b; García-Hermoso et al., 2018; Nemoto et al., 2018; Vancampfort et al., 2018; Martínez-Sanguinetti et al., 2019; Poblete-Valderrama et al., 2019; Jung and Chung, 2020; Cui et al., 2021; Du et al., 2022; Song and Park, 2022). The flow chart illustrating the literature screening process is shown in Figure 1.

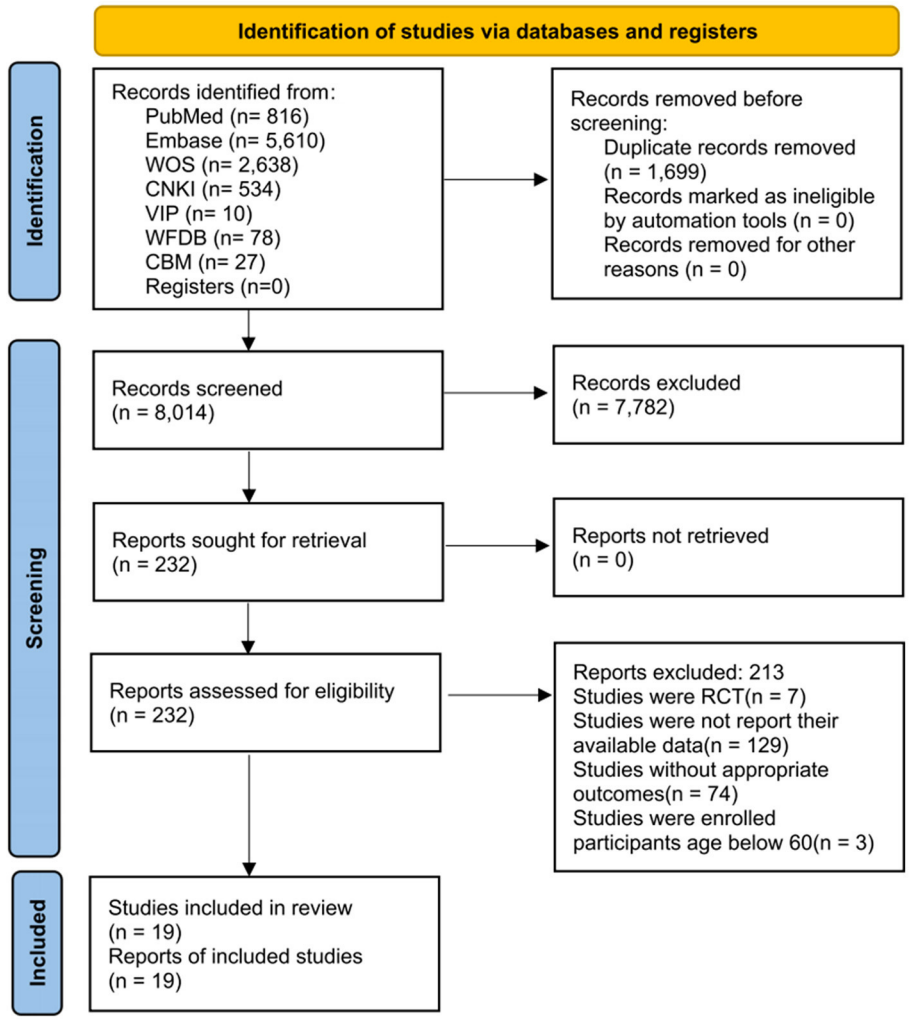

FIGURE 1
Literature review flowchart. CBM, China biology medicine; CNKI, China national knowledge infrastructure; RCT, randomized controlled trial; VIP, VIP database for Chinese technical periodicals; WFDB, Wanfang database; WOS, Web of Science.

Baseline data of included literature

A total of 19 articles involving 81,791 subjects were included. The included articles originated from 29 countries. In total, 10 of the articles came from developing countries, accounting for 53%, including four articles from China. Articles from developed countries accounted for 47%, with Japan and South Korea each having two articles. Moreover, six of the included articles were cohort studies, with a mean follow-up period of 4.3 years, and the others were cross-sectional studies published between 2012 and 2022. In total, 17 studies reported the sample sizes of the exposure and control groups, and only six reported the proportion of men and women. The method used for cognitive function testing in 11 articles was MMSE, and the testing method in two articles was AD 8. Eight articles analyzed different gradients of sedentary duration or physical inactivity. The detailed basic characteristics of the included studies are shown in Table 1.

Quality of the included studies

According to the quality evaluation standard, 17 of the articles were high-quality studies, while two were medium-quality studies. One study met all the quality evaluation criteria. Three studies were limited by one factor, and the others were limited by at least two factors, with a research quality score of 6–9. The loss-to-follow-up rate of two articles was >25%, and the follow-up period of three articles was <5 years. All articles did not provide clarity regarding whether the evaluators' factors covered other aspects of the research object. Furthermore, it remains unclear whether follow-up data were available, including information on the expected population with incomplete data or follow-up results. Seven articles explained how missing data were handled in the analysis. The quality assessment of the included studies is specified in Supplementary Tables 1, 2.

TABLE 1 Characteristics of included studies.

Publications	Region	Study design	Follow-up duration (year)	Number of participants		Proportion of female (%)		Age (mean±SD)		Exposure group	Control group	Outcomes
				EG	CG	EG	CG	EG	CG			
Ku et al. (2017a)	Taiwan, China	CS	2	133	86	NR		74.50 ± 6.10		Medium ST 7–10.99 h/day/High ST 11+ h/day	Low ST < 7 h/day	CD (①)
Ferreira et al. (2010)	Brazil	CS	3	628	232	NR		74.90 ± 6.70		Not favorable behavior trend in PAL + MMSE < 24	Not favorable behavior trend in PAL + MMSE 24+	CD (②)
Lee et al. (2013)	Japan	CS	8	550		47.40%		≥60		Second ST/third ST/highest ST ≤ 1.5 METs-per day (hours)	Lowest ST ≤ 1.5 METs-per day (hours)	CD (②)
Song and Park (2022)	Korea	CS	6	400	450	49.20%	36.60%	71.45 ± 5.32	71.16 ± 4.77	Became inactive/remained inactive	Remained active	CD (②)
				660		58.20%		72.29 ± 5.27				
Gomes et al. (2017)	16 European countries	CSS	1	4,006	1,005	NR		67.80 ± 8.90		Physical inactivity + very good memory	Physical inactivity + poor memory	CD (memory)
Brunner et al. (2017)	UK	CS	5	564	2,837	NR		≥60		Inactivity < 1 h/week moderate and <1 h/week vigorous PA	Sufficiently active ≥ 2.5 h/week moderate or ≥1 h/week vigorous PA	MCI (②)
Ku et al. (2017b)	Taiwan, China	CS	2	285		NR		≥65		ST ≥ 12 h/day	ST < 8 h/day	MCI (①)
a. Nemoto et al. (2018)	Japan	CSS	1	1,389	952	NR		≥65		Television viewing time 1–2 h/day/2–3 h/day/≥3 h/day	Television viewing time < 1 h/day	MCI
				1,254								
				1,427								
b. Nemoto et al. (2018)	Japan	CSS	1	1,240	1,094	NR		≥65		Time of reading books or newspapers 10–20 min/day/20–30 min/day/≥30 min/day	Time of reading books or newspapers < 10 min/day	MCI
				1,173								
				1,458								

(Continued)

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TABLE 1 (Continued)

Publications	Region	Study design	Follow-up duration (year)	Number of participants		Proportion of female (%)		Age (mean±SD)		Exposure group	Control group	Outcomes
				EG	CG	EG	CG	EG	CG			
García-Hermoso et al. (2018)	Chile	CSS	2	416/369	573/620	NR		74.13 ± 6.95		Sedentary ≥ 4 h/day/inactive < 600 METs value min/week	Active ≥ 600 METs value min/week/non-sedentary < 4 h/day	MCI (②)
				416/620						Sedentary/ active		
Dogra and Stathokostas (2012)	Canada	CSS	1	3,204	4,862	54.40%	56.40%	≥65		Moderately sedentary 2–4 h/day/Least sedentary < 2 h/day	Sedentary > 4 h/day	MCI
				1,412		53.00%						
Vancampfort et al. (2018)	China, Ghana, India, Mexico, Russia, and South Africa	CSS	4	3,304	29,411	NR		62.10 ± 15.60		SB ≥ 8 h/day/SB per 1 h increase	SB < 8 h/day	MCI
Lara et al. (2016)	Spain	CSS	2	1,160	1,385	NR		66.26 ± 0.18		Low PA	Moderate PA	MCI
Cui et al. (2021)	China	CSS	1	358	733	NR		70.40 ± 6.60		SB ≥ 5 h/day	SB < 5 h/day	CD+MCI (②)
Du et al. (2022)	China	CSS	1	139	287	47.40%	46.70%	69.90 ± 5.80		SB ≥ 8 h/day	SB < 8 h/day	MCI (②)
Gillum et al. (2015)	US	CSS	2	194	1,162	NR		≥60		Sitting screen-hours > 3 h/day	Sitting screen-hours-3.1 in others	MCI
Jung and Chung (2020)	Korea	CSS	1	7,888	1,776	59.40%	52.02%	74.08 ± 6.50	72.50 ± 6.14	TV viewing	Not involved in TV viewing	MCI (②)
Martínez-Sanguinetti et al. (2019)	Chile	CSS	2	169	1,215	NR		≥60		High SB ≥ 4 h/day	Low SB < 4 h/day	MCI (②)
Paulo et al. (2016)	Brazil	CSS	1	51	340	64.70%	60.60%	71.07 ± 7.77		Physical inactivity < 150 min of MVPA/week	PA ≥ 150 min of MVPA/week	MCI (②)
Poblete-Valderrama et al. (2019)	Chile	CSS	2	169	1,215	NR		>60		High SB 4–8 h/day/very high SB > 8 h/day	Low SB < 4 h/day	MCI (②)

CD, cognitive decline; CG, control group; CS, cohort study; CSS, cross-sectional study; EG, exposure group; MCI, mild cognitive impairment; METs, metabolic equivalants; MVPA, moderate to vigorous physical activity; NR, no reported; Outcome: ①AD8 (ascertain dementia8); ②MMSE (mini-mental state examination); PA, physical activity; PAL, physical activity level; SB, sedentary behavior; SD, standard deviation; ST, sedentary time. In addition, a. Nemoto and b. Nemoto are the same article. The characteristics of different exposure groups in the same article are distinguished by/markers.

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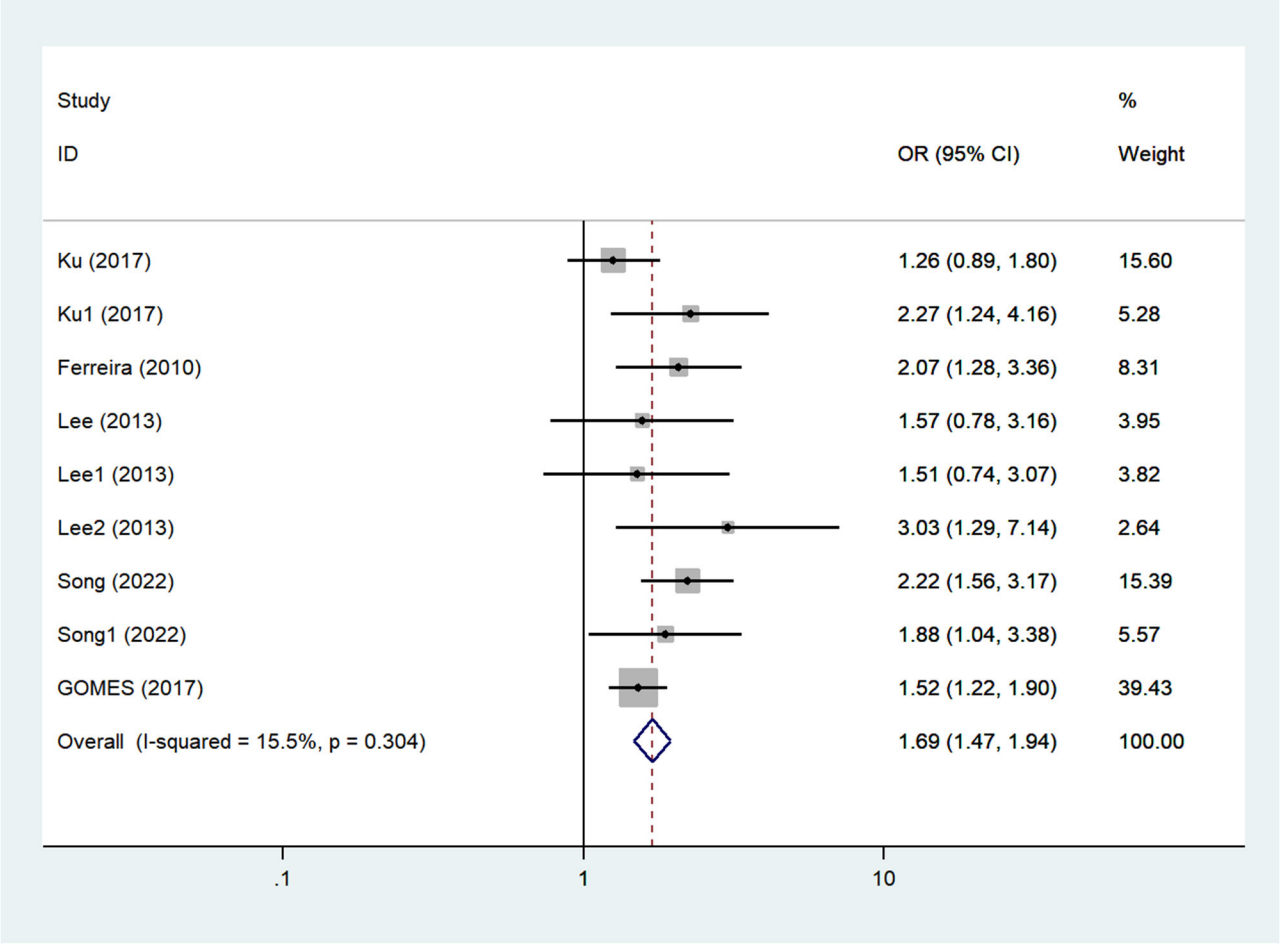

FIGURE 2
Forest plot of cognitive decline (CD).

Results of traditional meta-analysis

Association between SB and the risk of CD in the elderly

Five articles investigated the relationship between SB and the risk of CD in the elderly, with a sample size of 8,439 cases (Ferreira et al., 2010; Lee et al., 2013; Gomes et al., 2017; Ku et al., 2017a; Song and Park, 2022). The heterogeneity test showed that there was no heterogeneity among the studies (I^2 = 15.50%, $P_{\text{heterogeneity}}$ = 0.30); thus, the fixed effect model was used for meta-analysis. The combined meta-analysis results demonstrated a significant difference between the two groups (OR = 1.69, 95% CI: 1.47–1.94, P < 0.01), and long-term SB was found to increase the risk of CD in the elderly compared to the control group, as shown in Figure 2 and Table 2. The funnel diagram was relatively symmetrical, and Egger's test suggested that there was no publication bias within the studies ($P_{\text{Egger'stest}}$ = 0.19), as shown in Supplementary Figures 1, 2.

Association between SB and the risk of MCI in the elderly

In total, 14 articles investigated the relationship between SB and the risk of MCI in the elderly, with a sample size of 73,352 cases (Dogra and Stathokostas, 2012; Gillum et al., 2015; Lara et al., 2016; Paulo et al., 2016; Brunner et al., 2017; Ku et al., 2017b; García-Hermoso et al., 2018; Nemoto et al., 2018; Vancampfort et al., 2018; Martínez-Sanguinetti et al., 2019; Poblete-Valderrama et al., 2019; Jung and Chung, 2020; Cui et al., 2021; Du et al., 2022). The heterogeneity test showed that the studies were heterogenous (I^2 = 92.70%, $P_{\text{heterogeneity}}$ < 0.10), and a random effects model was used for the meta-analysis. The combined results showed a significant difference between the two groups (OR = 1.34, 95% CI: 1.14–1.56, P < 0.01), and prolonged SB was found to increase the risk of MCI in the elderly compared with control groups, as shown in Figure 3 and Table 2. The funnel diagram was relatively symmetrical, and Egger's test suggested that there was no publication bias within the studies ($P_{\text{Egger'stest}}$ = 0.20), as shown in Supplementary Figures 3, 4.

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TABLE 2 Results of traditional meta-analysis and subgroup analyses.

Meta-analyses outcomes/subgroup		Number of studies	OR, 95% CI	Heterogeneity		Effect model
				P	I^2 (%)	
Meta-analysis of the association between SB and risk of CD or MCI in elderly						
(High vs. Low) SB + CD		5	1.69 (1.47, 1.94)	0.30	15.50	Fixed effect model
(High vs. Low) SB + MCI		14	1.34 (1.14, 1.56)	<0.10	92.70	Random effects model
Results of subgroup analyses about SB and the risk of CD in elderly						
Duration of follow-up	Overall	5	1.69 (1.47, 1.94)	0.30	15.50	Fixed effect model
	≥3 years	3	2.03 (1.63, 2.53)	0.80	0.00	Fixed effect model
	<3 years	2	1.05 (1.25, 1.79)	0.25	27.40	Fixed effect model
Region	Overall	5	1.69 (1.47, 1.94)	0.30	15.50	Fixed effect model
	Developed countries	3	1.72 (1.46, 2.03)	0.39	2.90	Fixed effect model
	Developing or underdeveloped countries	2	1.61 (1.25, 2.09)	0.12	51.70	Fixed effect model
Publication year	Overall	5	1.69 (1.47, 1.94)	0.30	15.50	Fixed effect model
	≥2017	3	1.64 (1.41, 1.91)	0.15	40.50	Fixed effect model
	<2017	2	1.93 (1.40, 2.66)	0.58	0.00	Fixed effect model
Total sample size	Overall	5	1.69 (1.47, 1.94)	0.30	15.50	Fixed effect model
	≥1,000	2	1.71 (1.43, 2.04)	0.19	38.80	Fixed effect model
	<1,000	3	1.67 (1.34, 2.08)	0.28	19.00	Fixed effect model
SB exposure time	Overall	5	1.69 (1.47, 1.94)	0.30	15.50	Fixed effect model
	≥5 h/day	2	1.58 (1.23, 2.02)	0.26	23.10	Fixed effect model
	<5 h/day	3	1.75 (1.48, 2.07)	0.28	21.20	Fixed effect model
Complications	Overall	5	1.69 (1.47, 1.94)	0.30	15.50	Fixed effect model
	Yes	5	1.69 (1.47, 1.94)	0.30	15.50	Fixed effect model
	No		–	–	–	–
Comorbidities	Overall	5	1.69 (1.47, 1.94)	0.30	15.50	Fixed effect model
	Adjusted	5	1.69 (1.47, 1.94)	0.30	15.50	Fixed effect model
	Unadjusted		–	–	–	–
Lifestyle	Overall	5	1.69 (1.47, 1.94)	0.30	15.50	Fixed effect model
	Adjusted	3	1.78 (1.47, 2.15)	0.26	21.60	Fixed effect model
	Unadjusted	2	1.60 (1.31, 1.96)	0.25	23.10	Fixed effect model
Family structure	Overall	5	1.69 (1.47, 1.94)	0.30	15.50	Fixed effect model
	Adjusted	2	1.76 (1.42, 2.19)	0.12	48.60	Fixed effect model
	Unadjusted	3	1.64 (1.37, 1.97)	0.49	0.00	Fixed effect model
Results of subgroup analyses about SB and the risk of MCI in elderly						
Duration of follow-up	Overall	14	1.34 (1.14, 1.56)	0.00	92.70	Random effects model
	≥3 years	2	1.27 (0.99, 1.62)	0.00	85.50	Random effects model
	<3 years	12	1.41 (1.11, 1.78)	0.00	93.40	Random effects model
Region	Overall	14	1.34 (1.14, 1.56)	0.00	92.70	Random effects model
	Developed countries	6	0.99 (0.79, 1.23)	0.00	92.90	Random effects model
	Developing or Underdeveloped countries	8	2.18 (1.53, 3.09)	0.00	92.10	Random effects model
Publication year	Overall	14	1.34 (1.14, 1.56)	0.00	92.70	Random effects model

(Continued)

TABLE 2 (Continued)

Meta-analyses outcomes/subgroup		Number of studies	OR, 95% CI	Heterogeneity		Effect model
				P	I^2 (%)	
	≥2017	9	1.39 (1.14, 1.70)	0.00	94.50	Random effects model
	<2017	5	1.25 (1.10, 1.42)	0.34	11.60	Random effects model
Total sample size	Overall	14	1.34 (1.14, 1.56)	0.00	92.70	Random effects model
	≥1,000	10	1.14 (0.98, 1.33)	0.00	91.90	Random effects model
	<1,000	4	2.77 (1.47, 5.21)	0.00	85.00	Random effects model
SB exposure time	Overall	14	1.34 (1.14, 1.56)	0.00	92.70	Random effects model
	≥5 h/day	8	1.42 (1.14, 1.78)	0.00	94.70	Random effects model
	<5 h/day	6	1.26 (1.16, 1.37)	0.46	0.00	Random effects model
Complications	Overall	14	1.34 (1.14, 1.56)	0.00	92.70	Random effects model
	Yes	13	1.37 (1.15, 1.62)	0.00	93.40	Random effects model
	No	1	1.16 (0.98, 1.38)	0.52	0.00	Random effects model
Comorbidities	Overall	14	1.34 (1.14, 1.56)	0.00	92.70	Random effects model
	Adjusted	12	1.34 (1.12, 1.59)	0.00	93.50	Random effects model
	Unadjusted	2	1.33 (0.97, 1.83)	0.04	68.10	Random effects model
Lifestyle	Overall	14	1.34 (1.14, 1.56)	0.00	92.70	Random effects model
	Adjusted	10	1.32 (1.10, 1.59)	0.00,	94.00	Random effects model
	Unadjusted	4	1.38 (1.08, 1.77)	0.02	63.60	Random effects model
Family structure	Overall	14	1.34 (1.14, 1.56)	0.00	92.70	Random effects model
	Adjusted	7	1.27 (0.96, 1.69)	0.00	94.50	Random effects model
	Unadjusted	7	1.49 (1.24, 1.79)	0.00	83.30	Random effects model

SB, sedentary behavior; CD, cognitive decline; MCI, mild cognitive impairment.

Results of subgroup analyses

No subgroup statistical differences were observed in the relationship between SB and the risk of CD across the two groups or were any significant sources of heterogeneity identified. Significant statistical differences were observed in most subgroups regarding the relationship between SB and the risk of MCI. Furthermore, the consistency among these subgroups provided insights into the sources of heterogeneity. Subgroup analysis of SB exposure time showed significantly higher heterogeneity for sedentary time above 5 h/day (OR = 1.42, 95% CI: 1.14–1.78, $P_{\text{heterogeneity}} = 0.00$, $I^2 = 94.70\%$, random model) compared to that within 5 h/day (OR = 1.26, 95% CI: 1.16–1.37, $P_{\text{heterogeneity}} = 0.46$, $I^2 = 0.00\%$, random model) though no difference was observed between these two subgroups. Detailed results for other subgroup analyses are shown in Table 2.

Discussion

This study explored the association between SB and the risk of CD or MCI in the elderly from the perspective of evidence-based medicine. We found that elderly individuals with long-term SB were more likely to develop CD or MCI than those who engaged in physical activity (PA) or had short-term SB, and this trend is even more evident in Asian populations.

This study showed that prolonged SB increased the risk of CD in the elderly (OR = 1.69, 95% CI: 1.47–1.94), and there was a significant positive correlation between prolonged SB and increased risk of CD. Related studies have also revealed results consistent with ours (Kesse-Guyot et al., 2014; Falck et al., 2017). In a longitudinal study investigating the association of low PA, SB, smoking, and other lifestyle parameters with cognitive function in 2,430 middle-aged and older adults, Kesse-Guyot et al. (2014) showed that SB was associated with a decline in overall cognitive function in the elderly. In a systematic review of the association between SB and cognitive function, Falck et al. found that SB is not only associated with a higher risk of type 2 diabetes and cardiovascular disease but can also lead to a decline in overall cognitive, memory, and executive function in elderly individuals (Falck et al., 2017). In a cross-sectional study, Coelho et al. (2020) found that the negative association between SB and cognitive function was predominantly significant in the elderly with long-term SB. This could be attributed to the fact that with an increase in the sedentary time of elderly individuals, the body correspondingly induces an increase in white matter hyperintensity volume (WMHV), a decrease in the level of brain-derived neurotrophic factor (BD-NF), and a decrease in the level of medial temporal changes such as the thinning of leaf thickness and abnormal cerebral blood flow, which can lead

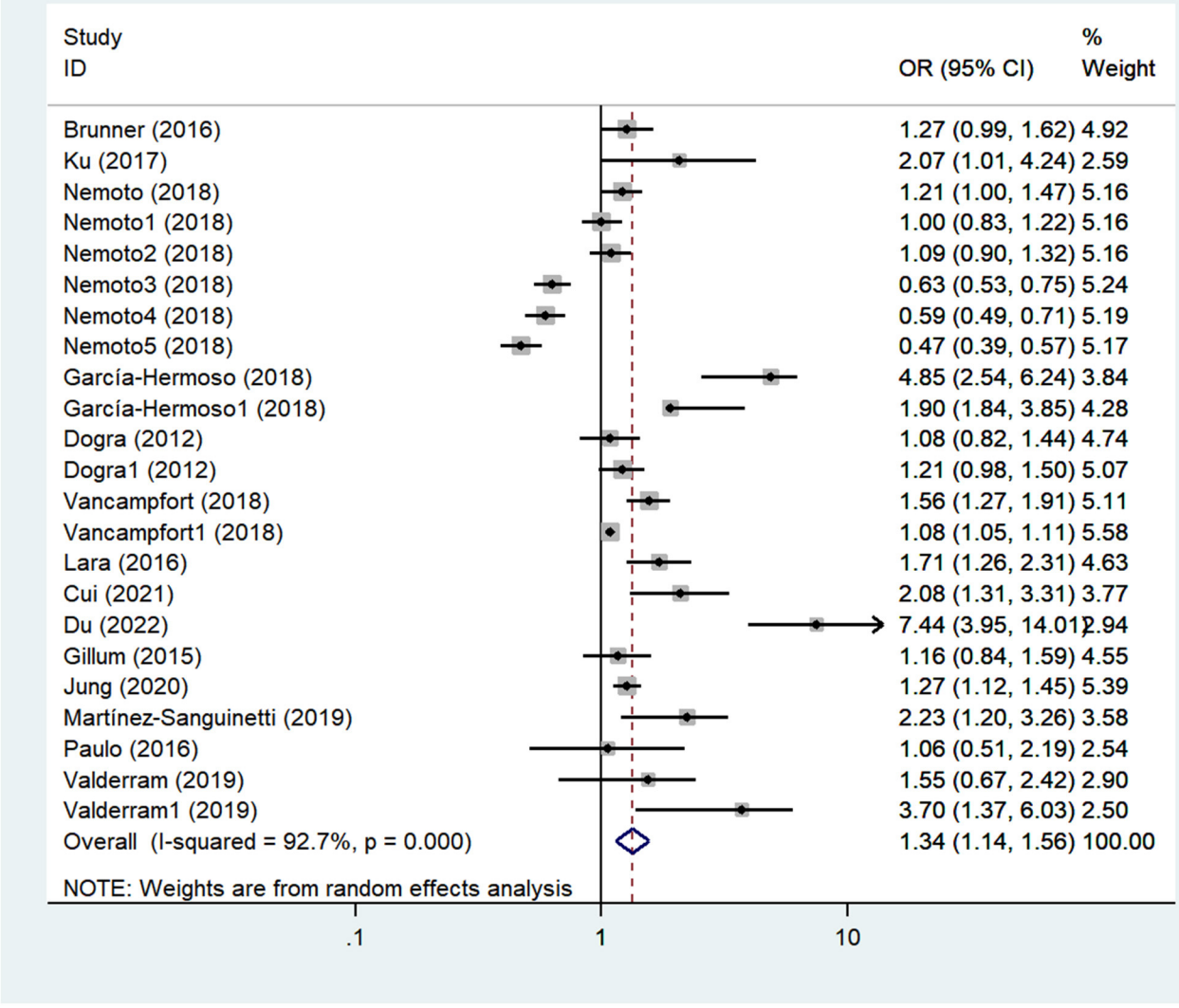

FIGURE 3
Forest plot of mild cognitive impairment (MCI).

to a decline of cognitive function in the elderly. In conclusion, the mechanisms through which SB causes CD are complex and multifaceted. Possible explanations for the discrepancy between existing relevant evidence (Kesse-Guyot et al., 2012; Hamer and Stamatakis, 2014) and the result of this article are that the sample size of their study was small and unrepresentative and that the short-term follow-up may not have been sufficient to detect a meaningful association between changes in cognition and SB. Moreover, the level of cognitive stimulation in the elderly also varies across SB measurement modes. In contrast, our study employed a comprehensive search strategy and involved multiple databases, and a complementary search was performed for potential literature such as meeting reports and abstracts. Consequently, the sample size of this study is large enough to provide strong evidence of the association under study. In addition, our results also found that prolonged SB significantly increased the risk of MCI in the elderly (OR = 1.34, 95% CI: 1.14–1.56), and there was a significant positive correlation between prolonged SB and the risk of MCI, consistent with previous studies (Xie et al., 2021; Gafni et al., 2022). In a cross-sectional study, Xie et al. (2021) found a significant relationship between excessive SB and MCI in the elderly. Their findings also revealed that limiting sedentary time is important as elderly patients with MCI tend to have a greater sedentary time, thereby leading to more adverse health outcomes. In another cross-sectional study, Gafni et al. (2022) found that insufficient PA and sitting for at least three-quarters of the day increased the risk of MCI in the elderly. In other words, low PA and prolonged SB adversely affect cognitive function in the elderly (Peng et al., 2022). This could be due to the high prevalence of chronic inflammation and reduced hormone levels associated with older stages of life. Long-term SB aggravates bone loss, reduces the size and quantity of muscle fibers, affects the contraction of skeletal muscles, and accelerates cell aging and brain atrophy, leading to MCI in the elderly. Thus, reducing sedentary time could prevent or retard the

development of MCI. Moreover, it is highly recommended that elderly individuals should increase their PA level and improve their sleep quality to enhance their individual cognitive function. Sleep duration, SB, and PA are co-dependent behaviors that constitute the movement/non-movement continuum and together account for the 24-h daily cycle (Zhu et al., 2020). Studies have shown that PA plays a positive role as an effective cognitive intervention in helping to improve cognitive function in older adults with AD or MCI (Liang et al., 2018). A minimum of 150 min of moderate-to-vigorous physical activity (MVPA) per week promotes an increased blood flow to the brain and improves metabolism and cardiovascular health (Liang et al., 2018). Deep sleep plays a crucial role in facilitating the clearance of amyloid-beta (Aβ) in the brain and improving overall sleep quality (Liang et al., 2020). They contribute to reducing the risk of MCI and dementia in the elderly population (Liang et al., 2020). Therefore, we encourage older adults to meet the 24-h healthy movement guidelines (i.e., ≥60 min of MVPA, ≤2 h of screentime, and age-appropriate sleep duration) (Zhu et al., 2020) in order to improve their cognitive health outcomes. In addition, we investigated whether there are gender differences in the cognitive impairment caused by SB. Studies have shown that the prevalence of MCI is 1.28 times higher in women than in men (Wang et al., 2020). Men who are engaged in mental work have rich knowledge reserves and strong thinking abilities and are not prone to cognitive impairment (Wang et al., 2020). Therefore, we suggest that elderly individuals should be encouraged to participate in educational activities, such as playing computer games or chess, to exercise their memory and potentially delay cognitive dysfunction.

In the subgroup analysis, we found significant differences between the two groups in terms of lifestyle, comorbidity, and family structure. The reason may be that sedentary elderly individuals live alone for a long time, have reduced daily communication, and find it difficult to overcome loneliness, anxiety, and depression, which could affect their cognitive function. The brain weight of elderly individuals decreases with increasing age, and there is a certain degree of inevitable physiological brain aging (Ma et al., 2019). The emergence of other comorbidities (such as hypertension and diabetes) accelerates the decline and impairment of cognitive function in the elderly. Simultaneously, there were differences in region, publication year, and the duration of SB between the two groups. This is due to the level of regional economic and medical resources, the construction of elderly activity venues, the lengthiness of publication, the short duration of the study, the sample size of the articles, and the quality of the content of the studies. In addition, this study mostly used scales, structured interview questionnaires, and self-reports to measure sedentary behavior, leading to possible bias in the results. Future research should use objective methods to more accurately measure the duration of SB, such as a three-dimensional accelerometer and an inclinometer.

Strengths and limitations

To the best of our knowledge, this is the first study to examine the relationship between SB and the risk of CD or MCI in the elderly. Given that this area of research is still developing, our study only provides some insight into the relationship between SB and the risk of CD or MCI in the elderly, providing reliable evidence for the development of future public health policies. The articles included in our study were small, and studies were not of high quality, which may have led to some bias in the interpretation of the results. In addition, the definition of "sedentary behavior" was inconsistent, which might induce bias in effect size estimates. For the evaluation of article quality, the existence of subjective judgment errors could lead to judgment bias. In the future, other assessment methods should be considered to minimize these errors to a great extent. When conducting subgroup analysis, some subgroups included a small number of articles and sample sizes, which reduced the reliability of the results. This requires further validation by high-quality and large-sample studies. This study is based on a systematic review and meta-analysis of observational studies. Most of the articles included in the analysis were from cross-sectional studies, limiting the ability to infer causality. In the future, more high-quality randomized controlled trials (RCTs), Mendelian randomization (MR) studies, or basic research would be needed.

Conclusion

In summary, our study reveals a positive association between SB and the risk of CD or MCI in the elderly. Long-term SB increases the risk of CD or MCI in the elderly. We recommend that the elderly reduce their SB time and increase their level of PA to promote healthy cognitive aging. Considering the quantity and quality of the included articles, our findings need to be interpreted with caution, and more high-quality longitudinal studies are required in the future to further demonstrate the association between SB and the risk of CD or MCI in the elderly.

Data availability statement

Data generated or analyzed during this study are included in this published article or in the data repositories listed in the references.

Author contributions

X-yC served as the principal author, had full access to all data in the study, and took responsibility for the accuracy of the data analysis and the integrity of the data. J-hL and FW contributed to the conception and design. M-yZ, G-pQ, and X-yC contributed to data acquisition and interpretation. X-yC and G-pQ contributed to the draft of the manuscript. Y-jD and J-hL revised the article and finally approved the study. All authors contributed to the article and approved the submitted version.

Funding

This research was supported by the Shanghai Education Science Research of China (No. C2021250) and the Shanghai Normal University Tianhua College.

Acknowledgments

We affirm that the study submitted for publication is original and has not been published other than as an abstract or preprint in any language or format and has not been submitted elsewhere for print or electronic publication consideration. We affirm that each person listed as the author participated in the study in a substantive manner, in accordance with ICMJE authorship guidelines, and is prepared to take public responsibility for it. All authors consent to the investigation of any improprieties that may be alleged regarding the study.

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/fnins.2023.1221990/full#supplementary-material

SUPPLEMENTARY MATERIAL 1
Search strategies.

SUPPLEMENTARY FIGURE 1
Funnel plot of cognitive decline (CD).

SUPPLEMENTARY FIGURE 2
Egger's test of cognitive decline (CD).

SUPPLEMENTARY FIGURE 3
Funnel plot of mild cognitive impairment (MCI).

SUPPLEMENTARY FIGURE 4
Egger's test of mild cognitive impairment (MCI).

SUPPLEMENTARY TABLE 1
Quality assessment for inclusion in cohort studies.

SUPPLEMENTARY TABLE 2
Quality assessment for inclusion in cross-sectional studies.

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frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 21 August 2023
DOI 10.3389/fpubh.2023.1193993

OPEN ACCESS

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RECEIVED 26 March 2023
ACCEPTED 31 July 2023
PUBLISHED 21 August 2023

CITATION
Huang J, Li R, Zhu H, Huang D, Li W, Wang J and Liu Z (2023) Association between serum globulin and cognitive impairment in older American adults.
Front. Public Health 11:1193993.
doi: 10.3389/fpubh.2023.1193993

Association between serum globulin and cognitive impairment in older American adults

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Background and aims: Cognitive impairment is on the rise around the world, with profound economic and social consequences. Serum globulin, a marker of liver function, may also play a role in cognitive function. Unfortunately, no consistent conclusion exists regarding the association between serum globulin and cognitive function.

Methods: Data from the 2011 to 2014 National Health and Nutrition Examination Survey were used to assess the association between serum globulin and cognitive impairment. Cognitive function was assessed by three tests: Consortium to Establish a Registry for Alzheimer's Disease (CERAD), Animal Fluency (AF), and Digit Symbol Substitution Test (DSST). Furthermore, the breakthrough point of cognitive impairment correlated with CERAD < 5, AF < 14, and DSST < 34. A weighted multiple logistics regression model was used to verify the association between serum globulin and cognitive impairment. Generalized additive models (GAMs) and a smooth curve fit (penalty spline method) were used to determine a non-linear relationship between serum globulin and cognitive impairment. Finally, subgroup analysis and interaction tests were conducted to further verify the association between serum globulin and cognitive impairment.

Results: Data from 2,768 participants aged ≥60 (in accordance with the study design) were collected for the final analysis. Data suggested that serum globulin levels were associated with an elevated cognitive impairment based on the AF [full adjustment, OR = 1.05, 95% *CI:* 1.01–1.08] and DSST [full adjustment, OR = 1.06, 95% *CI:* 1.02–1.10] tests. Eventually, the GAM and smooth curve fit model was conducted to confirm that the association between serum globulin and cognitive impairment was non-linear. Moreover, the inflection point was 27 g/L serum globulin based on the CERAD test and 35 g/L serum globulin based on the AF test. Finally, the interaction term between serum globulin and cognitive impairment based on the AF test indicated no significant interactions among all variables (all *p* for interaction >0.05).

Conclusion: The association between serum globulin levels and cognitive impairment is non-linear. A threshold effect exists between serum globulin and cognitive impairment. Large-scale prospective clinical trials are needed to validate our findings.

KEYWORDS

serum globulin, cognitive impairment, Consortium to Establish a Registry for Alzheimer's disease (CERAD), animal fluency (AF), Digit Symbol Substitution Test (DSST), smooth curve fit, generalized additive models (GAM)

Introduction

While globalization is sweeping the world, aging is also quietly hitting the world (1). Aging aggravates the prevalence of cognitive impairment (2). The most intuitive feeling is a sharp increase in the number of patients with cognitive impairment (3). Consequences of cognitive dysfunction include memory decline, reduced social mobility, and spatial cognitive impairment (4, 5). The disease specificity of cognitive impairment has brought serious economic and social burdens to society, especially in low-income countries (6, 7). A report estimated that the number of dementia cases will reach 150 million globally by 2050 (8). This figure is also very significant in the United States (US), which is estimated to be as high as 13.8 million by 2060 (9). This will pose serious economic and social challenges (10). Effective treatment methods and interventions will be worth investigating (4). Unfortunately, the current interventions have limited efficacy (11). Early prevention including identification of risk and protective factors may be an effective pathway (12–15).

Risk and protective factors of cognitive dysfunction and beneficial diet are important research directions and breakthroughs (4, 16–18). In recent years, serum globulin as a liver function marker has been used to predict other diseases such as stroke, ulcerative colitis, atrial fibrillation, rheumatoid arthritis, nasopharyngeal carcinoma, and hepatitis C virus and now it has become a hot spot of theoretical research (19–24). The relationship between serum globulin and cognitive function is also a current research hot spot (25–28). Data showed that serum globulin is related to cognitive function (29). However, Serum ApoB activity might relate to cognitive decline rather than serum globulin (30). Another research confirmed that there was a correlation between cognitive decline and serum albumin/globulin ratio (A/G ratio) (31).

Considering that existing studies do not fully understand the association between serum globulin and cognitive function, we consulted the National Health and Nutrition Examination Survey (NHANES) data analysis from 2011 to 2012 and 2013 to 2014 to verify the association between serum globulin and cognitive impairment in older American adults. To the best of our knowledge, this is the first study to determine the association between serum globulin and cognitive impairment based on clinical public data.

Methods

Study population

We extracted data from NHANES (2011–2012 and 2013–2014). The NHANES public database launched by the U.S. Centers for Disease Control and Prevention (CDC) is designed to evaluate the health status and nutrition level of the United States population, releasing data on a 2-year cycle (32–36). To date, thousands of secondary analyses have been performed globally based on NHANES data. Including 2011–2012 ($n = 9,756$) and 2013–2014 ($n = 10,175$), a total of 19,931 Americans participated. We had the following exclusion criteria: (1) <60 years old ($n = 16,299$), (2) inability to complete cognitive function tests ($n = 695$), (3) inability to complete blood tests ($n = 169$). Thus, 2,768 participants were eventually included in the analysis (Figure 1). In this study, written informed consent was obtained from all study participants and the Research Ethics Review Committee of the National Center for Health Statistics. The secondary analysis of the public database NHANES does not require specific informed consent. This research, with a secondary analysis of NHANES, was based on the guidelines of Strengthening the Reporting of Observation Studies in Epidemiology (STROBE) (37).

Primary exposure

In this study, we followed the guidelines in the NHANES Laboratory/Medical Technician Procedures Manual (LPM) for detailed specimen collection and processing instructions (38). Samples that needed to be tested were tested by the Collaborative Laboratory Services Department, and the samples for testing needed to be placed under specific conditions, such as the need to be packaged in vials and stored between 2 and 8°C. The value range of serum globulin was 14–65 g/L. In sensitive analysis, serum globulin was transferred into a categorical variable by quartile.

Outcome variable

The assessment of cognitive function, including working memory, delayed recall, and verbal fluency, was mainly conducted for American adults ≥60 years. The whole evaluation process was completed by the mobile detection center (MEC). Each participant recognized the recording quality and score of the completed examination.

The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) conducted research on new learning, recognition memory, and delayed recall. The CERAD Word Learning test (CERAD-WL) consists of three consecutive learning tests (39). During the assessment, after participants read 10 unrelated words aloud, they were instructed to recall as many words as they could from what they had just read. The total score of three trials was 30 points. The CERAD Delayed Recall (CERAD-DR) test asked participants to recall 10 words from the CERAD-WL test after completing other tests (16, 40).

Participants completed the Animal Fluency (AF) test, in which they were asked to name as many animals as possible within 1 min. Language fluency was judged during the test by the number of scores the participants named the animals (41). The operator used Digit Symbol Substitution Test (DSST) to evaluate participants' working memory, processing speed, and continuous attention. The whole test

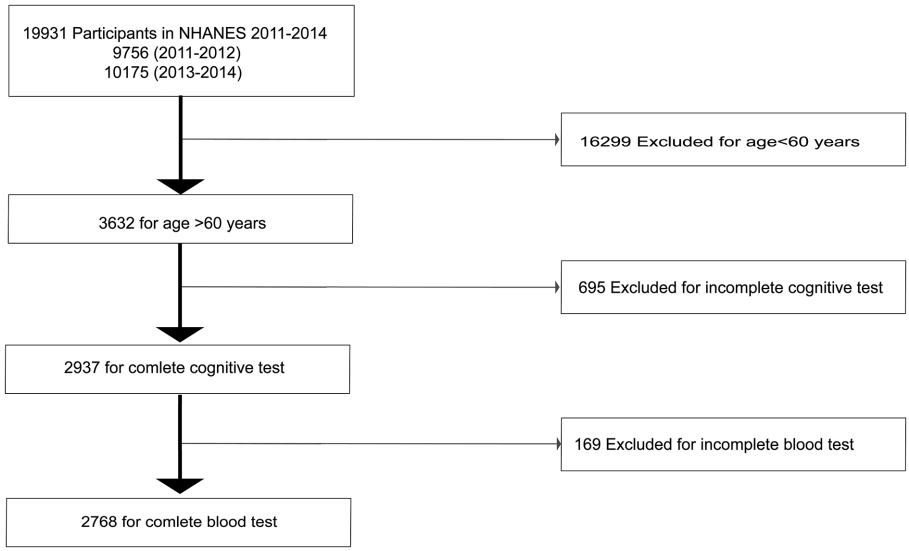

FIGURE 1
Flow chart showing the selection of study participants.

was completed in 2 min. By copying the symbols of 133 boxes, the more correct the matching, the higher the score (42).

At present, in the published literature, the scoring criteria of cognitive impairment have not been completely unified. The dividing point of cognitive impairment is usually 25% of the total score (43). Consistent with the references, CERAD < 5, AF < 14, and DSST < 34 were considered to suffer cognitive impairment.

Covariates

We referred to the historical literature for possible confounding factors, which mainly included three factors: sociodemographic factors, lifestyle, health status, and laboratory tests.

Sex, age, race, education, marital status, and poverty-to-income ratios were included in sociodemographic factors. Ages were divided into three groups: 60–69, 70–79, and ≥ 80 years. Race included five groups: Mexican American/Other Hispanic, Non-Hispanic White, Non-Hispanic Black, Non-Hispanic Asian, and Other. The educational levels of the subjects were classified as below high school, high school, and above high school. Marital status was divided into married/living with a partner, widowed/divorced/separated, and never married. The poverty-to-income ratio included two states: <1 and > 1.

In addition, lifestyle included alcohol consumption (12 alcoholic drinks per year), smoking habits (at least 100 cigarettes), and vigorous work activity (yes or no) (44). Health status was divided according to the history of coronary heart disease, stroke, diabetes, hypertension, and high cholesterol. Body mass index (BMI) included three statuses: <25, 25–30, and > 30 kg/m^2. A nine-question patient health questionnaire (PHQ9) was used to assess depressive status. Depression was defined as a score greater than 10 in historical literature (45). Laboratory tests included alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), total bilirubin, total protein, albumin, blood urea nitrogen (BUN), uric acid, and creatinine.

Statistical analysis

First, the two types of variables were expressed in different ways, in which continuous variables were described by weighted mean ± standard deviation, and differences were compared by one-way ANOVA. Conversely, weighted percentages were used to describe categorical variables and differences were compared by a chi-square test.

Second, in the current cross-sectional study, we used a weighted multivariate logistic regression model to effectively explore the association between serum globulin and cognitive impairment. Next, the model was fully adjusted in four areas: sociodemographic factors (sex, age, race, education level, marital status, and poverty-income ratio), lifestyle (alcohol consumption, smoking habit, and vigorous work activity), health status (BMI, depressive, and the history of coronary heart disease, stroke, diabetes, hypertension, and high cholesterol), and laboratory tests (ALT, AST, GGT, ALP, BUN, total bilirubin, total protein, albumin, creatinine, and uric acid). Whereas the minor model was just adjusted in three variables: sex, age, and race.

Third, we constructed generalized additive models (GAMs) and a smooth curve fit (penalty spline method) to detect any non-linear relationship between serum globulin and cognitive impairment. The linear fitting model (linear regression model) is significantly different from the non-linear fitting model (two-piecewise linear regression model) based on the p value of the log-likelihood ratio test <0.05. A two-piecewise linear regression model was suitable to evaluate the non-linear relationship between serum globulin and cognitive impairment. Moreover, a recursive algorithm method was used to automatically calculate threshold or inflection points.

Finally, we conducted subgroup analysis and interaction terms to verify the result. We divided each continuous variable into three groups in subgroup analysis. Furthermore, except for the subgroup variable itself, all variables were adjusted in the subgroup analysis.

Moreover, to more sensitively determine the association between serum globulin and cognitive impairment, serum globulin was transferred into a categorical variable by quartile and was assessed by *p* value for trend.

All statistical analyses were completed by R software,[1] EmpowerStats (http://www.empowerstats.com, X&Y Solutions, Inc., United States). We employed a full-sample 4-year MEC exam weighted to ensure that the survey was representative of all older adults. A bilateral test was performed, and $p < 0.05$ confirmed a statistically significant difference.

Results

Characteristics of study participants

Participants from 2011 to 2014 in NHANES were included in this study, and 2,768 participants over the age of 60 met the study design and entered the final statistical analysis. The overall characteristics of all study populations are statistically analyzed in Table 1, which is the quartile of serum globulin. First, the distribution of cognitive impairment for the primary outcome measure was that in all samples, 21.13% of CERAD < 5, 21.19% of AF < 14, and 14.54% of DSST < 34. Except for three variables, namely, age, smoking history, and coronary heart disease history ($p > 0.05$), the differences of other variables in serum globulin after quartile grouping were statistically significant. First, higher levels of serum globulin were found in women aged 60–69 years old with a BMI > 30 and a history of coronary heart disease, stroke, diabetes, and hypertension. However, lower levels of serum globulin were associated with the following factors: non-Hispanic White, above high school, married/living with a partner, poverty-income ratio > 1, alcohol, BMI 25–30, and history of high cholesterol.

Association between serum globulin and cognitive impairment

The association between serum globulin and cognitive impairment based on the CERAD, AF, and DSST tests is shown in Table 2. Three multivariate logistical regression models were applied to evaluate the association between serum globulin and cognitive impairment: model 1 (non-adjusted model), model 2 (minor adjusted model), and model 3 (fully adjusted model).

First, a statistically significant difference was not present in each model between serum globulin and cognitive impairment based on the CERAD test.

Second, a statistically significant difference was shown in each model between serum globulin and elevated risk of cognitive impairment based on the AF test. In the non-adjust model, the OR with 95% *CI* was 1.06 (1.04, 1.07), and AF in Q3-Q4 [Q3: OR = 1.58, 95% *CI:* 1.22–2.06, Q4: OR = 2.29, 95% *CI:* 1.79–2.94]. After adjusting for age, sex, and race, statistically significant differences existed between serum globulin and elevated risk of cognitive impairment [OR = 1.03, 95% *CI:* 1.01–1.05] and AF in Q4 [Q4: OR = 1.68, 95% *CI:* 1.28–2.21]. A fully adjusted model also showed a statistically significant difference between serum globulin and cognitive impairment [OR = 1.05, 95% *CI:* 1.01–1.08].

Third, statistically significant differences were identified in each model between serum globulin and elevated risk of cognitive impairment based on the DSST test [full adjustment, OR = 1.06, 95% *CI:* 1.02–1.10].

Identification of non-linear relationship

The GAM was conducted to assess whether there was a non-linear relationship between serum globulin and cognitive impairment (Figure 2). After full adjustment, results showed that the association between serum globulin and cognitive impairment was non-linear based on the CERAD and AF tests.

Adopting a weighted two-piecewise linear regression model and a recursive algorithm method, confirmed the turning point was 27 g/L based on the CERAD test (Table 3). On the left of the turning point or less than 27 g/L, the OR value and 95% *CI* were 1.07 and (1.00, 1.14; $p = 0.0392$), respectively. On the right of the inflection point or more than 27 g/L, the OR value and 95% *CI* were 0.98 and (0.94, 1.02), respectively.

Using a weighted two-piecewise linear regression model and a recursive algorithm method, data indicated that the inflection point was 35 g/L based on the AF test (Table 3). On the left of the turning point, OR with 95% *CI* were 1.07 and (1.03, 1.11; $p = 0.0004$). On the right of the turning point or more than 35 g/L, OR value and 95% *CI* were 0.96 and (0.90, 1.03), respectively.

Subgroup analyses outcomes

Table 4 presents the subgroup analysis and interaction results based on the CERAD, AF, and DSST tests.

First, interaction term results revealed a significant difference for smokers, alcohol users, and participants that reported high creatinine between serum globulin and cognitive impairment based on the CERAD test (all *p* for interaction <0.05). Subgroup analysis terms based on the CERAD test suggested that participants aged ≥80 years, those with diabetes, and 53–67 g/L total protein levels were associated with an increased risk of cognitive impairment (all $p < 0.05$).

Second, the interaction term between serum globulin and cognitive impairment based on the AF test indicated no significant interactions among all variables (all *p* for interaction >0.05). Moreover, subgroup analyses based on the AF test confirmed that participants who were aged 60–69 years old, women, or Mexican American/other Hispanic, educated above high school, widowed/divorced/separated, and never married, those with a poverty-income ratio > 1, those who consumed alcohol, performed no vigorous work activity, had no history of coronary heart disease or stroke, had diabetes, high cholesterol levels, depression, or those who had 4–15 U/L GGT, 59–74 U/L ALP, 1.07–5.71 mmol/L BUN, 65.4–362.8 μmol/L uric acid, 37.13–72.49 U/L creatinine, and 1.71–8.55 μmol/L total bilirubin had a significantly increased risk of cognitive impairment (all $p < 0.05$).

Third, interaction terms based on a DSST test between serum globulin and cognitive impairment were significant for total protein (*p* for

1 http://www.R-project.org

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TABLE 1 General characteristics of participants (n = 2,768) stratified by serum globulin (1–4, g/L) in the NHANES 2011–2014.

Characters	Total (n = 2,768)	Quartiles 1 (<25; n = 537)	Quartiles 2 (25–28; n = 707)	Quartiles 3 (28–31; n = 689)	Quartiles 4 (>31; n = 835)	p value
Sex						0.0021
Male	46.05	44.64	50.9	45.34	41.03	
Female	53.95	55.36	49.1	54.66	58.97	
Age (years)						0.2186
60–69	56.05	55.67	58.04	53.08	56.72	
70–79	29.43	27.66	29.23	32.13	29.02	
≥80	14.52	16.67	12.73	14.79	14.26	
Race						<0.0001
Mexican American/ other Hispanic	6.94	3.49	5	9.28	11.85	
Non-Hispanic White	80.22	91.81	87.99	74.87	58.94	
Non-Hispanic Black	7.96	1.8	4.29	8.3	21.32	
Non-Hispanic Asian	3.27	1.48	2.32	4.2	6.02	
Other Race	1.61	1.41	0.39	3.36	1.86	
Education						<0.0001
Less than high school	15.72	10.53	11.58	21.65	22.33	
High school	22.3	20.9	21.26	19.92	28.4	
Above high school	61.97	68.56	67.17	58.44	49.19	
Not recorded	0.02				0.08	
Marital status						<0.0001
Married/living with a partner	64.83	68.63	69.98	60.17	57	
Widowed/divorced/ separated	30.74	26.87	25.79	36.69	36.91	
Never married	4.4	4.44	4.23	3.14	6.04	
Not recorded	0.02	0.05			0.05	
Poverty-income ratio						<0.0001
<1	8.37	5.39	5.33	12.03	12.94	
>1	85.41	88.67	88.56	83.56	78.31	
Not recorded	6.22	5.94	6.11	4.41	8.75	
Alcohol (12 alcoholic drinks per year)						<0.0001
Yes	72.82	78.43	75.23	69.67	65.28	
Smoked (at least 100 cigarettes)						0.3553
Yes	50.1	49.83	48.56	54.24	48.26	
Vigorous work activity						0.0159
Yes	12.9	12.18	16	12.28	9.64	
BMI (kg/m^2)						<0.0001
<25	26	29.71	25.34	24.8	23.59	
25–30	36.17	39.75	38.58	33.45	30.79	
>30	36.36	29.97	34.13	40.22	43.85	

(Continued)

TABLE 1 (Continued)

Characters	Total (n = 2,768)	Quartiles 1 (<25; n = 537)	Quartiles 2 (25–28; n = 707)	Quartiles 3 (28–31; n = 689)	Quartiles 4 (>31; n = 835)	p value
History of coronary heart disease						0.191
Yes	9.66	9.44	10.33	10.16	8.33	
History of stroke						<0.0001
Yes	6.52	7.09	3.61	6.73	10.13	
History of diabetes						<0.0001
Yes	18.96	18.86	14.3	17.88	27.62	
History of hypertension						<0.0001
Yes	58.35	52.9	55.94	60.15	67.2	
History of high cholesterol						0.0498
Yes	57.49	59.94	54.86	58.65	57.16	
Depressive (>10)	6.98	6.36	4.86	7.1	10.98	0.0001
ALT (U/L)	22.13 ± 11.43	21.54 ± 7.66	22.13 ± 11.14	21.30 ± 9.34	23.82 ± 16.68	0.0006
AST (U/L)	25.02 ± 9.72	24.17 ± 6.48	24.33 ± 6.69	24.71 ± 8.35	27.58 ± 16.14	<0.0001
ALP (U/L)	67.50 ± 22.16	62.51 ± 18.12	64.26 ± 17.60	69.55 ± 21.26	76.79 ± 29.88	<0.0001
GGT (U/L).	25.58 ± 30.52	23.18 ± 20.94	21.61 ± 16.42	26.51 ± 28.71	33.91 ± 51.32	<0.0001
Total protein (g/L)	69.38 ± 4.56	65.12 ± 3.04	68.56 ± 2.67	70.69 ± 2.96	74.71 ± 4.01	<0.0001
Albumin (g/L)	42.10 ± 2.91	42.81 ± 2.57	42.51 ± 2.57	41.80 ± 2.96	40.89 ± 3.32	<0.0001
Total bilirubin (μmol/L)	11.76 ± 4.72	12.00 ± 4.43	11.91 ± 4.89	11.42 ± 3.96	11.60 ± 5.50	0.0884
Creatinine (μmol/L)	87.84 ± 51.49	86.54 ± 48.23	86.85 ± 31.92	85.08 ± 28.02	94.17 ± 87.58	0.0119
BUN (mmol/L)	5.81 ± 2.44	5.74 ± 2.10	5.78 ± 2.30	5.82 ± 2.29	5.91 ± 3.11	0.6745
Uric acid (μmol/L)	333.59 ± 85.02	315.21 ± 78.48	331.66 ± 81.53	337.81 ± 82.57	355.72 ± 95.07	
CERAD (<5)	21.13	19.7	19.46	25.06	21.24	0.0444
AF (<14)	21.19	15.56	18.38	23.67	30.13	<0.0001
DSST (<34)	14.54	8.03	11.01	17.93	24.75	<0.0001

Mean ± SD for: ALT (U/L), AST (U/L), ALP (U/L), GGT (U/L), total bilirubin (μmol/L), total protein (g/L), albumin (g/L), BUN (mmol/L), creatinine (μmol/L), and uric acid (μmol/L). p value was calculated by one-way ANOVA.

% for: sex, age, race, education, marital status, poverty-income ratio, alcohol consumption, smoking status, vigorous work activity, BMI (kg/m^2), depression, history of coronary heart disease, history of stroke, history of diabetes, history of hypertension, history of high cholesterol, CERAD, and AF, DSST. p value was calculated by a weighted chi-square test.

interaction <0.05). Subgroup analysis terms based on the DSST test revealed that participants who were men, 70–79 years old, Mexican American/other Hispanic, Non-Hispanic White, educated to less than high school, educated above high school, widowed/divorced/separated, poverty-income ratio > 1, consumed alcohol, smoked, performed no vigorous work activity, had a BMI >30, had no coronary heart disease, had no stroke, had diabetes, had high cholesterol, had depression, or had 4–15 U/L GGT, 21–40 g/L albumin, 75–336 U/L ALP, 25–1,197 U/L GGT, 6.07–33.92 mmol/L BUN, 73.37–91.94 U/L creatinine, 11.97–66.69 μmol/L total bilirubin, 72–95 g/L total protein, and 53–67 g/L total protein had a significantly increased risk of cognitive impairment (all $p < 0.05$).

Discussion

To the best of our knowledge, this is the first study to use the public sample data from 2011 to 2014 in the NHANES database to understand the association between serum globulin and cognitive impairment. At the same time, this study also conducted a beneficial exploration of the correlation between liver function and cognitive function. After adjusting for all possible confounding factors, serum globulin was associated with an elevated risk of cognitive impairment in the AF and DSST tests. Moreover, we used GAM and the smooth curve fit model to verify that this association between serum globulin and cognitive impairment is non-linear. There is an obvious serum globulin threshold of 27 g/L based on the CERAD test and 35 g/L based on the AF test. Our study differs from most previous studies in that we are the first to demonstrate the association between serum globulin and cognitive impairment.

In 2018, Frith et al. applied NHANES data to confirm the effect of physical activity on cognitive function, and their results revealed that an elevated gamma gap existed in the relationship. Gamma gaps indicate high serum globulin concentrations. All data indirectly confirmed that globulin proteins may correlate with cognitive function (46). Another study demonstrated that lower serum globulin and a higher albumin/globulin ratio were associated with increased gray matter volume in the olfactory cortex and parahippocampal gyrus (29). Our results are consistent with those of previous studies. Maeda

10.3389/fpubh.2023.1193993

TABLE 2 Associations between serum globulin (g/L) and cognitive impairment (CERAD <5, AF <14, and DSST <34; *n* = 2,768), NHANES 2011–2014.

	Model 1 OR (95% CI), *p*	Model 2 OR (95% CI), *p*	Model 3 OR (95% CI), *p*
CERAD < 5			
Globulin (g/L)	1.00 (0.99, 1.02) 0.6381	1.00 (0.98, 1.02) 0.7266	1.01 (0.97, 1.04) 0.7312
Quintiles of globulin			
Q1 (<25)	1	1	1
Q2 (25–28)	1.09 (0.84, 1.42) 0.5097	1.15 (0.87, 1.52) 0.3173	1.31 (0.94, 1.82) 0.1149
Q3 (28–31)	1.21 (0.93, 1.57) 0.1535	1.24 (0.93, 1.64) 0.1373	1.30 (0.87, 1.95) 0.2067
Q4 (>31)	1.11 (0.86, 1.44) 0.4025	1.12 (0.84, 1.49) 0.4285	1.24 (0.69, 2.23) 0.4650
p for trend	0.943	0.995	0.501
AF < 14			
Globulin (g/L)	1.06 (1.04, 1.07) <0.0001	1.03 (1.01, 1.05) 0.0020	1.05 (1.01, 1.08) 0.0075
Quintiles of globulin			
Q1 (<25)	1	1	1
Q2 (25–28)	1.26 (0.96, 1.64) 0.0926	1.19 (0.90, 1.58) 0.2093	1.31 (0.95, 1.82) 0.1000
Q3 (28–31)	1.58 (1.22, 2.06) 0.0006	1.32 (1.00, 1.74) 0.0518	1.48 (1.01, 2.18) 0.0463
Q4 (>31)	2.29 (1.79, 2.94) <0.0001	1.68 (1.28, 2.21) 0.0002	1.98 (1.15, 3.41) 0.0134
p for trend	<0.001	<0.001	0.12
DSST < 34			
Globulin (g/L)	1.09 (1.07, 1.11) <0.0001	1.07 (1.05, 1.09) <0.0001	1.06 (1.02, 1.10) 0.0040
Quintiles of globulin			
Q1 (<25)	1	1	1
Q2 (25–28)	1.59 (1.17, 2.17) 0.0031	1.51 (1.09, 2.10) 0.0141	1.46 (0.97, 2.18) 0.0700
Q3 (28–31)	2.49 (1.85, 3.36) <0.0001	2.06 (1.50, 2.85) <0.0001	1.59 (1.00, 2.54) 0.0501
Q4 (>31)	3.60 (2.71, 4.79) <0.0001	2.65 (1.93, 3.64) <0.0001	1.63 (0.85, 3.10) 0.1402
p for trend	<0.001	<0.001	0.711

Model 1: non-adjusted model; Model 2: adjust for age, race, sex; Model 3: adjust for age, race, sex, education, marital status, poverty-income ratio, alcohol consumption, smoking status, vigorous work activity, BMI, history of coronary heart disease, diabetes, stroke, hypertension, high cholesterol, depressive, ALT (U/L), AST (U/L), ALP (U/L), GGT (U/L), total bilirubin (μmol/L), total protein (g/L), Albumin (g/L), BUN (mmol/L), uric acid (μmol/L), and creatinine (μmol/L).

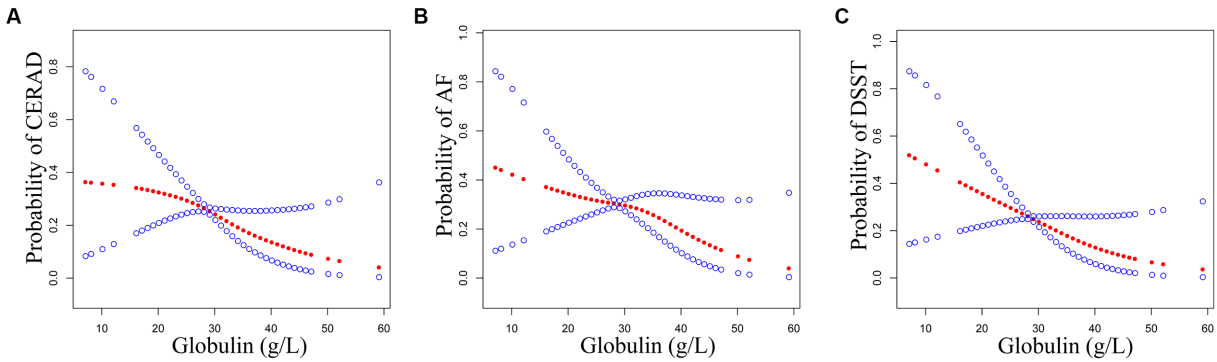

FIGURE 2
Association between serum globulin (g/L) and cognitive impairment. The probability of CERAD **(A)**, AF **(B)**, and DSST **(C)** represent the probability of cognitive impairment by GAM and smooth curve fit. The red points show a smooth curve fitting line and the blue points show a 95% confidence interval. The relationship adjusted for age, race, sex, education, marital status, poverty-income ratio, alcohol consumption, smoking status, vigorous work activity, BMI, history of coronary heart disease, diabetes, stroke, hypertension, high cholesterol, depression, ALT (U/L), AST (U/L), ALP (U/L), GGT (U/L), total bilirubin (μmol/L), total protein (g/L), Albumin (g/L), BUN (mmol/L), uric acid (μmol/L), and creatinine (μmol/L).

et al. reported that the serum albumin/globulin ratio was correlated with cognitive function in 1,827 Japanese older adults. However, serum albumin and globulin levels were not associated with cognitive function (31). Zhao et al. confirmed whether cognitive function was correlated to liver function. Data demonstrated that only serum ApoB activity, rather than serum globulin levels, may be associated with cognitive deficits (30). Another study revealed that the A/G ratio was the only factor that significantly lowered cognitive decline risk (27).

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TABLE 3 Nonlinearity addressing by weighted two-piecewise linear model based on CERAD and AF tests.

Outcome	CERAD log_2 transform OR (95% CI), *p*	Outcome	AF log_2 transform OR (95% CI), *p*
Fitting by a weighted linear regression model	1.01 (0.97, 1.04) 0.7312	Fitting by a weighted linear regression model	1.05 (1.01, 1.08) 0.0075
Fitting by a weighted two-piecewise logistic regression model			
Inflection point	27	Inflection point	35
< 27	1.07 (1.00, 1.14) 0.0392	< 35	1.07 (1.03, 1.11) 0.0004
> 27	0.98 (0.94, 1.02) 0.4072	> 35	0.96 (0.90, 1.03) 0.3133
Log-likelihood ratio test	0.02	Log-likelihood ratio test	0.007

The relationship adjusted for age, race, sex, education, marital status, poverty-income ratio, alcohol consumption, smoking status, vigorous work activity, BMI, history of coronary heart disease, diabetes, stroke, hypertension, high cholesterol, depression, ALT (U/L), AST (U/L), ALP (U/L), GGT (U/L), total bilirubin (μmol/L), total protein (g/L), Albumin (g/L), BUN (mmol/L), uric acid (μmol/L), and creatinine (μmol/L).

TABLE 4 Subgroup analysis of all variables and interaction tests.

	CERAD < 5		AF <14		DSST <34	
	OR (95% CI), *p*	*p* value of interaction	OR (95% CI), *p*	*p* value of interaction	OR (95% CI), *p*	*p* value of interaction
Sex		0.7520		0.0831		0.9344
Male	1.00 (0.95, 1.05) 0.9136		1.04 (0.99, 1.09) 0.0942		1.06 (1.01, 1.12) 0.0248	
Female	1.01 (0.96, 1.07) 0.6399		1.06 (1.01, 1.11) 0.0200		1.05 (0.99, 1.11) 0.1366	
Age (years)		0.1943		0.5520		0.0731
60–69	1.04 (0.99, 1.10) 0.1072		1.07 (1.02, 1.12) 0.0075		1.05 (0.99, 1.11) 0.1241	
70–79	1.02 (0.95, 1.09) 0.6097		1.02 (0.96, 1.09) 0.4934		1.09 (1.01, 1.18) 0.0246	
≥80	0.92 (0.85, 0.99) 0.0246		1.03 (0.95, 1.11) 0.4930		1.06 (0.97, 1.16) 0.1797	
Race		0.2158		0.1726		0.0567
Mexican American/other Hispanic	1.04 (0.96, 1.13) 0.3514		1.11 (1.03, 1.21) 0.0095		1.11 (1.01, 1.22) 0.0229	
Non-Hispanic White	1.00 (0.95, 1.06) 0.9375		1.06 (1.00, 1.11) 0.0541		1.10 (1.03, 1.17) 0.0057	
Non-Hispanic Black	1.00 (0.93, 1.08) 0.9676		1.01 (0.95, 1.08) 0.7222		1.01 (0.93, 1.08) 0.8808	
Non-Hispanic Asian	0.86 (0.70, 1.06) 0.1657		1.15 (1.00, 1.31) 0.0505		0.88 (0.63, 1.22) 0.4458	
Other race	0.00 (0.00, Inf) 0.9999		0.03 (0.00, Inf) 1.0000		30.05 (0.00, Inf) 1.0000	
Education		0.0678		0.2566		0.0795
Less than high school	1.01 (0.95, 1.08) 0.6792		1.03 (0.97, 1.09) 0.3707		1.10 (1.03, 1.18) 0.0045	
High school	0.98 (0.91, 1.05) 0.5563		1.05 (0.98, 1.13) 0.1687		0.97 (0.90, 1.05) 0.4817	
Above high school	1.01 (0.96, 1.07) 0.6300		1.09 (1.03, 1.15) 0.0018		1.10 (1.02, 1.19) 0.0150	
Marital status		0.7011		0.2534		0.8970
Married/living with a partner	1.00 (0.95, 1.05) 0.9625		1.04 (0.99, 1.09) 0.1466		1.04 (0.98, 1.10) 0.2116	
Widowed/ divorced/ separated	1.00 (0.95, 1.06) 0.8875		1.08 (1.03, 1.14) 0.0037		1.09 (1.02, 1.15) 0.0100	
Never married	1.15 (0.96, 1.39) 0.1370		0.80 (0.65, 0.99) 0.0399		0.96 (0.76, 1.22) 0.7478	
Poverty-income ratio		0.6168		0.8312		0.5524

(Continued)

TABLE 4 (Continued)

	CERAD < 5		AF <14		DSST <34	
	OR (95% CI), *p*	*p* value of interaction	OR (95% CI), *p*	*p* value of interaction	OR (95% CI), *p*	*p* value of interaction
<1	0.93 (0.85, 1.02) 0.1147		1.01 (0.93, 1.10) 0.8418		1.06 (0.97, 1.17) 0.1977	
>1	1.01 (0.97 1.06) 0.5184		1.06 (1.02, 1.10) 0.0069		1.06 (1.01, 1.11) 0.0227	
Not recorded	1.00 (0.85, 1.17) 0.9911		1.04 (0.91, 1.20) 0.5298		1.08 (0.90, 1.31) 0.4023	
Alcohol (12 alcoholic drinks per year)		0.0065		0.9875		0.4077
Yes	1.03 (0.99, 1.08) 0.1377		1.05 (1.01, 1.09) 0.0234		1.05 (1.00, 1.10) 0.0468	
No	0.95 (0.89, 1.01) 0.1010		1.05 (0.99, 1.11) 0.1107		1.06 (0.99, 1.14) 0.0847	
Smoking status		0.0174		0.6608		0.3638
Yes	1.03 (0.98, 1.08) 0.2390		1.05 (1.01, 1.10) 0.0294		1.07 (1.02, 1.13) 0.0118	
No	0.98 (0.93, 1.03) 0.3928		1.05 (0.99, 1.10) 0.0853		1.05 (0.98, 1.11) 0.1551	
Vigorous work activity		0.5468		0.3027		0.6181
Yes	0.91 (0.79, 1.05) 0.1902		1.11 (0.97, 1.26) 0.1216		1.06 (0.87, 1.29) 0.5524	
No	1.01 (0.97, 1.05) 0.5479		1.04 (1.00, 1.08) 0.0256		1.06 (1.02, 1.10) 0.0076	
BMI (kg/m^2)		0.4885		0.9796		0.2832
<25	1.00 (0.93, 1.08) 0.9524		1.02 (0.96, 1.10) 0.4826		1.01 (0.93, 1.10) 0.8661	
25–30	1.01 (0.95, 1.07) 0.8336		1.06 (1.00, 1.13) 0.0578		1.03 (0.96, 1.12) 0.4101	
>30	1.00 (0.95, 1.06) 0.8841		1.06 (1.01, 1.12) 0.0243		1.09 (1.03, 1.16) 0.0061	
Coronary heart disease		0.4671		0.9795		0.3984
Yes	1.06 (0.92, 1.22) 0.4338		1.08 (0.94, 1.25) 0.2748		1.13 (0.95, 1.35) 0.1646	
No	1.01 (0.97, 1.04) 0.7596		1.05 (1.01, 1.09) 0.0080		1.05 (1.01, 1.10) 0.0182	
Not recorded	1.00 (0.00, Inf) 1.0000		2.06 (0.00, Inf) 1.0000		1.00 (0.00, Inf) 1.0000	
Stroke		0.6883		0.3734		0.9590
Yes	0.91 (0.79, 1.06) 0.2347		1.02 (0.88, 1.18) 0.8042		1.01 (0.86, 1.17) 0.9365	
No	1.01 (0.97, 1.04) 0.7379		1.05 (1.01, 1.08) 0.0086		1.06 (1.02, 1.11) 0.0061	
Diabetes		0.6855		0.0836		0.0969
Yes	1.07 (1.00, 1.15) 0.0472		1.07 (1.00, 1.15) 0.0374		1.08 (1.00, 1.16) 0.0488	
No	0.99 (0.95, 1.03) 0.6424		1.04 (1.00, 1.09) 0.0412		1.05 (1.00, 1.11) 0.0443	
Not recorded	1.01 (0.78, 1.31) 0.9379		1.06 (0.82, 1.38) 0.6408		1.02 (0.61, 1.72) 0.9372	
Hypertension		0.3908		0.8641		0.3865
Yes	1.00 (0.96, 1.05) 0.8410		1.04 (0.99, 1.08) 0.0935		1.05 (1.00, 1.10) 0.0304	
No	1.01 (0.95, 1.08) 0.7781		1.07 (1.01, 1.14) 0.0281		1.06 (0.98, 1.15) 0.1666	
High cholesterol		0.9164		0.1109		0.6929
Yes	1.02 (0.97, 1.07) 0.4390		1.05 (1.00, 1.10) 0.0313		1.09 (1.03, 1.15) 0.0040	
No	1.00 (0.95, 1.06) 0.9393		1.06 (1.01, 1.11) 0.0304		1.03 (0.98, 1.10) 0.2561	
Not recorded	0.00 (0.00, Inf) 0.9998		0.00 (0.00, Inf) 0.9999		0.06 (0.00, Inf) 1.0000	
Depression		0.5030		0.4279		0.6631
Yes	1.00 (0.96, 1.04) 0.8537		1.04 (1.00, 1.08) 0.0268		1.06 (1.01, 1.10) 0.0137	
No	1.03 (0.92, 1.15) 0.5742		1.06 (0.95, 1.18) 0.2778		1.02 (0.90, 1.14) 0.8011	
ALT (U/L)		0.8356		0.0743		0.7686

(Continued)

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TABLE 4 (Continued)

	CERAD < 5		AF <14		DSST <34	
	OR (95% CI), *p*	*p* value of interaction	OR (95% CI), *p*	*p* value of interaction	OR (95% CI), *p*	*p* value of interaction
5–16	0.97 (0.91, 1.03) 0.3212		1.09 (1.03, 1.16) 0.0063		1.06 (0.99, 1.14) 0.0979	
17–22	1.05 (0.98, 1.12) 0.1423		1.01 (0.95, 1.08) 0.6769		1.07 (0.99, 1.15) 0.0863	
23–228	0.99 (0.93, 1.06) 0.8431		1.05 (0.99, 1.11) 0.1019		1.03 (0.96, 1.10) 0.4252	
AST (U/L)		0.2914		0.8673		0.0358
9–20	0.95 (0.88, 1.02) 0.1475		1.06 (0.99, 1.14) 0.0784		1.03 (0.95, 1.12) 0.5104	
21–25	1.03 (0.97, 1.10) 0.3603		1.02 (0.96, 1.09) 0.4597		1.07 (0.99, 1.16) 0.0734	
26–220	1.00 (0.94, 1.06) 0.9932		1.04 (0.98, 1.09) 0.2052		1.05 (0.99, 1.12) 0.1279	
GGT (U/L)		0.5691		0.8454		0.2023
4–15	1.04 (0.97, 1.11) 0.2266		1.11 (1.04, 1.19) 0.0021		1.14 (1.05, 1.23) 0.0009	
16–24	0.99 (0.93, 1.06) 0.7950		1.04 (0.97, 1.11) 0.2577		1.04 (0.96, 1.12) 0.3444	
25–1,197	0.99 (0.93, 1.05) 0.7194		1.03 (0.98, 1.09) 0.2674		1.01 (0.95, 1.08) 0.6781	
Albumin (g/L)		0.3568		0.1653		0.1073
21–40	1.00 (0.92, 1.09) 0.9350		1.07 (0.99, 1.16) 0.1066		1.16 (1.05, 1.28) 0.0046	
41–42	0.99 (0.67, 1.45) 0.9466		0.84 (0.58, 1.22) 0.3706		1.33 (0.85, 2.08) 0.2093	
43–54	0.99 (0.90, 1.09) 0.8379		1.00 (0.91, 1.10) 0.9924		1.05 (0.94, 1.17) 0.4144	
ALP (U/L)		0.1517		0.8475		0.3536
14–58	1.00 (0.94, 1.08) 0.9180		1.05 (0.98, 1.12) 0.1454		1.03 (0.95, 1.11) 0.5326	
59–74	1.00 (0.93, 1.07) 0.9833		1.11 (1.04, 1.18) 0.0017		1.06 (0.98, 1.15) 0.1244	
75–336	1.01 (0.96, 1.07) 0.6695		1.03 (0.97, 1.08) 0.3189		1.08 (1.01, 1.15) 0.0173	
BUN (mmol/L)		0.6675		0.4950		0.5258
1.07–4.28	0.99 (0.92, 1.06) 0.6899		1.10 (1.03, 1.18) 0.0044		1.06 (0.98, 1.15) 0.1324	
4.64–5.71	1.02 (0.96, 1.10) 0.4985		1.08 (1.01, 1.15) 0.0220		1.04 (0.96, 1.12) 0.3482	
6.07–33.92	1.00 (0.95, 1.06) 0.9070		1.01 (0.95, 1.06) 0.7875		1.07 (1.00, 1.13) 0.0454	
Uric acid (μmol/L)		0.0300		0.0949		0.3157
65.4–291.5	0.98 (0.92, 1.05) 0.5959		1.09 (1.03, 1.16) 0.0059		1.06 (0.99, 1.14) 0.1031	
297.4–362.8	1.04 (0.98, 1.11) 0.1841		1.09 (1.03, 1.16) 0.0058		1.05 (0.97, 1.13) 0.2350	
368.8–701.9	0.98 (0.92, 1.04) 0.5164		0.97 (0.92, 1.03) 0.3497		1.05 (0.99, 1.13) 0.1281	
Cre (U/L)		0.0070		0.4761		0.2468
37.13–72.49	1.02 (0.95, 1.09) 0.5679		1.08 (1.01, 1.15) 0.0249		1.04 (0.96, 1.13) 0.2857	
73.37–91.94	1.04 (0.97, 1.11) 0.3138		1.06 (0.99, 1.12) 0.0868		1.10 (1.02, 1.19) 0.0098	
92.82–1539.04	0.97 (0.92, 1.03) 0.3630		1.03 (0.97, 1.08) 0.3487		1.05 (0.99, 1.12) 0.1108	
Total bilirubin (μmol/L)		0.2539		0.9277		0.7501
1.71–8.55	0.97 (0.91, 1.03) 0.2755		1.07 (1.01, 1.13) 0.0283		1.04 (0.97, 1.11) 0.2801	
10.26–10.26	1.00 (0.92, 1.09) 0.9647		1.07 (0.98, 1.16) 0.1362		1.06 (0.96, 1.17) 0.2206	
11.97–66.69	1.02 (0.97, 1.08) 0.4426		1.03 (0.98, 1.09) 0.1878		1.08 (1.01, 1.15) 0.0218	
Total protein (g/L)		0.1363		0.0625		<0.0001
53–67	1.11 (1.01, 1.21) 0.0240		0.99 (0.90, 1.07) 0.7637		1.21 (1.07, 1.38) 0.0024	
68–71	1.00 (0.85, 1.17) 0.9623		1.04 (0.90, 1.21) 0.5693		0.96 (0.79, 1.17) 0.6887	
72–95	0.97 (0.92, 1.02) 0.2539		0.99 (0.95, 1.04) 0.8145		1.06 (1.00, 1.11) 0.0367	

Each continuous variable was divided into three groups according to its value. Each subgroup analysis adjusted for all the founders except the subgroup factor itself. Potential interactions between serum globulin and cognitive impairment were tested by a likelihood ratio test.

Compared with the recent literature, the present study has some main advantages. First, the large sample size may be more statistically significant in exploring the effect of serum globulin on cognitive impairment. This study included 2,768 older adults to better study the effect of serum globulin levels on cognitive function. Second, this study eliminated different categories of missing data to decrease the potential impact of missing data. Third, as many confounding factors as possible were included, including the participants' chronic disease history and depression status, and three mainstream experiments were adopted to evaluate cognitive function. Finally, the non-linear relationship between serum globulin levels and cognitive impairment was verified using a smooth curve fitting model, and the serum globulin threshold level was confirmed via threshold analysis.

However, this study had some limitations, which might have affected its outcomes. First, a causal relationship between serum globulin and cognitive impairment is difficult to distinguish, which is determined via the inherent characteristics of cross-sectional studies. Second, the NHANES study population was limited to Americans, so the generalizability of our results is geographically limited. Third, some older adults with potential cognitive impairment might have been excluded due to their inability to complete the interviews for cognitive function assessment.

Conclusion

The association between serum globulin and cognitive impairment is non-linear. A threshold effect was confirmed between serum globulin levels and cognitive impairment. Larger prospective clinical trials such as cohort studies and Mendelian analysis based on the association between serum globulin and cognitive impairment are needed in the future to confirm the current results.

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 Research Ethics Review Committee of the 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. The manuscript presents research on animals that do not require ethical approval for their study.

Author contributions

JH and ZL planned and executed the studies, data analysis, and drafted the manuscript. RL processed and analysis the data. HZ and DH have made great efforts to revise the manuscript. WL conceived the item. JW facilitated design and analysis of the experiments. All authors contributed to the article and approved the submitted version.

Funding

The study was funded by the National Natural Science Foundation of China (81471197 and 81070950).

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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frontiers | Frontiers in Aging Neuroscience

TYPE Original Research
PUBLISHED 14 September 2023
DOI 10.3389/fnagi.2023.1261026

OPEN ACCESS

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RECEIVED 18 July 2023
ACCEPTED 01 September 2023
PUBLISHED 14 September 2023

CITATION
Li S, Chen X, Gao M, Zhang X, Han P, Cao L, Gao J, Tao Q, Zhai J, Liang D and Guo Q (2023) The neutrophil-to-lymphocyte ratio is associated with mild cognitive impairment in community-dwelling older women aged over 70 years: a population-based cross-sectional study.
Front. Aging Neurosci. 15:1261026.
doi: 10.3389/fnagi.2023.1261026

The neutrophil-to-lymphocyte ratio is associated with mild cognitive impairment in community-dwelling older women aged over 70 years: a population-based cross-sectional study

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Background: The neutrophil-to-lymphocyte ratio (NLR) is a marker of inflammation that can be obtained quickly, conveniently, and cheaply from blood samples. However, there is no research to explore the effects of sex and age on the relationship between the NLR and mild cognitive impairment (MCI) in community-dwelling older adults.

Methods: A total of 3,169 individuals aged over 60 years in Shanghai were recruited for face-to-face interviews, and blood samples were collected. MCI was assessed by the Mini-Mental State Examination (MMSE) and the Instrumental Activities of Daily Living (IADL) scale, and neutrophil count and lymphocyte counts were measured in fasting blood samples. The NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count.

Results: In females, the NLR in the MCI group was significantly higher than that in the cognitively normal group (2.13 ± 0.94 vs. 1.85 ± 0.83, $p < 0.001$) but not in men. Logistic regression showed that a higher NLR was an independent risk factor for MCI in women [odds ratio (OR) = 1.28; 95% confidence interval (CI) = 1.09–1.49]. In addition, the elevated NLR quartile was associated with an increased risk of MCI, especially in women older than 70 years (p-value for trend = 0.011).

Conclusion: Compared with males, female MCI patients had a significantly higher NLR than cognitively normal controls. In addition, elevated NLR was found to be significantly associated with MCI risk in women older than 70 years. Therefore, elderly Chinese women with a higher NLR value may be the target population for effective prevention of MCI.

KEYWORDS

inflammations, mild cognitive impairment, sex difference, population-based study, neutrophil-to-lymphocyte ratio (NLR)

Introduction

With the rise in the aging of the population, age-related cognitive decline has become a major global public health concern and caused a huge economic and social burden, particularly in developing countries (Winblad et al., 2004). Mild cognitive impairment (MCI) is considered a transitional state between normal cognitive function and dementia. MCI is characterized as a risk factor for dementia (Liu et al., 2022). Patients with MCI will progress to dementia at a significantly greater rate of acceleration than that of healthy people of a similar age. Approximately 32% of patients with MCI develop Alzheimer's disease (AD) after five years (2021 Alzheimer's disease facts and figures, 2021). However, guidelines suggest that early detection and timely treatment of MCI can reverse the decline in cognitive function (Petersen et al., 2018). It is possible to prevent or delay the onset of dementia or AD with early diagnosis of and intervention in MCI.

The immune system is irreversibly impaired by aging, and that impairment is considered to be the most important risk factor for MCI. Inflammatory processes play a complex role in the progression of cognitive impairment (Pillai et al., 2019). Disorders of immune and inflammatory responses have been considered important risk components of MCI. Previous literature suggests that many common peripheral blood parameters may be novel inflammatory markers and may be associated with the pathogenesis or prognosis of central nervous system diseases (Shen et al., 2019). According to several studies, abnormal levels of peripheral inflammatory markers have been widely associated with MCI (Sağlam Aykut et al., 2018; Dong et al., 2019; An et al., 2020). According to a study from China, an increased risk of MCI was significantly associated with an elevated neutrophil-to-lymphocyte ratio (NLR) (An et al., 2020). Another study showed that the NLR and neutrophil percentage (neutrophil%) may be useful for identifying patients with MCI, as biomarkers in routine blood samples may correlate with cognitive impairment (Dong et al., 2019). However, there was also a study that showed a negative correlation between cognitive function and the NLR (Sağlam Aykut et al., 2018). Further, these studies were limited by relatively small sample sizes and did not consider several important confounding factors, especially sex and age.

In fact, age and sex may affect the relationship between MCI and NLR. A study from South America showed that the NLR had different age distribution characteristics between sexes. Many studies have demonstrated that sex hormones are closely linked to inflammation and cognitive impairment (Mf et al., 2016; Boccardi et al., 2019). Compared with men, postmenopausal women have a more rapid decline in peripheral sex hormone levels, as well as a higher inflammatory burden (Engler et al., 2016). According to a study by Minhas et al. (2021), aging promotes maladaptive inflammation that affects cognitive function. A decline in cognitive function as well as an increased risk of dementia is associated with aging and premature menopause in women (Duarte et al., 2016). The relationship between MCI and peripheral inflammatory markers in different sexes and ages remains uncertain. To date, no study has investigated the relationship between the NLR and MCI when stratified by age and sex, so the effect of age and sex on this relationship remains unclear.

Therefore, the aim of this study was to explore the relationship between MCI and peripheral inflammatory markers in different sex and age groups and provide a theoretical basis for the prevention and identification of MCI through an increased understanding of MCI.

Methods

Subjects

All participants, who were residents from six communities in Shanghai, were invited to engage in a comprehensive geriatric assessment in Shanghai from 2019 to 2023, during which they completed a face-to-face interview questionnaire as well as a physical examination. The study was approved by the Ethics Committee of Shanghai University of Medicine and Health Sciences, and the methods were carried out in accordance with the principles of the Declaration of Helsinki.

The inclusion criteria for this study were age 60 years or older and completion of relevant tests. The exclusion criteria were as follows: (1) persons with severe mental disorders, dementia, or other neurodegenerative diseases; (2) persons who did not provide informed consent or were unable to communicate with investigators; (3) persons with severe sensory impairments and unable to complete the assessment; and (4) persons for whom blood samples were not collected. A total of 4,046 participants were enrolled in the study. Of these, 310 individuals had an incomplete assessment of cognition and were excluded from the analysis. Additionally, 544 participants lacked blood samples, and 23 lacked other covariates and were also excluded from the analysis. The final analysis of the study included 3,169 participants (1,368 men and 1,801 women).

Definition of MCI

MCI was defined as patients with low cognitive ability [Mini-Mental State Examination (MMSE) score below the educational level cut point] and normal activities of daily living [Instrumental Activities of Daily Living (IADL) score ≥ 6] (Arevalo-Rodriguez et al., 2015). The Chinese version of the MMSE was used to assess cognitive impairment, with the following cutoff points: illiterate ≤ 17 points, primary school ≤ 20 points, and high school education level ≤ 24 points (Liu et al., 2022). The MMSE has been shown to be a reliable indicator of the cognitive status of Chinese individuals (Zhang et al., 2006).

Inflammatory markers

Peripheral inflammatory cells, including white blood cell (WBC), neutrophil, lymphocyte, and monocyte counts, were assessed by a

hematology analyzer XE-2100 (Sysmex). NLR values were calculated by dividing the absolute neutrophil count by the absolute lymphocyte count: neutrophil count/lymphocyte count.

Covariates

All participants were invited to participate in a face-to-face interview to answer a standardized questionnaire to obtain baseline data. Baseline data on sociodemographic characteristics, chronic disease status, and health behaviors were treated as covariates. Demographic characteristics included age, sex, height, weight, and education level. Health behaviors included smoking and alcohol consumption habits. Depressive symptoms were assessed using the Chinese version of the Geriatric Depression Scale (GDS), which was standardized in 1996 after its reliability and validity were tested (Yesavage et al., 1982). Nutritional status was measured by the Mini Nutritional Assessment (MNA) containing 18 items. A score of more than 23.5 was well-nourished, a score of 17 to 23.5 was at risk of malnutrition, and a score of less than 17 was malnourished. Physical activity was assessed by the International Physical Activity Questionnaire (IPAQ), total minutes of vigorous activity, moderate activity, and walking during a week were multiplied by 8.0, 4.0, and 3.3, respectively, and then added to represent total physical activity. The medical history of the participants was based on a combination of questionnaires answered by the participants, physician diagnoses, and taking medications or other current or past treatments, including hypertension, hyperlipidemia, diabetes mellitus, or coronary heart disease. Fasting plasma glucose was used to diagnose diabetes, lipid markers was used to diagnose hyperlipidemia, blood pressure was used to diagnose hypertension.

Statistical analysis

The following data analysis was conducted to investigate the correlation between MCI and inflammation among different sexes. Sociodemographic and health-related characteristics were collected at baseline. Normally distributed data are expressed as the mean and standard deviation, while nonnormally distributed data are expressed as the median and quartile. The t test or Mann–Whitney U test was used to analyze differences in baseline characteristics. Categorical variables were expressed as percentages (%) and analyzed using the $\chi 2$ test. Logistic regression models were used to examine the relationship between MCI and peripheral inflammatory cells by sex. Adjusted model included age, BMI, education, depression, widow, hypertension, coronary heart disease, smoking, and drinking. Further, we explored the relationship between MCI and age and sex using logistic regression. Adjusted model included BMI, education, depression, widow, hypertension, coronary heart disease, smoking, and drinking. The results are expressed as odds ratios, 95% confidence intervals, and corresponding p values. p value for trend was calculated from a one degree-of-freedom trend test. A p value of less than 0.05 was considered to indicate statistical significance. Statistical analysis was performed using SPSS v26.0.

Results

In total, 3,169 individuals participated in the study (mean age, 72.18 ± 5.34 years; 56.8% women). The prevalence of MCI was 8.4% and 11.5% among men and women, respectively. Table 1 presents the characteristics of the study participants (n = 3,169) stratified by sex. In men, participants with MCI tended to have a lower level of nutritional status and education but had high levels of depression and hypertension ($p < 0.05$). In women, participants with MCI tended to have a lower level of education, lymphocytes% and lymphocytes but had a higher level of age, neutrophils%, NLR, hyperlipidemia and platelets; in addition, they were more likely to be widows ($p < 0.05$) (Figure 1).

Table 2 presents the results of the sex-specific crude and adjusted associations between inflammatory markers and the prevalence of MCI. Among women, the NLR was positively associated with the presence of MCI in all models. The prevalence of MCI was highest in the fourth quartile of the NLR [odds ratio (OR) = 2.10; 95% confidence interval (CI) = 1.35–3.25]. However, in men, no significant association of these peripheral inflammatory parameters with MCI was found in the final multivariate model. Similar results were obtained when these peripheral inflammatory parameters were analyzed as continuous variables.

Table 3 shows that the prevalence of MCI was higher in the third (OR = 1.76; 95% CI = 1.01–3.08), and fourth quartiles of the NLR (OR = 2.56; 95% CI = 1.47–4.40) than in the first quartile of women older than 70 years. This suggests that the risk of MCI increased with increasing NLR in older women (p value for trend = 0.011) but not in younger women and men (See Figure 2).

Discussion

In this cross-sectional study, we found that the prevalence of MCI differed significantly between men and women and was influenced by age. We evaluated the effect of sex and age on the relationship between MCI and peripheral inflammatory markers in elderly individuals in rural areas of China. We found significant differences in NLR, lymphocytes and neutrophils% between patients with MCI and those without MCI in women but not in men. In addition, the NLR was significantly associated with the prevalence of MCI in women over 70 years of age but not in the other groups.

Studies in China have shown a higher risk of MCI in older women than in men (Nie et al., 2011; Xue et al., 2018), but studies from other countries have not found sex-based differences in MCI prevalence (Ravaglia et al., 2008; Katz et al., 2012). Additionally, some studies have shown a higher prevalence of MCI in men than in women (Bae et al., 2015). Sex differences in MCI prevalence may be due to risk factors like hyperlipidemia and malnutrition, along with a lower education level among Chinese elderly women. These risk factors were also found in our study. Inadequate education for women may lead to poorer career achievement, lower earnings, poorer health, and lower cognitive outcomes compared to men. In addition, the present study found that the association between hyperlipidemia and MCI was seen only in women, and women with hyperlipidemia had higher cognitive function than women without hyperlipidemia. This finding is consistent with a previous study conducted by our team (Liu et al., 2022). Women with MCI were found to have a protective factor against hyperlipidemia (Kim and Park, 2017). Studies indicate that higher serum cholesterol levels are associated with a reduced risk of cognitive impairment. However, the mechanisms linking sex, hyperlipidemia, and cognitive impairment are not well understood.

TABLE 1 Baseline characteristics of study participants with and without mild cognitive impairment.

Characteristic	Men			Women		
	Normal (n = 1,252)	MCI (n = 116)	p value	Normal (n = 1,593)	MCI (n = 208)	p value
Age (years)	72.37 ± 5.20	74.19 ± 6.53	0.004	71.56 ± 5.10	74.60 ± 6.11	<0.001
BMI (kg/m^2)	23.84 ± 3.17	23.88 ± 3.51	0.900	23.81 ± 3.48	24.20 ± 3.52	0.166
Widow (%)	92 (7.3)	14 (12.1)	0.069	341 (21.4)	65 (31.3)	0.001
Education (%)			0.001			<0.001
Illiteracy	37 (3.0)	11 (9.5)		183 (11.5)	80 (38.5)	
Primary school	447 (35.7)	39 (33.6)		604 (37.9)	78 (37.5)	
Junior high school or above	768 (61.3)	66 (56.9)		806 (50.6)	50 (24.0)	
Drinking (%)	523 (41.8)	51 (44.0)	0.647	146 (9.2)	15 (7.2)	0.353
Smoking (%)	389 (31.1)	44 (37.9)	0.129	10 (0.6)	0 (0)	0.252
MNA	19.47 ± 11.25	22.50 ± 8.11	0.007	21.88 ± 8.83	20.36 ± 9.45	0.304
IPAQ (Met-min/wk)	5,175 (1431–6,516)	4,591 (938–5,219)	0.810	4,270 (1509–8,106)	3,822 (1386–7,413)	0.090
Chronic disease (%)						
Hyperlipidemia	357 (28.5)	37 (31.25)	0.442	670 (42.1)	69 (33.2)	0.001
Hypertension	778 (62.1)	83 (71.6)	0.045	1,003 (63.0)	148 (71.2)	0.021
Diabetes	259 (20.7)	28 (24.1)	0.382	306 (19.2)	47 (22.6)	0.247
Coronary heart disease	261 (21.6)	30 (25.9)	0.294	431 (27.1)	74 (35.6)	0.010
Depression (%)	105 (8.4)	23 (19.8)	<0.001	225 (14.1)	43 (20.7)	0.013
Peripheral Blood Biomarkers						
WBC (×10^9/ L)	6.21 ± 1.53	6.08 ± 1.40	0.410	5.86 ± 1.45	5.88 ± 1.46	0.854
Lymphocytes%	31.93 ± 8.38	30.72 ± 8.13	0.135	34.89 ± 8.29	32.43 ± 8.34	<0.001
Neutrophils%	60.44 ± 9.57	62.05 ± 9.63	0.082	58.48 ± 9.22	61.89 ± 9.25	<0.001
Lymphocytes (×10^9/L)	1.96 ± 0.66	1.85 ± 0.60	0.083	2.02 ± 0.63	1.87 ± 0.57	0.001
Neutrophils (×10^9/L)	3.77 ± 1.21	3.80 ± 1.11	0.837	3.46 ± 1.14	3.68 ± 1.20	0.009
NLR	2.13 ± 1.01	2.25 ± 0.96	0.177	1.85 ± 0.83	2.13 ± 0.94	<0.001

MCI, mild cognitive impairment; BMI, body mass index; MNA, Mini-nutritional assessment; IPAQ, international physical activity questionnaire; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio.

Similar to the present study, a recent meta-analysis has shown sex differences in the relationship between cognitive impairment and malnutrition. Cognitive impairment was an independent predictor of malnutrition development at the 2-year follow-up among female participants (Corish and Bardon, 2019). Further research is required to investigate the underlying mechanisms.

Chronic low-grade systemic inflammation is regarded as one of the most relevant features characterizing aging and related diseases. Studies have shown that NLR values are significantly higher in AD (Kuyumcu et al., 2012) and MCI (An et al., 2020) patients than in controls. This is consistent with the results of our study, there is a significant difference in NLR between women with and without MCI (2.13 ± 0.94 vs. 1.85 ± 0.83). It has also been suggested that the NLR is a predictor of cognitive impairment (Halazun et al., 2014). Dong et al. (2019) showed that the NLR, neutrophil%, and mean platelet volume (MPV) were potentially useful for the identification of patients with MCI. Le et al. showed that peripheral B lymphocyte depletion was associated with increased Aβ burden (le Page et al., 2017). In contrast, a case–control study by Sağlam Aykut et al. (2018) reported a negative correlation between cognitive function and the NLR. In addition, other studies have shown that NLR values were significantly lower in Parkinson's disease patients with MCI compared with those without MCI (Contaldi et al., 2022). The differences in results may be due to differences in sample size, age, disease, and scales that measure cognitive function. Moreover, NLR values may vary among individuals from different racial and ethnic backgrounds. Nonetheless, several studies and this study have demonstrated a correlation between the NLR and cognitive impairment, suggesting that peripheral inflammation may play a crucial role in the pathogenesis of MCI.

Sex differences in immune systems can affect memory and cognitive function (Zhu et al., 2021). Women generally have stronger immune responses than men, which can lead to higher susceptibility to infections in men and a higher incidence of autoimmune disorders in women (Tronson and Collette, 2017). The APOE4 allele, which is the greatest genetic risk factor for cognitive impairment, has been shown to increase susceptibility to inflammation (Zhu et al., 2021). The APOE4 allele increases the risk of cognitive impairment to a significantly greater extent in women than in men (Altmann et al., 2014). Moreover, sex hormones can cause differences in the biology and/or effector functions of neutrophils between men and women

TABLE 2 Association between NLR and MCI in older adults by sex.

NLR	Men		Women	
	Crude	Adjusted model	Crude	Adjusted model
Quartile 1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Quartile 2	0.68 (0.36–1.28)	0.66 (0.35–1.26)	1.47 (0.96–2.25)	1.34 (0.86–2.08)
Quartile 3	1.37 (0.78–2.38)	1.31 (0.74–2.33)	1.68 (1.09–2.60)	1.38 (0.88–2.18)
Quartile 4	1.26 (0.73–2.17)	1.16 (0.66–2.04)	2.61*** (1.72–3.96)	2.10** (1.35–3.25)
Continuous	1.12 (0.94–1.33)	1.08 (0.91–1.30)	1.38*** (1.19–1.59)	1.28** (1.09–1.49)

Adjusted model: adjusted for age, education, BMI, depression, widow, hypertension, coronary heart disease, smoking, and drinking. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$ Values are odds ratio (95% confidence interval). BMI, body mass index; MCI, mild cognitive impairment; NLR, neutrophil-to-lymphocyte ratio.

TABLE 3 Association between NLR and MCI in four subgroups by sex and age.

NLR	Men				Women			
	Age ≤ 70		Age > 70		Age ≤ 70		Age > 70	
	Crude	Adjusted model	Crude	Adjusted model	Crude	Adjusted model	Crude	Adjusted model
Quartile 1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Quartile 2	0.62 (0.19–2.00)	0.68 (0.20–2.29)	0.70 (0.89–1.33)	0.68 (0.32–1.47)	0.96 (0.46–2.00)	0.96 (0.46–2.03)	1.81* (1.06–3.09)	1.60 (0.91–2.80)
Quartile 3	1.39 (0.52–3.74)	1.40 (0.49–4.05)	1.34 (0.67–3.47)	1.34 (0.67–2.71)	0.82 (0.34–1.95)	0.73 (0.30–1.76)	2.09* (1.22–3.55)	1.76* (1.01–3.08)
Quartile 4	1.32 (0.49–3.53)	1.42 (0.50–4.02)	1.22 (0.63–2.34)	1.10 (0.56–2.17)	1.74 (0.84–3.62)	1.44 (0.67–3.09)	3.04*** (1.81–5.11)	2.56** (1.47–4.40)
P value for trend	0.381	0.285	0.443	0.611	0.239	0.395	0.011	0.011
Continuous	1.19 (0.85–1.68)	1.23 (0.85–1.78)	1.09 (0.89–1.33)	1.04 (0.85–1.28)	1.24 (0.96–1.61)	1.16 (0.87–1.53)	1.43*** (1.19–1.72)	1.36** (1.11–1.65)

Adjusted model: adjusted for BMI, education, depression, widow, hypertension, coronary heart disease, smoking, and drinking. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$ values are odds ratio (95% confidence interval). BMI, body mass index; MCI, mild cognitive impairment; NLR, neutrophil-to-lymphocyte ratio.

(Bouman et al., 2005). Estradiol and progesterone, two types of female hormones, have been found to delay the death of neutrophils and change their movement (Jaillon et al., 2019). Older women exhibit different inflammatory responses under the influence of multiple pathways, including an increase in neutrophils and a decrease in lymphocytes (Dodd and Menon, 2022). Meanwhile, sex differences in age-related reduction of sex hormones may contribute to the difference in cognitive impairment between men and women (Li and Singh, 2014). Sex hormones and the differences in related genes such as APOE4 allele, can all be associated with maladaptive microglia as well as sex differences in the immune system (Mf et al., 2016). Coronary heart disease is associated with APOE4 allele (Liu et al., 2021), and we found its incidence is significantly higher in women than in men (women,28.0% vs. men, 22.0%). Sex-specific differences in microglial responses to neuroinflammation may imply that women are more susceptible to inflammatory stimuli leading to cognitive decline, whereas men are more tolerant to these stimuli (Zhu et al., 2021). Therefore, sex differences may be an important factor affecting inflammation and cognitive function. Further research is needed to understand the mechanisms underlying these sex-specific differences.

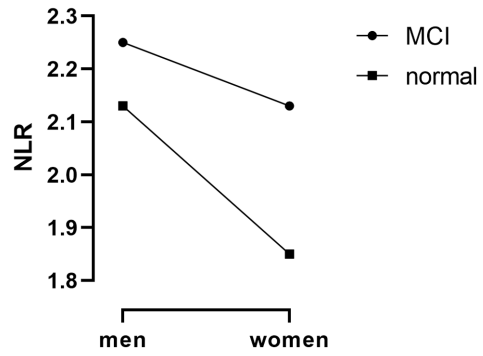

FIGURE 1
The relationship between NLR and MCI in men and women. Data are shown as medians.

The aging of peripheral cells may lead to chronic systemic inflammation during the aging process and the excessive release of various inflammatory mediators under inflammatory stimulation (Budamagunta et al., 2023). Animal models suggest that aging may reduce neutrophil clearance, which could compromise inflammation resolution following injury (Ramos-Cejudo et al., 2021). Systemic inflammation can promote aging-like brain changes, which may lead to a trajectory of cognitive decline. In addition, aging can affect cholinergic regulation of the nervous system and reduce acetylcholine activity, thereby activating multiple

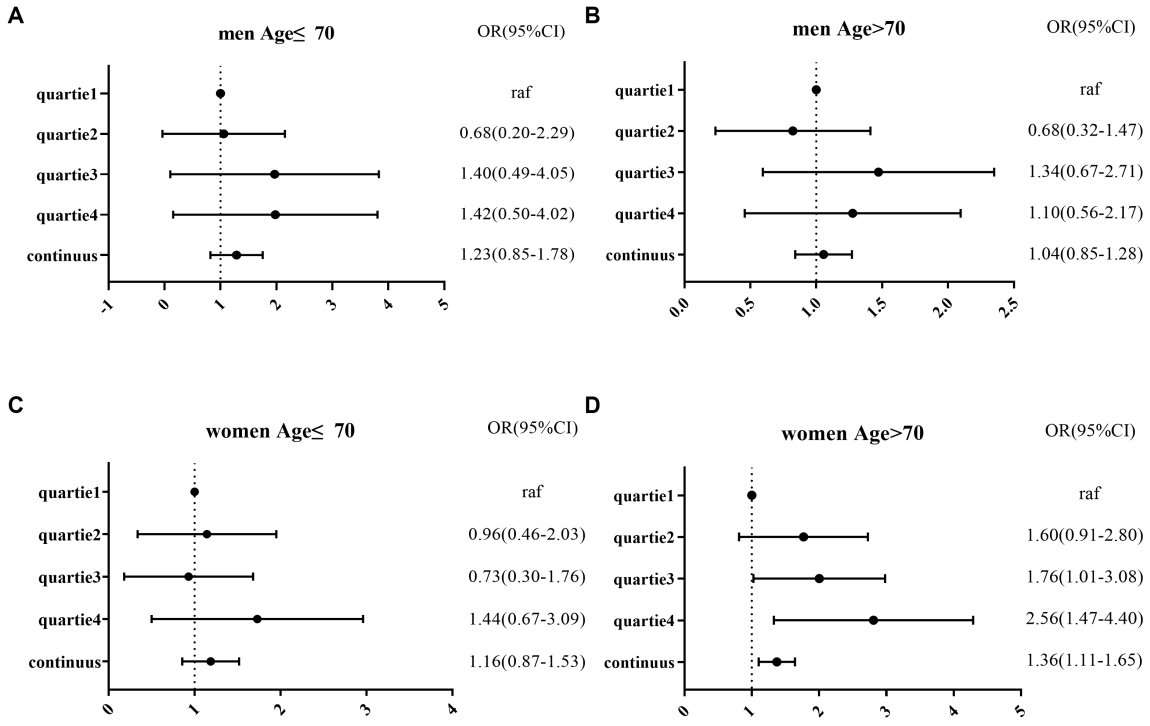

FIGURE 2
Logistic regression of MCI and NLR after adjusted model in four subgroups by sex and age **(A–D)**.

signaling pathways that regulate oxidative stress, inflammation of the nervous system, and interference with brain neurotrophic factors (Wang et al., 2023). Therefore, in age-related and pathological conditions, the accumulation of cell aging in peripheral tissues may lead to impaired memory function. A cohort study identified age as an important factor affecting cognitive ability in rural elderly people and related to the progression of cognitive impairment (Xu et al., 2023). Our study also observed that MCI patients were older than controls in both men and women. Aging increases the risk of cognitive impairment and causes low-grade systemic inflammation in the peripheral and central areas, but the interaction among these three factors is unclear and requires further study.

This study presents several strengths. First, this study sampled a relatively large number of settled older men and women who were relatively stable in their communities for a long period of time. Second, the study subjects came from different communities, and they had different lifestyles, which made our study subjects more representative. However, there are several limitations in this study. First, the participants in this study were in relatively good health, as we excluded patients who could not complete a full medical evaluation. Second, cognitive function was assessed by the MMSE. Therefore, this study could not further diagnose different types of cognitive impairment, including non-amnestic MCI and amnestic MCI. Third, alternatively, this study did not consider other factors that may contribute to cognitive impairment, including the APOE4 allele, atrial fibrillation, and carotid stenosis. Finally, this study was a cross-sectional study, and further longitudinal studies are needed to determine the causal relationship between MCI and inflammation.

Conclusion

In conclusion, we found that the NLR was significantly higher in female patients with MCI than in cognitively normal controls but it was not significantly increased in men. Moreover, the NLR was significantly associated with the risk of MCI in women older than 70 years of age. Further prospective studies are needed to confirm the causal relationship between inflammation and MCI in elderly women. This study has important implications for the early differential diagnosis of MCI and the improvement of cognitive status in elderly individuals.

Data availability statement

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

Ethics statement

The studies involving humans were approved by the Institutional Review Board of the Ethics Committee at Shanghai University of Medicine and Health Sciences. 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

SL: Formal analysis, Investigation, Methodology, Writing – original draft, Funding acquisition. XC: Conceptualization, Data curation, Writing – review & editing. MG: Investigation, Methodology, Project administration, Writing – review & editing. XZ: Data curation, Investigation, Project administration, Writing – review & editing. PH: Investigation, Writing – review & editing. LC: Project administration, Supervision, Writing – review & editing. JG: Resources, Writing – review & editing. QT: Resources, Writing – review & editing. JZ: Writing – review & editing. DL: Writing – review & editing. QG: Formal analysis, Supervision, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by the funding of Shanghai Municipal Health Commission (202240367), Capacity Building project of Local Colleges of Shanghai Science and Technology Commission (23010502800), and Shanghai Sailing Program (22YF1417900).

Acknowledgments

The authors thank all the members of the Department of Rehabilitation Medicine for their generous technical assistance and guidance. They also thank all the study participants for their kind participation and cooperation.

Conflict of interest

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

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2023.1261026/full#supplementary-material

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frontiers | Frontiers in Aging Neuroscience

TYPE Systematic Review
PUBLISHED 27 October 2023
DOI 10.3389/fnagi.2023.1227112

OPEN ACCESS

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RECEIVED 22 May 2023
ACCEPTED 26 September 2023
PUBLISHED 27 October 2023

CITATION
Song W-x, Wu W-w, Zhao Y-y, Xu H-l, Chen G-c, Jin S-y, Chen J, Xian S-x and Liang J-h (2023) Evidence from a meta-analysis and systematic review reveals the global prevalence of mild cognitive impairment. *Front. Aging Neurosci.* 15:1227112. doi: 10.3389/fnagi.2023.1227112

Evidence from a meta-analysis and systematic review reveals the global prevalence of mild cognitive impairment

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Objective: Mild cognitive impairment (MCI) is a preclinical and transitional stage between healthy ageing and dementia. The purpose of our study was to investigate the recent pooled global prevalence of MCI.

Methods: This meta-analysis was in line with the recommendations of Cochrane's Handbook and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020. We conducted a comprehensive search using the PubMed, Embase, Web of Science, CNKI, WFD, VIP, and CBM from their inception to March 1, 2023. Quality assessment was guided by the Agency for Healthcare Research and Quality (AHRQ) methodology checklist. The pooled global prevalence of MCI was synthesized using meta-analysis via random effect model. Subgroup analyses were performed to examine considered factors potentially associated with MCI prevalence.

Results: We identified 233 studies involving 676,974 individuals aged above 50 years. All the studies rated as moderated-to-high quality. The overall prevalence of MCI was 19.7% [95% confidence interval (95% CI): 18.3–21.1%]. Subgroup analyses revealed that the global prevalence of MCI increased over time, with a significant rise [32.1% (95% CI: 22.6–41.6%)] after 2019. Additionally, MCI prevalence in hospitals [34.0% (95% CI: 22.2–45.7%)] was higher than in nursing homes [22.6% (95% CI: 15.5–29.8%)] and communities [17.9% (95% CI: 16.6–19.2%)], particularly after the epidemic of coronavirus disease 2019 (COVID-19).

Conclusion: The global prevalence of MCI was 19.7% and mainly correlated with beginning year of survey and sample source. The MCI prevalence increased largely in hospitals after 2019 may be related to the outbreak of COVID-19. Further attention to MCI is necessary in the future to inform allocation of health resources for at-risk populations.

KEYWORDS

mild cognitive impairment, global prevalence, COVID-19, meta-analysis, systematic review

1. Introduction

Mild cognitive impairment (MCI) is a condition characterized by mild cognitive deficit, while still retains the ability to perform daily living activities (Petersen et al., 2014). A recent review reported that up to 15.56% of community dwellers aged over 50 years were affected by MCI worldwide (Bai et al., 2022). MCI is considered as a symptomatic precursor of dementia, serving as an intermediate stage between normal aging and dementia. Over 46% of individuals with MCI progressed to clinical dementia within 3 years, which is one of the major causes of disability and dependency among older people (Trambaiolli et al., 2021). Therefore, MCI as predementia imposes potential economic burden on individuals, families, and society (Wang et al., 2022).

MCI is currently viewed as an "intervention window" for delaying the onset of dementia (Anderson, 2019; Liang et al., 2019; Wang et al., 2020). Understanding the global prevalence of MCI is essential for developing relevant strategies to prevent dementia. In recent years, several epidemiological studies have been conducted on MCI prevalence at different levels. For instance, Bai et al. revealed that the prevalence of MCI among community dwellers worldwide was over 15% and influenced by factors such as age, sex, educational level, and sample source (Bai et al., 2022). Deng et al. reported a prevalence rate of MCI in China was 15.4%, which was associated with unhealthy lifestyles such as alcohol consumption and lack of exercise, as well as health conditions like diabetes, hypertension, coronary heart disease, and depression (Deng et al., 2021). This information is crucial for developing prevention strategies aimed at addressing these risk factors. However, there are significant heterogeneities among previous studies. First, some studies may reveal the partial results when investigating the prevalence of MCI among the global population. On the one hand, differences in population characteristics could lead to variation in prevalence. Specifically, populations with the high-risk diseases, such as diabetes and depression, have a higher MCI prevalence (Hasche et al., 2010; Bo et al., 2015), which could affect the accuracy of total prevalence in healthy individuals. On the other hand, differences in geographical distribution could also affect the precision of global MCI prevalence when investigators omitted evidence from other geographical areas and sample source (Bai et al., 2022; Chen et al., 2023). Second, during the same period and in the same region, different studies have reported significant disparities in results. For instance, two studies from China in 2019 produced significantly different prevalence: one reported 9.67% (Ruan et al., 2020), while the other reported 27.8% (Lu et al., 2019). Similarly, two studies conducted 1 year apart reported nearly a threefold difference in MCI prevalence results in China: one reported 33.3% in 2015, while the other reported 10.42% in 2016 (McGrattan et al., 2021). These discrepancies may be attributed to variations in study design, such as search sources, screening tools, and diagnostic criteria for MCI. Lastly, the outbreak of the coronavirus disease 2019 (COVID-19) has significantly impacted society, affecting the lifestyle and health of everyone. There is evidence suggesting that some patients who have recovered from COVID-19 exhibit cognitive deficits (Liu et al., 2021; Crivelli et al., 2022). Consequently, the prevalence of neurological diseases, including MCI, may be even more severe as a result of COVID-19. However, whether COVID-19 has increased MCI prevalence remains unknown, highlighting the need for more updated research into the prevalence of MCI. Therefore, a comprehensive and updated meta-analysis on the global prevalence of MCI is urgently needed to identify the risk factors and provide a reference for researchers and clinicians. The purpose of this study is to investigate the recent global prevalence of MCI among the widest possible population.

2. Methods

This systematic review was conducted in accordance with the recommendations of Cochrane's Handbook (Cumpston et al., 2019) and the Systematic Reviews and Meta-Analyses (PRISMA) 2020 (Page et al., 2021) (Supplementary File S2). These analyses relied solely on previously published studies, so ethical approval or patient consent was not required.

2.1. Search strategies

The eligible studies were identified through a comprehensive literature search in PubMed, Embase, Web of Science, CNKI, WFD, VIP, and CBM databases from their inception to March 1, 2023. A search strategy was employed using Medical Subject Headings (MeSH) terms associated with keywords and Boolean operators on "cognitive dysfunction," "mild cognitive impairment," "mild cognitive disorder," "prevalence," "epidemiology," and "epidemiological study" et al. In addition, manual retrieval was performed on the reference lists of relevant reviews and meta-analysis to search for additional studies on MCI prevalence. All database specific search queries could be found in Supplementary File S1.

2.2. Inclusion and exclusion criteria

Inclusion criteria were developed based on the PICOS principle, including participants (P), outcomes (O), and study design (S):

1. Participants: Studies were included when participants were diagnosed with MCI using recognized criteria, such as Petersen criteria (P-MCI) (Ronald, 2011), Diagnostic and Statistical Manual of Mental Disorders (DSM) (Sharp, 2022), etc.
2. Outcomes: Prevalence of MCI (or any of MCI subtypes) or data regarding the prevalence of MCI were provided in the report. If multiple articles were published based on the same dataset, only the most recent study was included.
3. Study design: Our study included all types of cohort and cross-sectional studies without any restriction in language, region, or publication date.

Studies were excluded if they met the following conditions:

1. Participants: Studies involving other types of cognitive dysfunction, such as dementia.
2. Outcomes: Studies involving the prevalence of comorbidity with MCI, such as hypertension, coronary heart disease, and depression.
3. Study design: Randomized controlled trials (RCT), systematic reviews, meta-analysis, case–control studies, bibliographic

review articles, letters to the editor, and articles published only in abstract form.

4. Full texts or data could not be obtained for our analyses.

2.3. Literature selection and data extraction

All citations were downloaded and managed using EndNote X9 software (Thompson ISI Research Soft, Clarivate Analytics, Philadelphia, United States). First, duplicate items were retrieved and removed. Then, based on inclusion and exclusion criteria, three investigators (WXS, YYZ, and HLX) independently reviewed the titles, abstracts, and full texts of publications to exclude irrelevant studies. All the eligible citations were cross-checked again to ensure accuracy. The relevant key data from the included studies were extracted into Microsoft Excel worksheets: (1) basic information: first author, publication year; (2) baseline characteristics: sample size, cases, age, proportion of males, beginning of survey, diagnostic criteria, region. The corresponding authors were consulted to obtain the essential information missing in the original studies.

2.4. Quality assessment

Three researchers (WXS, YYZ, and HLX) independently assessed the methodological quality of the included studies using the Agency for Healthcare Research and Quality (AHRQ) methodology checklist (Rostom et al., 2004). The checklist included 11 items: (I) Define the source of information; (II) List inclusion and exclusion criteria for exposed and unexposed subjects or provide a reference to previous publications that describe these criteria; (III) Indicate time period used for identifying patients; (IV) Indicate whether or not subjects were consecutive if not population-based; (V) Indicate if evaluators of subjective components of were masked to other aspects of the status of the participants; (VI) Describe any assessments undertaken for quality control purposes; (VII) Explain any patient exclusions from analysis; (VIII) Describe how confounding was assessed and/or controlled; (IX) If applicable, explain how missing data were handled in the analysis; (X) Summarize patient response rates and completeness of data collection; (XI) Clarify what follow-up, if any, was expected and the percentage of patients for which incomplete data or follow-up was obtained. The quality score for individual study ranges from 0 to 11, with 1 point for each item, and the study quality is separated into three levels: low (0–3), moderate (4–7), and high (8–11) (Hu et al., 2015). Any disagreements and uncertainty were resolved by discussion.

2.5. Statistical analyses

The overall prevalence and 95% confidence intervals (95% CI) was estimated using a random-effects model (Hedges, 1984). Heterogeneity was assessed by utilizing I^2 statistics, with $I^2 > 50\%$ or $p < 0.1$ indicating high heterogeneity (Higgins et al., 2003). A series of subgroup analyses were conducted to examine considered factors potentially associated with MCI prevalence. The subgroup variables included study type (cohort, cross-sectional), diagnostic method (P-MCI, DSM), male-to-female ratio (male/female ≥1, male/female <1), region[1] (developing country, developed country), regions[2] (Asia, Europe, North America, Africa, Oceania, South America), beginning year of survey (≤ 2009, 2010–2018, ≥ 2019), sample size (0–1,000, 1,001–5,000, 5,001–10,000, ≥10,001), sample source (community, nursing home, hospital), MCI subtype (aMCI/naMCI ≥1, aMCI/naMCI <1), basic diseases/non basic diseases (≥ 1, < 1) and the time trends in prevalence from different sample sources. Potential publication bias was assessed by using the funnel plot (Sedgwick, 2015) and Egger's test (Egger et al., 2003). All the aforementioned sequences of analyses were performed in Stata version 15.0 (Nyaga et al., 2014) using "metan" and "metabias" packages.

3. Results

3.1. Literature selection

We initially obtained 143,006 studies, including 142,706 citations from databases and 300 additional studies from manual retrieval. Then, 33,931 studies were excluded for duplication, 108,457 articles were removed due to irrelevant titles and abstracts. Subsequently, 385 studies were excluded for various reasons: 66 were not available in full, 31 were non-observational studies (RCT, reviews, commentaries, systematic reviews, meta-analysis, conference abstracts, case reports), 159 had no available data, 83 had unclear diagnostic criteria, and 46 were reduplicated. Finally, 233 studies were included in this meta-analysis. The study selection process is shown in Figure 1. And all included studies in this systematic review and meta-analysis showed in Supplementary File S4.

3.2. Characteristics and quality of included studies

The 233 included studies were conducted between 1981 and 2021, enrolling 676,974 individuals aged from 50 to 107 years old. Most studies were cross-sectional studies ($N = 207$, 88.8%) and conducted in Asia ($N = 171$, 75.0%). The common diagnostic criteria for MCI was P-MCI ($N = 150$, 77.7%). Other detailed information on study characteristics is presented in Table 1.

Study quality assessment scores ranged from 4 to 11, with 76 studies (32.6%) rated as "high quality" and 157 studies (67.4%) rated as "moderate quality." All the 233 studies scored no less than 3, so no study was excluded. Further details of the quality assessment are shown in Supplementary File S3.

3.3. Prevalence of MCI

A total of 233 studies were included in the analysis of overall pooled prevalence of MCI via a random effect model. The total global prevalence of MCI was 19.7% [(95% CI: 18.3–21.1%), p-value[1] < 0.001, $I^2 = 99.80\%$], showing significant heterogeneity among studies. The funnel plot and Egger's test (P-Egger's test < 0.001) both detected potential publication bias among the pooled results (Figure 2).

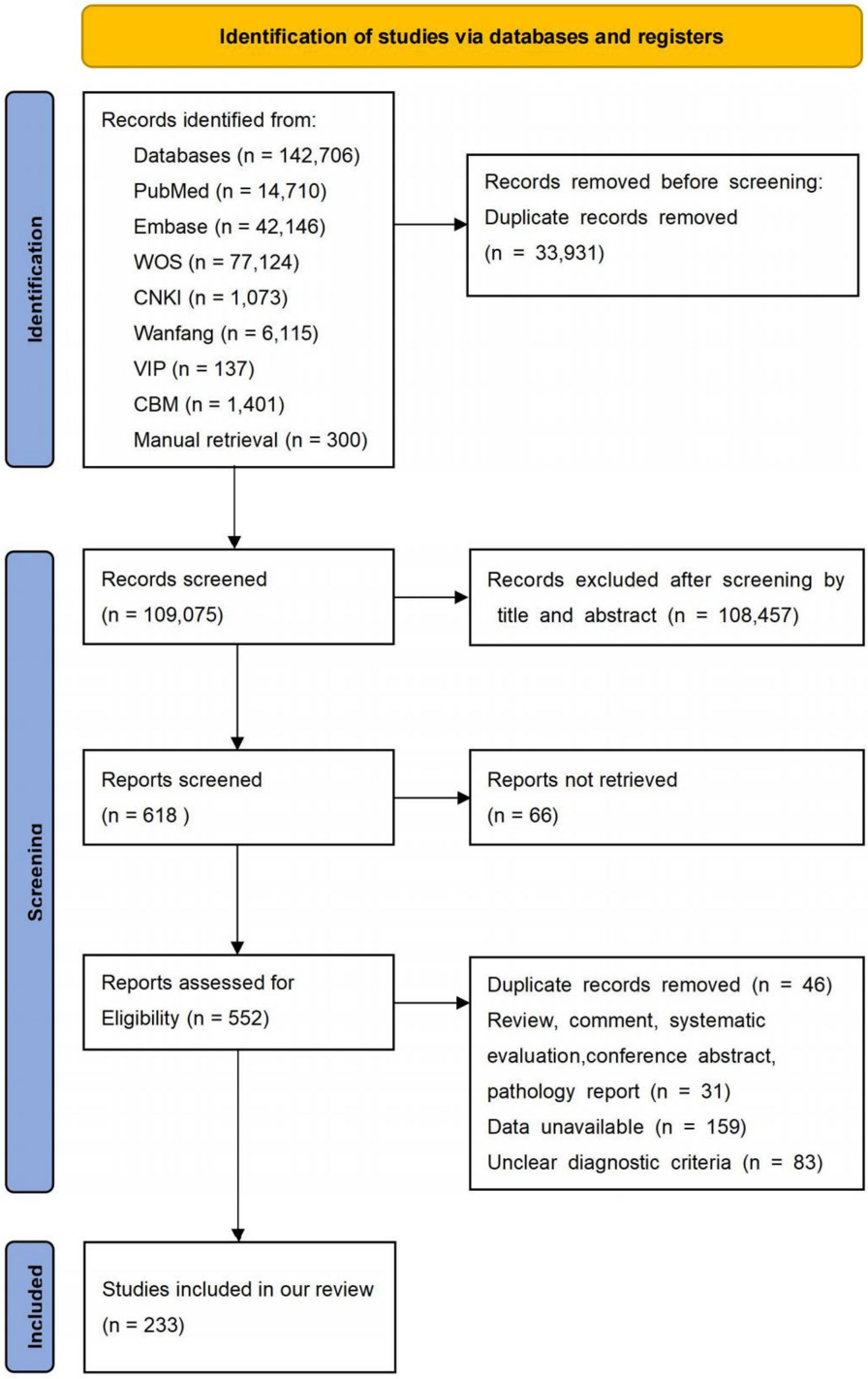

FIGURE 1
The screening process of the literature.

3.4. Subgroup analyses

Subgroup analyses indicated that the possible sources of heterogeneity were the sample source and beginning year of survey. The total prevalence of MCI in hospitals [34.0% (95% CI: 22.2–45.7%)] was the highest compared to that in nursing homes [22.6% (95% CI: 15.5–29.8%)] and communities [17.9% (95% CI: 16.6–19.2%)]. Moreover, MCI prevalence increased significantly over time. In particular, the global prevalence rose sharply after 2019 [32.1% (95% CI: 22.6–41.6%)] compared to the rates between 2010 and 2018 [19.8% (95% CI: 17.1–22.5%)] and before 2009 [14.5% (95% CI: 12.1–16.9%)]. Subsequently, we conducted further subgroup analyses to explore the time trends in prevalence from different sample sources (Table 2). Surprisingly, there were no significant differences in MCI prevalence among hospitals, nursing homes and communities before 2019. However, the MCI prevalence in hospitals [61.7% (95% CI:

TABLE 1 Characteristics of studies included in this meta-analysis.

ID	Study	Study design	Cases	Sample	Age, mean ± sd (range)	Proportion of males (%)	Beginning of survey	Diagnostic criteria	Region	Quality score
1	Björk et al. (2018)	Cross-sectional	1,067	4,545	85.50 ± 7.80	36.41%	2013–2014	P-MCI	Swedish	9
2	Tiwari et al. (2013)	Cross-sectional	98	2,146	≥60	47.44%	2008–2010	P-MCI	India	8
3	Rao et al. (2018)	Cross-sectional	299	2,111	≥65	40.50%	2009	P-MCI	China	8
4	VancamPfort et al. (2017)	Cross-sectional	5,005	32,715	≥50	48.30%	2007–2010	DSM-IV	China, Ghana, India, Mexico, Russia, South africa	7
5	Lu et al. (2019)	Cross-sectional	1,541	5,542	≥60	46.26%	2010 and 2015	P-MCI	China	7
6	Su et al. (2013)	Cross-sectional	145	796	≥60	32.79%	2012	P-MCI	China	4
7	Zhang et al. (2013)	Cross-sectional	450	2,460	60–89	45.98%	NR	P-MCI	China	5
8	Zhang et al. (2015)	Cross-sectional	651	1,971	≥60	37.44%	NR	DSM-IV	China	6
9	Li et al. (2013)	Cross-sectional	332	3,484	≥65	41.30%	2007–2009	P-MCI	China	9
10	Guo et al. (2013)	Cross-sectional	136	940	≥60	43.19%	NR	P-MCI	China	6
11	Yin et al. (2012)	Cross-sectional	67	1,011	≥65	40.55%	2007–2009	P-MCI	China	7
12	Pan et al. (2012)	Cross-sectional	154	897	69.68 ± 7.06	48.38%	2011–2011	P-MCI	China	9
13	Xia et al. (2006)	Cross-sectional	16	145	67.96 ± 6.49	39.31%	2000–2004	DSM-IV	China	7
14	Yang et al. (2017)	Cross-sectional	296	1,000	71.45 ± 5.86	48.60%	NR	P-MCI	China	7
15	Zhang et al. (2018)	Cohort study	430	1,033	≥55	33.69%	2016–2017	P-MCI	China	7
16	Jiang et al. (2019)	Cross-sectional	833	2,886	69.98 ± 5.90	41.61%	2017	P-MCI	China	7
17	Dai et al. (2019)	Cross-sectional	201	1,184	67.96 ± 6.49	50.17%	2019	CDGM	China	8
18	Liu et al. (2019)	Cross-sectional	73	554	≥60	64.80%	2018	CDGM	China	9
19	Yuan et al. (2019)	Cross-sectional	199	1,032	66 ± 7	38.19%	2015	P-MCI	China	6
20	Yuan et al. (2021)	Cross-sectional	613	3,043	≥60	51.36%	2016	P-MCI	China	8
21	Luo et al. (2015)	Cross-sectional	554	3,063	70.00 ± 7.70	45.60%	2010	P-MCI	China	6
22	Xu et al. (2014)	Cross-sectional	526	2,426	69.10 ± 6.80	39.30%	2010–2011	P-MCI	China	8
23	Tang et al. (2007)	Cross-sectional	217	1,865	60–100	48.10%	2004	P-MCI	China	6
24	Gang et al. (2008)	Cross-sectional	203	1,750	60–100	48.51%	2004	P-MCI	China	8
25	Huang et al. (2008)	Cross-sectional	257	4,697	≥60	41.15%	2001–2002	P-MCI	China	8
26	Ren et al. (2013)	Cross-sectional	99	946	≥60	50.74%	2011	DSM-IV	China	8
27	Zhou et al. (2011)	Cross-sectional	107	1,227	≥60	43.68%	2009–2010	DSM-IV	China	8
28	Chen et al. (2015)	Cross-sectional	352	1,695	≥60	46.90%	NR	P-MCI	China	4
29	Pan et al. (2012)	Cross-sectional	67	287	≥60	42.86%	NR	P-MCI	China	7
30	Song et al. (2012)	Cross-sectional	167	2,279	≥60	48.79%	2010–2011	P-MCI	China	8
31	Zhu et al. (2009)	Cross-sectional	148	1,511	≥60	45.40%	2008	DSM-IV	China	8
32	Wu et al. (2012)	Cross-sectional	396	1,583	≥60	50.28%	2011–2012	CDGM	China	7
33	Liao et al. (2012)	Cross-sectional	41	399	60–92	46.37%	NR	P-MCI	China	5
34	Zhang et al. (2014)	Cross-sectional	287	1,764	≥60	44.05%	2012	P-MCI	China	7
35	Afgin et al. (2012)	Cohort study	303	944	≥65	49.30%	NR	DSM-IV	Israel	10
36	Artero et al. (2008)	Cohort study	2,882	6,892	≥65	53.19%	1991–2001	DSM-IV	French	9
37	Lee et al. (2009)	Cohort study	188	927	≥60	33.66%	2005–2007	P-MCI	Korea	8

(Continued)

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TABLE 1 (Continued)

ID	Study	Study design	Cases	Sample	Age, mean ± sd (range)	Proportion of males (%)	Beginning of survey	Diagnostic criteria	Region	Quality score
38	Ogunniyi et al. (2016)	Cross-sectional	111	613	72.90 ± 8.50	68.35%	2013–2014	DSM-IV and P-MCI	Nigerian	9
39	Petersen et al. (2010)	Cross-sectional	329	1,969	70–89	50.89%	2004–2007	DSM-IV	United States	11
40	Pilleron et al. (2015)	Cohort study	133	2,002	≥65	NR	2011–2012	P-MCI	Central Africa	6
41	Richard et al. (2013)	Cohort study	429	2,160	NR	NR	1999–2001	P-MCI	United States	8
42	Kumar et al. (2005)	Cohort study	93	2,518	NR	NR	2001–2002	P-MCI	Australia	9
43	Lee et al. (2009)	Cohort study	197	714	71.90 ± 5.70	42.16%	2005	P-MCI	Korea	6
44	Lee et al. (2012)	Cross-sectional	67	318	65.90 ± 5.30	40.88%	2008–2009	P-MCI	Malaysian	8
45	Purser et al. (2005)	Cohort study	810	3,673	74	38.69%	1981, 1984, 1987, and 1990	P-MCI	United States	8
46	De Jager et al. (2005)	Cohort study	40	157	NR	NR	NR	P-MCI	United Kingdom	7
47	Khedr et al. (2015)	Cross-sectional	12	691	≥60	NR	2011–2013	DSM-IV	Egypt	7
48	Yu et al. (2016)	Cohort study	66	376	68.60 ± 4.70	NR	NR	DSM-IV	China	5
49	Ma et al. (2016)	Cross-sectional	574	5,241	72.13 ± 4.22	43.90%	2012–2012	P-MCI	China	9
50	Wang et al. (2015)	Cross-sectional	625	3,136	69.30 ± 6.80	40.66%	2012–2012	P-MCI	China	8
51	Jia et al. (2013)	Cross-sectional	2,137	10,276	NR	42.41%	2008–2009	DSM-IV	China	9
52	Hu et al. (2012)	Cross-sectional	1,782	9,146	65.62 ± 7.52	43.83%	2008–2009	DSM-IV	China	7
53	Qiu et al. (2003)	Cross-sectional	92	3,910	66.97 ± 8.44	49.68%	2000–2001	P-MCI	China	8
54	Lei et al. (2008)	Cross-sectional	680	4,419	66.40 ± 5.60	41.68%	2005	The diagnostic criteria for MCI in Sweden, 2001	China	8
55	Lao et al. (2011)	Cross-sectional	326	7,665	≥55	45.78%	2010	P-MCI	China	5
56	Yang et al. (2011)	Cross-sectional	337	454	72.67 ± 6.34	69.16%	2009	Chinese guidelines and P-MCI	China	4
57	Yin et al. (2011)	Cross-sectional	310	2,164	≥60	45.84%	2010	P-MCI	China	6
58	Tong et al. (2013)	Cross-sectional	200	1,575	≥60	NR	2012	P-MCI	China	6
59	Xiong et al. (2013)	Cross-sectional	339	2,978	≥65	44.12%	2011	DSM-IV	China	7
60	Zhang et al. (2013)	Cross-sectional	450	2,460	≥60	45.98%	NR	P-MCI	China	8
61	Gu et al. (2014)	Cohort study	92	679	60–91	44.33%	2010–2013	IWG	China	7
62	Qin et al. (2014)	Cross-sectional	612	4,086	≥55	35.00%	2011–2012	P-MCI	China	8
63	Sun et al. (2016)	Cross-sectional	40	384	≥65	52.08%	NR	IWG and ADNI	China	4
64	Zhou et al. (2016)	Cross-sectional	221	804	60–88	46.52%	2014–2015	Chinese guidelines and P-MCI	China	7
65	Guo et al. (2012)	Cross-sectional	35	264	≥65	50.76%	2008–2009	P-MCI	China	8
66	Jia et al. (2014)	Cross-sectional	2,137	10,276	≥65	42.61%	2008–2009	DSM-IV	China	8
67	Li et al. (2013)	Cross-sectional	160	1,020	≥55	36.67%	NR	P-MCI	China	8
68	Ding et al. (2015)	Cross-sectional	601	2,985	≥60	NR	2010–2011	DSM-IV	China	8
69	Xu et al. (2014)	Cross-sectional	526	2,426	≥60	39.32%	2010–2011	P-MCI	China	8
70	Zanetti et al. (2006)	Cohort study	65	400	≥65	NR	2000	DSM-IV	Italy	7
71	Pioggiosi et al. (2006)	Cross-sectional	11	34	96.40 ± 3.90	20.59%	1994–1996	DSM-IV	Italy	7
72	Manly et al. (2005)	Cohort study	372	1,315	≥65	31.18%	NR	P-MCI	United States	6
73	Purser et al. (2005)	Cohort study	810	3,673	≥65	38.69%	1981–1991	P-MCI	United States	6

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TABLE 1 (Continued)

ID	Study	Study design	Cases	Sample	Age, mean ± sd (range)	Proportion of males (%)	Beginning of survey	Diagnostic criteria	Region	Quality score
74	Kim et al. (2007)	Cohort study	388	1,215	≥60	42.80%	2004–2006	P-MCI	Korea	8
75	Jungwirth et al. (2005)	Cross-sectional	41	592	75	NR	2002	P-MCI	Australia	7
76	Das et al. (2007)	Cross-sectional	111	745	≥50	49.26%	2003–2004	DSM-IV	India	8
77	Tognoni et al. (2005)	Cross-sectional	79	1,600	≥65	40.38%	2000–2001	P-MCI	Italy	8
78	Boeve et al. (2003)	Cross-sectional	13	111	90–99	20.72%	1997–1999	P-MCI	United States	8
79	Ganguli et al. (2004)	Cohort study	40	1,248	NR	39.26%	1987–2001	P-MCI	United States	7
80	Ravaglia et al. (2008)	Cohort study	72	865	≥65	NR	1999–2004	IWG	United States	8
81	Xie et al. (2003)	Cross-sectional	54	311	≥75	100%	1998	P-MCI	NR	4
82	Yu et al. (2003)	Cross-sectional	216	2,674	≥60	60.96%	2001	DSM-IV	China	6
83	Wu et al. (2005)	Cross-sectional	45	267	≥80	37.08%	NR	Chinese guidelines and P-MCI	China	4
84	Yang et al. (2008)	Cross-sectional	647	3,175	≥60	38.33%	NR	Chinese guidelines and P-MCI	China	4
85	Liu et al. (2007)	Cross-sectional	838	2,944	≥60	84.65%	NR	Chinese guidelines and P-MCI	China	6
86	Wada-isoe et al. (2012)	Cohort study	211	723	77.80 ± 6.79	NR	2010	IWG	Japan	7
87	Vlachos et al. (2020)	Cohort study	243	1,960	≥65	40.61%	NR	P-MCI	Greece	4
88	Bickel et al. (2006)	Cross-sectional	287	794	65–85	40.68%	NR	DSM-IV	German	8
89	Busse et al. (2003)	Cohort study	116	1,045	NR	NR	1997–1998	P-MCI	German	6
90	Rahman et al. (2009)	Cross-sectional	104	268	60–76	54.48%	NR	DSM-IV	Egypt	5
91	Yu et al. (2003)	Cross-sectional	216	2,674	≥60	60.96%	NR	P-MCI	China	7
92	Assaf et al. (2021)	Cross-sectional	50	337	≥60	54.70%	NR	IWG	Lebanon	8
93	Eramudugolla et al. (2022)	Cohort study	132	1,427	60–64	44.11%	NR	DSM-IV	Australia	8
94	Hussenoeder et al. (2020)	Cross-sectional	110	903	86.50 ± 3.10	33.22%	2003–2013	IWG	Germany	8
95	Mooldijk et al. (2022)	Cohort study	648	7,058	≥60	42.87%	2002–2014	P-MCI	Netherland	8
96	Nakahata et al. (2021)	Cross-sectional	191	2,286	69	NR	2014–2017	NIA-AA	Japan	7
97	Samson et al. (2022)	Cross-sectional	255	506	55–93	47.23%	NR	P-MCI	United States	8
98	Lee et al. (2022)	Cross-sectional	2,520	13,623	≥65	45.50%	2007–2010	DSM-IV	China, Ghana, India, Mexico, Russia, South Africa	7
99	Smith et al. (2022)	Cross-sectional	5,005	32,715	50–65	48.30%	2007–2010	DSM-IV	China, Ghana, India, Mexico, Russia, South Africa	7
100	Xu et al. (2021)	Cross-sectional	55	171	70.68 ± 7.92	49.12%	2010–2010	P-MCI	China	7
101	Yamane et al. (2022)	Cross-sectional	61	865	≥65	38.96%	2014–2017	P-MCI	Japan	4
102	Yang et al. (2021)	Cross-sectional	276	925	71.16 ± 4.41	NR	NR	DSM-IV	China	7
103	Yu et al. (2022)	Cross-sectional	86	163	81.20 ± 4.70	28.83%	2018–2021	ADNI	Spanish	8
104	Tang al. 2007	Cross-sectional	217	1,865	≥60	48.10%	2004–2004	P-MCI	China	7
105	Gjøra et al. (2021)	Cross-sectional	3,382	9,663	≥70	43.25%	2017–2019	DSM-V	Swedish	9
106	Ramlall et al. (2013)	Cross-sectional	38	140	75.20 ± 8.90	30.71%	NR	IWG	South Africa	6
107	Yang et al. (2019)	Cross-sectional	318	2,015	79.5	NR	2014	NIA-AA	China	10
108	Amoo et al. (2020)	Cross-sectional	397	532	71.40 ± 8.86	35.30%	NR	P-MCI	Nigera	5
109	Bae et al. (2017)	Cross-sectional	698	3,312	NR	44.17%	NR	IWG	Japan	6
110	Fernández-Blázquez et al. (2021)	Cross-sectional	83	1,180	74.90 ± 3.90	36.44%	2011	NIA-AA	Spanish	8

(Continued)

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TABLE 1 (Continued)

ID	Study	Study design	Cases	Sample	Age, mean ± sd (range)	Proportion of males (%)	Beginning of survey	Diagnostic criteria	Region	Quality score
111	Ganguli et al. (2010)	Cross-sectional	697	1,982	77.60 ± 7.40	38.90%	NR	P-MCI	United States	6
112	González et al. (2019)	Cross-sectional	5,851	59,714	63.00 ± 6.80	45.00%	NR	NIA-AA	Spanish	8
113	Guaita et al. (2015)	Cross-sectional	65	1,321	71.68 ± 1.43	54.05%	NR	P-MCI	Italy	8
114	Heywood et al. (2017)	Cross-sectional	507	2,599	≥55	36.24%	2006–2009	P-MCI	Singapore	9
115	Kivipelto et al. (2001)	Cross-sectional	82	1,352	65–79	37.87%	NR	P-MCI	Finland	6
116	Lara et al. (2016)	Cross-sectional	348	3,625	66.26 ± 0.18	45.32%	NR	NIA-AA	Spanish	6
117	Chong et al. (2019)	Cross-sectional	158	1,209	68.08 ± 5.63	49.96%	NR	P-MCI	Malaysia	6
118	Das et al. (2007)	Cross-sectional	111	745	66.75 ± 9.96	49.26%	2003–2004	P-MCI	India	7
119	Juarez- Cedillo et al. (2012)	Cross-sectional	190	2,944	71.00 ± 7.10	42.19%	NR	P-MCI	Mexico	7
120	Ding et al. (2015)	Cross-sectional	601	3,141	73.30 ± 8.60	45.78%	NR	P-MCI	China	9
121	Jia et al. (2014)	Cross-sectional	2,137	13,806	≥65	31.72%	NR	P-MCI	China	8
122	Jia et al. (2020)	Cross-sectional	7,215	46,011	70.00 ± 7.51	49.70%	2015–2018	NIA-AA	China	11
123	Anstey et al. (2013)	Cross-sectional	141	2,551	68–72	39.98%	1999–2007	P-MCI	Australia	8
124	Dimitrov et al. (2012)	Cross-sectional	37	605	73.20 ± 5.70	42.98%	NR	P-MCI	Bulgaria	6
125	Gavrila et al. (2009)	Cross-sectional	88	1,074	74.30 ± 6.50	48.23%	2003–2005	P-MCI	Spanish	6
126	Han et al. (2017)	Cross-sectional	305	755	≥65	NR	2012	P-MCI	Korea	7
127	Hänninen et al. (2002)	Cross-sectional	43	806	68.10 ± 4.50	39.83%	NR	P-MCI	Finland	6
128	Juncos-Rabadán et al. (2012)	Cross-sectional	169	580	≥50	30.86%	NR	P-MCI	Spanish	5
129	Kim et al. (2011)	Cross-sectional	1,455	6,141	≥65	39.81%	2008	P-MCI	Korea	5
130	Limongi et al. (2017)	Cross-sectional	505	2,337	74	41.68%	2002–2004	P-MCI	Italy	9
131	Liu et al. (2022)	Cross-sectional	122	1,010	≥60	31.49%	2011–2016	P-MCI	Singapore	8
132	Lopez-Anton et al. (2015)	Cross-sectional	323	4,803	≥65	NR	NR	DSM-IV	Spanish	6
133	Luck et al. (2007)	Cross-sectional	499	3,242	≥75	34.42%	2003–2004	IWG	Germany	9
134	Mohan et al. (2019)	Cross-sectional	111	426	69.90 ± 7.90	38.03%	2012–2014	P-MCI	India	8
135	Mooi et al. (2016)	Cross-sectional	1,442	2,112	68.80 ± 6.10	48.58%	2013–2014	P-MCI	Malaysia	8
136	Moretti et al. (2013)	Cross-sectional	3,351	7,930	61–107	39.66%	NR	IWG and P-MCI	Italy	9
137	Noguchi-Shinohara et al. (2013)	Cross-sectional	107	650	76	40.46%	NR	IWG and P-MCI	Japan	7
138	Peltz et al. (2012)	Cross-sectional	70	420	≥90	34.05%	2003 and 2008	DSM-IV	USA	5
139	Robertson et al. (2019)	Cross-sectional	964	1,721	≥65	40.44%	2008–2011	DSM-IV	Canada	6
140	Sasaki et al. (2009)	Cross-sectional	557	1,433	≥65	NR	2001–2002	DSM-IV	Japan	5
141	Shahnawaz et al. (2013)	Cross-sectional	299	767	70–90	43.55%	NR	IWG	Australia	4
142	Teh et al. (2021)	Cross-sectional	32	2,165	≥60	45.87%	2012–2013	IWG and P-MCI	Singapore	7
143	Tsoy et al. (2019)	Cross-sectional	201	662	≥60	24.32%	NR	IWG	Kazakhstan	8
144	Vlachos et al. (2020)	Cross-sectional	243	1,960	73.46 ± 5.47	40.61%	NR	IWG and P-MCI	Greece	6
145	Liu et al. (2022)	Cross-sectional	5,432	10,432	≥65	47.68%	2011–2013	ADNI	China	7
146	Su et al. (2014)	Cross-sectional	145	796	≥60	32.79%	NR	P-MCI	China	6
147	Mías et al. (2007)	Cross-sectional	102	418	≥50	22.01%	2004–2005	P-MCI	Argentina	8

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TABLE 1 (Continued)

ID	Study	Study design	Cases	Sample	Age, mean ± sd (range)	Proportion of males (%)	Beginning of survey	Diagnostic criteria	Region	Quality score
148	Pedraza et al. (2017)	Cross-sectional	421	1,235	≥50	24.78%	NR	P-MCI	Bogotá	8
149	Sánchez et al. (2019)	Cross-sectional	63	352	≥60	27.05%	NR	P-MCI	Peru	7
150	Monteagudo Torres et al. (2009)	Cross-sectional	19	201	≥60	NR	2006–2007	P-MCI	Cuba	6
151	Wesseling et al. (2013)	Cross-sectional	35	401	≥65	39.65%	2010–2011	P-MCI	Costa Rica	7
152	Li et al. (2020)	Cohort study	535	3,135	71.58 ± 8.06	NR	2011–2012	P-MCI	China	9
153	Rao et al. (2018)	Cross-sectional	299	2,111	≥65	40.50%	NR	P-MCI	China	7
154	Sun et al. (2014)	Cross-sectional	1,957	10,432	≥65	47.70%	NR	ADNI	China	5
155	Xiao et al. (2016)	Cohort study	267	1,068	72.80 ± 8.50	42.23%	NR	P-MCI	China	9
156	Liu et al. (2018)	Cross-sectional	317	1,796	≥60	46.05%	NR	DSM-IV	China	6
157	Wu et al. (2017)	Cross-sectional	371	1,846	69.52 ± 6.86	46.64%	2013–2014	P-MCI	China	8
158	Chuang et al. (2021)	Cross-sectional	82	470	71.20 ± 5.40	38.72%	2017–2019	NIA-AA	China	7
159	Janelidze et al. (2018)	Cross-sectional	113	851	56.50 ± 11.80	37.02%	NR	DSM-IV	Georgia	6
160	Pilleron et al. (2015)	Cross-sectional	266	2,002	≥65	NR	2011–2012	P-MCI and DSM-IV	South Africa	8
161	Vancampfort et al. (2017)	Cross-sectional	5,005	32,715	62.10 ± 15.60	48.30%	NR	P-MCI	China, Ghana, India, Mexico, Russia, South africa	9
162	Koyanagi et al. (2019)	Cross-sectional	312	3,672	≥50	44.01%	2007–2008	P-MCI	South Africa	7
163	Li et al. (2013)	Cross-sectional	160	1,020	63.90 ± 6.60	36.67%	NR	P-MCI	China	8
164	Kang et al. (2016)	Cross-sectional	180	1,248	≥60	51.68%	2015–2016	P-MCI	China	6
165	Huang et al. (2021)	Cross-sectional	1,830	5,103	≥55	44.95%	2018–2019	P-MCI	China	6
166	Bai et al. (2021)	Cross-sectional	92	428	86.34 ± 3.57	28.97%	2018–2019	P-MCI	China	6
167	Lu et al. (2022)	Cross-sectional	47	260	≥60	53.46%	2021	CGDM	China	6
168	Shi et al. (2019)	Cross-sectional	175	513	40–98	86.74%	2015–2019	P-MCI	China	6
169	Liu et al. (2005)	Cross-sectional	88	410	≥60	35.12%	2004	P-MCI	China	5
170	Sun et al. (2013)	Cross-sectional	53	471	83.00 ± 3.50	97.45%	2009–2010	IWG and P-MCI	China	7
171	Hai et al. (2010)	Cross-sectional	61	202	82.51 ± 2.14	74.26%	2007	IWG and P-MCI	China	6
172	Yuan et al. (2017)	Cross-sectional	158	1,013	60–96	52.82%	2014–2016	P-MCI.	China	8
173	Ji et al. (2017)	Cross-sectional	318	3,200	≥60	49.76%	NR	P-MCI	China	4
174	Wang et al. (2013)	Cross-sectional	199	1,033	≥55	38.14%	NR	P-MCI	China	6
175	Zhao et al. (2015)	Cross-sectional	171	976	≥60	46.82%	2013–2014	P-MCI	China	5
176	Li et al. (2013)	Cross-sectional	115	1,226	≥60	46.74%	NR	P-MCI	China	5
177	Pan et al. (2020)	Cross-sectional	214	1,012	≥60	47.23%	2015	P-MCI	China	6
178	Yu et al. (2012)	Cross-sectional	168	1,086	84.80 ± 4.40	100%	2010	IWG	China	7
179	Yu et al. (2002)	Cross-sectional	123	1,630	65–92	100%	2001	P-MCI	China	6
180	Cai et al. (2010)	Cross-sectional	105	1,498	≥60	NR	2004–2005	P-MCI	China	7
181	Chen et al. (2009)	Cross-sectional	195	925	≥60	40.65%	NR	P-MCI	China	5
182	Zhang et al. (2013)	Cross-sectional	86	321	81.55 ± 4.14	100%	2009	P-MCI	China	6
183	Sun et al. (2008)	Cross-sectional	45	536	72.60 ± 5.60	79.85%	2005	P-MCI and DSM-IV	China	5
184	Yu et al. (2004)	Cross-sectional	36	420	73.60 ± 5.60	74.29%	NR	P-MCI and DSM-IV	China	4

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TABLE 1 (Continued)

ID	Study	Study design	Cases	Sample	Age, mean ± sd (range)	Proportion of males (%)	Beginning of survey	Diagnostic criteria	Region	Quality score
185	Zhang et al. (2008)	Cross-sectional	104	586	75.92 ± 4.35	70.48%	2005–2007	P-MCI and DSM-IV	China	6
186	Jiang et al. (2019)	Cross-sectional	833	2,886	≥60	41.61%	2017–2017	P-MCI and DSM-IV	China	8
187	Hu et al. (2012)	Cross-sectional	1,782	9,146	≥55	43.83%	2008–2009	DSM-IV	China	6
188	Guo et al. (2013)	Cross-sectional	178	1,367	≥60	49.60%	2011	DSM-IV	China	5
189	Li et al. (2015)	Cross-sectional	260	1,971	≥60	37.39%	NR	DSM-IV	China	5
190	Fan et al. (2014)	Cross-sectional	73	213	65.70 ± 6.08	36.15%	2012	P-MCI and DSM-IV	China	5
191	Lv et al. (2016)	Cross-sectional	95	820	60–85	47.68%	NR	P-MCI and DSM-IV	China	6
192	Zhang et al. (2021)	Cross-sectional	253	309	58.85 ± 0.58	53.40%	2019	P-MCI	China	7
193	Yuan et al. (2013)	Cross-sectional	631	3,311	≥60	32.47%	NR	P-MCI	China	6
194	Fang et al. (2015)	Cross-sectional	137	1,059	≥60	46.18%	NR	P-MCI	China	5
195	Pan et al. (2021)	Cross-sectional	326	734	≥60	40.74%	2019	P-MCI	China	5
196	Tao et al. (2016)	Cross-sectional	1,546	9,121	70.50 ± 7.68	53.95%	2013–2014	P-MCI	China	7
197	Li et al. (2021)	Cross-sectional	177	413	≥60	41.65%	2019	P-MCI	China	5
198	Xu et al. (2001)	Cross-sectional	417	1,516	≥65	NR	NR	P-MCI	China	5
199	Zhou et al. (2020)	Cross-sectional	49	114	81.30 ± 7.87	55.26%	2018–2019	P-MCI	China	4
200	Qiu et al. (2018)	Cross-sectional	65	239	65.68 ± 6.16	49.79%	NR	P-MCI	China	4
201	Xia et al. (2011)	Cross-sectional	47	20,367	NR	NR	2009–2019	DSM-IV	China	4
202	Wang et al. (2015)	Cross-sectional	236	718	NR	47.63%	2013–2014	ADNI	China	4
203	Zhang et al. (2020)	Cross-sectional	260	1,614	≥60	60.22%	2019–2019	P-MCI	China	4
204	Gao et al. (2011)	Cross-sectional	243	1,773	≥60	44.21%	2010–2011	P-MCI	China	8
205	Xue et al. (2010)	Cross-sectional	93	1,713	≥60	NR	2006	P-MCI	China	6
206	Zhou et al. (2010)	Cross-sectional	136	1,065	≥60	43.29%	NR	DSM-IV	China	5
207	Liang et al. (2008)	Cross-sectional	220	2,895	≥60	50.09%	NR	P-MCI	China	4
208	He et al. (2013)	Cross-sectional	69	598	60–90	71.57%	2011–2012	P-MCI	China	5
209	Zhang et al. (2014)	Cross-sectional	152	826	67.50 ± 7.03	60.65%	2012	P-MCI	China	5
210	Sun et al. (2012)	Cross-sectional	131	505	75.91 ± 7.96	34.46%	2011–2012	P-MCI	China	5
211	Sun et al. (2019)	Cross-sectional	402	2,105	74.35 ± 6.92	67.70%	2018	P-MCI	China	6
212	Xiong et al. (2013)	Cross-sectional	339	2,978	≥65	44.12%	NR	Chinese guidelines and P-MCI	China	4
213	Zhao et al. (2015)	Cross-sectional	174	1,598	≥60	54.26%	NR	DSM-IV	China	5
214	Sun et al. (2013)	Cross-sectional	74	427	79.17 ± 7.22	38.64%	2011	P-MCI	China	5
215	Song et al. (2019)	Cross-sectional	85	106	64.99 ± 7.05	NR	1987–2017	Chinese guidelines and P-MCI	China	6
216	Wu et al. (2017)	Cross-sectional	371	1,996	69.50 ± 6.86	46.39%	NR	P-MCI	China	7
217	Yang et al. (2016)	Cross-sectional	340	1,218	≥65	44.01%	NR	Chinese guidelines and P-MCI	China	5
218	Su et al. (2016)	Cross-sectional	145	796	≥60	32.79%	NR	P-MCI	China	5
219	Xiang et al. (2009)	Cross-sectional	72	532	≥60	47.37%	NR	Chinese guidelines and P-MCI	China	5
220	Xu et al. (2010)	Cross-sectional	571	2,161	≥60	50.49%	2007–2009	Chinese guidelines and P-MCI	China	6
221	Ma et al. (2019)	Cross-sectional	224	1,005	≥60	41.69%	2017–2018	P-MCI	China	5

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TABLE 1 (Continued)

ID	Study	Study design	Cases	Sample	Age, mean ± sd (range)	Proportion of males (%)	Beginning of survey	Diagnostic criteria	Region	Quality score
222	An et al. (2020)	Cross-sectional	396	3,247	71.58 ± 5.41	45.64%	2019	Chinese guidelines and P-MCI	China	6
223	Yang et al. (2019)	Cross-sectional	319	2,015	≥65	NR	2014	NIA-AA	China	7
224	Liu et al. (2022)	Cross-sectional	69	476	≥60	45.38%	2018–2021	CDGM	China	7
225	Wang et al. (2017)	Cross-sectional	209	1,781	≥60	39.53%	2015	P-MCI	China	6
226	Wang et al. (2017)	Cross-sectional	25	84	≥60	60.71%	2015	P-MCI	China	6
227	Liu et al. (2021)	Cross-sectional	64	287	≥65	50.17%	2019–2020	Chinese guidelines and P-MCI	China	6
228	Zhou et al. (2013)	Cross-sectional	59	218	≥60	49.08%	2012	Chinese guidelines and P-MCI	China	5
229	Jia et al. (2020)	Cross-sectional	87	255	>80	100%	NR	P-MCI	China	5
230	Song et al. (2011)	Cross-sectional	11	88	74–89	44.32%	NR	COMD-3	China	4
231	Xu et al. (2016)	Cross-sectional	24	206	≥75	100%	2012	DSM-IV	China	6
232	Ma et al. (2017)	Cross-sectional	148	895	≥60	48.94%	NR	ADNI	China	5
233	Zhang et al. (2014)	Cross-sectional	287	1,764	≥60	44.05%	2012	Chinese guidelines and P-MCI	China	6

The number of amnestic MCI (aMCI) and no amnestic MCI (naMCI) were reported in these studies.
@NR, not reported; @P-MCI, classical Petersen's criteria of MCI; @DSM, diagnostic and statistical manual of mental disorders; @ANDI, Alzheimer's disease neruimaging initiative; @NIA-AA, the National Institute on Aging-Alzheimer's Association; @CDGM, Chinese guidelines for diagnosis and management of cognitive impairment and dementia; @IWG, international working group; @COMD-3, the spirit of China disorders classification and diagnostic criteria, third edition.

FIGURE 2
Funnel plot of pooled prevalence of MCI.

27.8–95.7%)] was significantly higher than in nursing homes [16.1% (95% CI: 14.3–17.9%)] and communities [25.3% (95% CI: 17.4–33.2%)] after 2019. Additionally details of the subgroup analyses can be found in Table 3.

4. Discussion

Previous studies revealed partial results when investigating the prevalence of MCI with different degrees of limitation. In our study, we conducted an extensive literature search based on seven electronic databases and manual retrieval, ultimately identifying 233 studies with a total of 115,958 participants. Furthermore, we included more variables of interest into subgroup analyses, such as sample source, basic diseases, the beginning year of survey, and others. Considering the COVID-19 pandemic period, we attached importance to the MCI prevalence before and after 2019. To our knowledge, this is the most recent meta-analysis to provide a comprehensive overview of MCI prevalence without any limitations in age or region.

We concluded that the global total prevalence of MCI is 19.7% (95% CI: 18.3–21.1%) among 233 included studies. In addition, Subgroup analyses revealed that the sample source and beginning year of survey were considered factors potentially associated with MCI prevalence (p-value^2 < 0.05) (Table 3).

On the one hand, the prevalence of MCI patients in hospitals [34.0% (95% CI: 22.2–45.7%)] was higher than those in nursing homes [22.6% (95% CI: 15.5–29.8%)] and communities [17.9% (95% CI: 16.6–19.2%)]. Several previous studies also draw the consistent conclusions. For example, Xue et al. reported that clinical patients [16.72% (95% CI: 15.6–17.7%)] have a higher MCI prevalence than nonclinical patients [14.61% (95% CI: 14.4–14.8%)] (Xue et al., 2018). The higher MCI prevalence in hospitals may be attributed to professional diagnosis and treatment procedures. Meanwhile, patients in hospitals have more apparent clinical symptoms of MCI and receive more attention from clinicians, which greatly improves the detection rate of MCI. Similarly, the population in nursing homes [21.2% (95% CI: 18.7–23.6%)] have a higher MCI prevalence than community dwellers [5.56% (95% CI: 13.2–18.0%)] (Bai et al., 2022; Chen et al., 2023). Compared to those living in nursing homes, people living in the communities have better material and emotional support from

TABLE 2 The time trends in MCI prevalence from different sample sources.

Subgroup	No. of cases	No. of samples	Prevalence, 95%CI (%)	*p*-value[1]	*p*-value[2]
≤ 2009					0.228
Community	18,914	106,057	15.8 (13.0–18.6)	<0.001	
Nursing home	356	3,460	13.1 (9.4–16.8)	<0.001	
Hospital	1,513	23,330	35.7 (4.2–67.1)	0.026	
2010–2018					0.565
Community	33,245	169,301	18.7 (15.7–21.6)	<0.001	
Nursing home	999	9,438	27.7 (11.4–44.0)	0.001	
Hospital	1,163	6,087	18.8 (13.8–23.8)	<0.001	
≥ 2019					0.003
Community	934	5,505	25.3 (17.4–33.2)	<0.001	
Nursing home	260	1,614	16.1 (14.3–17.9)	<0.001	
Hospital	579	1,054	61.7 (27.8–95.7)	<0.001	

p-value[1] is the *p*-value within subgroups; *p*-value[2] is the *p*-value across subgroups; 95%CI, 95% confidence interval.

TABLE 3 Subgroup analyses of MCI prevalence.

Subgroup	No. study	No. of cases	No. of sample	Prevalence, 95%CI (%)	*p*-value[1]	*p*-value[2]
Overall	233	115,958	676,974	19.7 (18.3–21.1)	<0.001	
Study type						0.976
Cross-sectional	207	106,067	627,798	19.7 (18.2–21.2)	<0.001	
Cohort	26	9,891	49,176	19.6 (15.3–24.0)	<0.001	
Diagnostic method						0.786
P-MCI	150	54,227	309,548	20.1 (18.5–21.6)	<0.001	
DSM	43	34,003	196,537	19.5 (15.7–23.3)	<0.001	
Male to female Ratio						0.918
Male/female ≥1	43	11,351	57,164	20.1 (16.9–23.3)	<0.001	
Male/female <1	164	99,214	560,490	20.3 (18.9–21.7)	<0.001	
Region1						0.856
Developing country	168	66,411	382,725	19.7 (17.9–21.5)	<0.001	
Developed country	60	31,958	182,170	20.0 (17.3–22.7)	<0.001	
Region2						0.909
Asia	171	70,205	400,010	19.8 (18.0–21.5)	<0.001	
Europe	27	20,703	125,743	18.0 (14.0–22.1)	<0.001	
North America	14	4,599	18,936	21.6 (14.1–29.1)	<0.001	
Africa	8	1,251	9,192	23.1 (14.5–31.6)	<0.001	
Oceania	4	713	5,337	19.3 (8.5–30.0)	<0.001	
South America	4	898	5,677	21.2 (7.0–35.3)	0.003	
Beginning year of Survey						<0.001
≤ 2009	54	162,314	20,548	14.5 (12.1–16.9)	<0.001	
2010–2018	72	195,203	40,908	19.8 (17.1–22.5)	<0.001	
≥ 2019	9	2,025	10,024	32.1 (22.6–41.6)	<0.001	

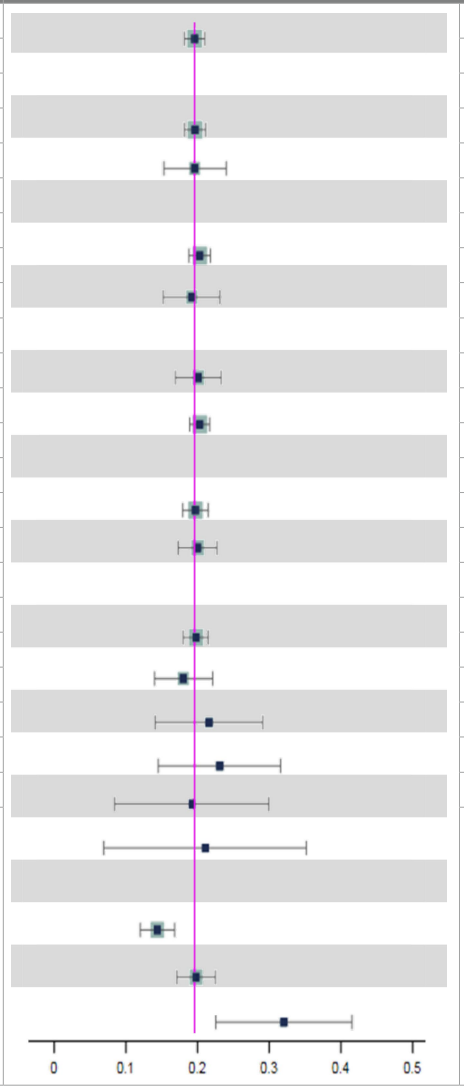

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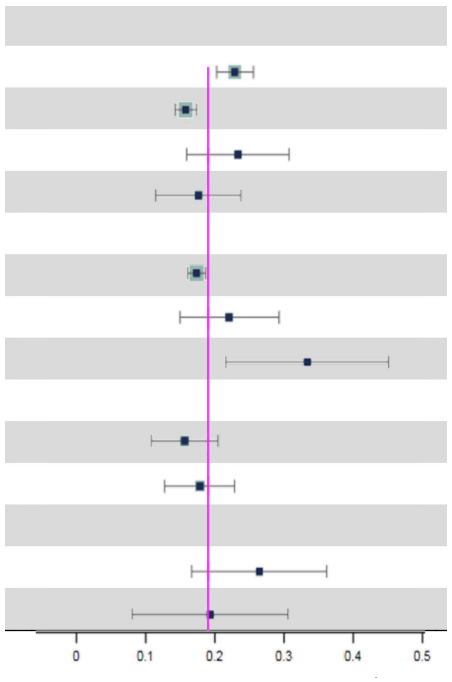
TABLE 3 (Continued)

Subgroup	No. study	No. of cases	No. of sample	Prevalence, 95%CI (%)		p-value[1]	p-value[2]
Sample size							<0.001
0–1,000	94	10,760	48,769		23.5 (20.9–26.2)	<0.001	
1,001–5,000	115	39,651	246,475		16.4 (14.9–18.0)	<0.001	
5,001–10,000	12	21,099	88,648		23.9 (16.5–31.3)	<0.001	
≥10,001	12	44,448	293,082		18.2 (12.0–24.3)	<0.001	
Sample source							0.014
Community	170	84,742	498,057		17.9 (16.6–19.2)	<0.001	
Nursing home	21	8,754	30,251		22.6 (15.5–29.8)	<0.001	
Hospital	16	3,541	31,239		34.0 (22.2–45.7)	<0.001	
MCI subtype							0.555
aMCI/naMCI ≥1	17	7,174	41,589		16.2 (11.4–21.0)	<0.001	
aMCI/naMCI <1	5	1,252	6,535		18.4 (13.3–23.4)	<0.001	
Basic diseases/Non basic diseases							0.349
≥ 1	7	2,026	10,049		27.0 (17.2–36.7)	<0.001	
< 1	6	3,211	15,800		19.9 (8.6–31.1)	0.001	



p-value[1] is the p-value within subgroups; p-value[2] is the p-value across subgroups; Region[1] is classified according to developed/developing countries; Region[2] is based on the region of each country.

①95%CI, 95% confidence interval; ②P-MCI, classical Petersen's criteria of MCI; ③DSM, diagnostic and statistical manual of mental disorders; ④MCI, mild cognitive impairment.

their families, which might make a difference in reducing MCI prevalence.

On the other hand, we found that the total prevalence of MCI increased over time, especially after 2019. Notably, before 2019, there were no significant differences in MCI prevalence among three sample sources. However, the MCI prevalence after 2019 in hospitals [61.7% (95% CI: 27.8–95.7%)] was significantly higher than those in nursing homes [16.1% (95% CI: 14.3–17.9%)] and communities [25.3% (95% CI: 17.4–33.2%)] (Table 2). Since the COVID-19 outbreak globally in 2019, hospital with the support of limited health resources and medical personnel with professional clinical knowledge has become the main refuge for COVID-19 patients (Kadri et al., 2020; Wadhera et al., 2020). There is cumulative evidence suggesting that COVID-19 impacts brain function and is associated with an elevated risk of neurodegenerative conditions, including cognitive dysfunction (Miners et al., 2020; Nath, 2020; Alquisiras-Burgos et al., 2021). Various post-COVID-19 symptoms indicate that coronaviruses, including SARS-CoV-2, could infect the central nervous system (CNS) through hematogenous pathways or neuronal retrograde neuro-invasion. This infiltration leads to subsequent microglial activation and enduring neuroinflammation, with dysregulated neuro-immunity serving as a foundational cause of nerve cell damage (Ellul et al., 2020; Troyer et al., 2020). Supporting the theory that COVID-19 can influence and exacerbate cognitive dysfunction, our data reveals a notable spike in the prevalence of MCI in hospitals post-2019. However, this rate may be conservative. The causes for this speculation are likely multifactorial, such as patients avoidance of emergency care due to fear of COVID-19 or the increased threshold for hospitalization of non-COVID-19 patients by clinicians due to the severity and urgency of COVID-19 (Blecker et al., 2021), which could masks the true prevalence. Therefore, more studies are needed in the future to investigate the potential link between COVID-19 and MCI.

5. Strengths and limitations

Based on previous research, this meta-analysis is the latest meta-analysis to provide a comprehensive overview of MCI prevalence without any age and regional limitations. This meta-analysis may aid policymakers, clinicians in making decisions and clinical directions, thus facilitating future studies and clinical applications. Our study, including the most extensive information currently available, is the first to analyze the association between COVID-19 and global MCI prevalence. However, there are also some limitations. First, the included data is unevenly distributed across regions. A large number of studies have been included from Asia, Europe, and North America, while relatively few have been included from Africa, Oceania, and South America. This unbalanced distribution of literature across regions may introduce bias in subgroups. Naturally, due to the vast amount of data included, our study unavoidably presents significant publication bias. Finally, the MCI prevalence in post-COVID-19 era still requires further investigation to provide more accurate evidence for the allocation of medical and health resources.

6. Conclusion

Our systematic review indicates that the current pooled global prevalence of Mild Cognitive Impairment (MCI) stands at 19.7%.

Notably, we found a significant correlation between beginning year of survey and the global prevalence of MCI, with prevalence rates rising significantly after 2019. Furthermore, it is noteworthy that the prevalence of MCI in hospital settings outstripped those in nursing homes and community settings, especially after 2019. This trend may be in part attributable to the outbreak of COVID-19. The potential connection between COVID-19 and MCI warrants further investigation in future studies. Lastly, we posit that our review holds substantial value for policymakers and clinicians. The insights gleaned can guide health-related decision-making processes and inform the strategic allocation of health resources to better serve patients with MCI.

Data availability statement

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

Author contributions

J-hL, JC, and S-xX conceived and designed the study. W-xS and W-wW performed the data analysis and wrote the manuscript. Y-yZ, H-lX, S-yJ, and G-cC assessed the literature and extracted the data. All authors contributed to the article and approved the submitted version.

Funding

This study was supported by the National Natural Science Foundation of China (82174316), Shenzhen Medical and Health Three Projects (SZZYSM202106006), National TCM Clinical Research Base Construction Project [No. State TCM Science and Technology Letter (2018) No. 131], Shaoxiang Xian National Famous Elder TCM Experts Inheritance Studio [State TCM Human Education Letter (2022) No. 75], Basic and Applied Research of Guangzhou Municipal University Joint Funding Project (202201020342), Qihuang Scholar Training program and Guangzhou Science and Technology Bureau 2022 Key R&D Project (2060404).

Acknowledgments

We affirm that the work submitted for publication is original and has not been published other than as an abstract or preprint in any language or format and has not been submitted elsewhere for print or electronic publication consideration. We affirm that each person listed as the author participated in the work in a substantive manner, in accordance with ICMJE authorship guidelines, and is prepared to take public responsibility for it. All authors consent to the investigation of any improprieties that may be alleged regarding the work.

Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2023.1227112/full#supplementary-material

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frontiers | Frontiers in Aging Neuroscience

TYPE Original Research
PUBLISHED 14 December 2023
DOI 10.3389/fnagi.2023.1297622

OPEN ACCESS

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RECEIVED 20 September 2023
ACCEPTED 27 November 2023
PUBLISHED 14 December 2023

CITATION
Chen F, Chen Y, Jiang X, Li X, Ning H, Hu M, Jiang W, Zhang N, Feng H and Yan P (2023) Impact of hearing loss on cognitive function in community-dwelling older adults: serial mediation of self-rated health and depressive anxiety symptoms.
Front. Aging Neurosci. 15:1297622.
doi: 10.3389/fnagi.2023.1297622

Impact of hearing loss on cognitive function in community-dwelling older adults: serial mediation of self-rated health and depressive anxiety symptoms

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Background: Hearing loss can exacerbate cognitive decline; therefore, exploring the mechanisms through which hearing loss affects cognitive function is crucial. The current study aimed to investigate the impact of hearing loss on cognitive function and the mediating role played by self-rated health and depressive anxiety symptoms.

Methods: Using stratified whole-group random sampling, the study employed a cross-sectional design and included 624 participants aged ≥65 years from three communities in Urumqi, China. Cognitive function was assessed using the Mini-Mental State Examination. Hearing function and self-rated health were determined by self-report. The 15-item Geriatric Depression Scale and the 7-item Generalized Anxiety Disorder Scale were used to assess depressive anxiety symptoms. Serial mediation analysis was performed using AMOS 26.0.

Results: Hearing loss can not only negatively affect cognitive function in older adults directly (direct effect = −0.106; SE = 0.045; 95% confidence interval (CI): −0.201 to −0.016), but also indirectly affect the relationship between hearing loss and cognitive function through self-rated health and depressive anxiety symptoms. The results of the serial mediation analysis showed that the total indirect effect of self-rated health and depressive anxiety symptoms was −0.115 (95% CI: −0.168 to −0.070), and the total effect of the model was −0.221 (95% CI: −0.307 to −0.132), with the total indirect effect accounting for 52.04% of the total effect of the model.

Conclusion: Our study discovered that there is a partial mediation of the relationship between hearing loss and cognitive function by self-rated health and depressive anxiety symptoms. It is suggested that by enhancing self-rated health and ensuring good mental health, the decline in cognitive function among older adults with hearing loss can be delayed.

KEYWORDS

hearing loss, self-rated health, anxiety, depression, cognitive function

1 Introduction

Mild cognitive impairment (MCI) is regarded as the subclinical stage of dementia, and about 10–15% of patients with MCI develop dementia each year (Petersen et al., 2001). According to the World Health Organization (WHO), over 55 million individuals globally suffer from dementia, with approximately 10 million newly diagnosed cases annually, which presents a huge challenge to the long-term care and healthcare system worldwide (WHO, 2023). However, most people with MCI do not necessarily develop dementia. Several studies have found that MCI is reversible, which can restore normal cognitive function. A meta-analysis of 17 studies reported a general reversal that was 27.57% in MCI patients (Xue et al., 2019). Therefore, considering the rapidly aging global population, it is clinically meaningful to search for risk factors associated with cognitive decline, which may help to formulate precise preventive strategies to protect cognitive function and delay the progression of MCI to dementia.

Hearing loss is a sensory impairment that is highly prevalent in the elderly population. The Global Burden of Disease (GBD) Study 2019 showed that hearing loss, as the third disabling factor globally, has affected 1.57 billion people worldwide (GBD 2019 Hearing Loss Collaborators, 2021). Long-term hearing loss interferes with communication and social interaction activities, triggers loneliness and social isolation (Shukla et al., 2020), and has been linked to an increased risk for MCI and dementia (Vassilaki et al., 2019). Over the past few years, there has been significant research conducted on the impact of hearing loss on cognitive abilities, yielding varying outcomes. In the Rancho Bernard Study (RBS), the severity of hearing loss was strongly related to a reduction in overall cognitive and executive function throughout a 24-year follow-up period, and the rate of decline increased over time (Alattar et al., 2020), while in the Blue Mountain Eye Study, cognitive function was not significantly affected by hearing loss (Hong et al., 2016). Although the evidence is inconsistent, hearing loss has been widely recognized as a modifiable risk factor that causes cognitive impairment (Livingston et al., 2020). Notably, the mechanism of action between the two has yet to be completely elucidated. As a result, the current study endeavored to investigate the association between hearing loss and cognitive function as well as identify other modifiable risk factors.

Self-rated health (SRH) is an individual's subjective assessment based on objective health status (Jylhä, 2009). SRH has been proven to accurately reflect the health status of individuals, and can also predict health-related outcomes such as the decline in physical function, the incidence of chronic diseases, and the mortality of the elderly (Latham and Peek, 2013; Brenowitz et al., 2014; Dramé et al., 2023). Although research on how hearing loss affects SRH in older adults is limited, findings from empirical studies demonstrate that older adults with hearing loss are likely to rate their health as poorer. A recent study conducted in Brazil found that 50.3% of patients with hearing loss reported poor SRH (Anderle et al., 2023). Participating in community events, such as club activities and outings with friends, is extremely important for the physical and social engagement of many older adults. Unfortunately, hearing loss often hinders their ability to participate in these activities (Arnadottir et al., 2011). Hearing loss reduces their involvement in social settings, leading to negative effects on their overall health and well-being. These impairments can have a significant impact on older adults' perceptions of their health condition (Solheim et al., 2011). Notably, SRH was also used as a predictor of cognitive decline (Aguiñaga et al., 2023). Previous studies found that older adults with good and stable changes in SRH over 8 years had the slowest rate of memory decline (Bendayan et al., 2017). An American cohort study found that poorer SRH in midlife was related to a higher likelihood of cognitive impairment 18 years later (Wu et al., 2022). However, some research also exists that suggests that cognitive impairment is not directly related to SRH unless sensory impairments are present at the same time (Liu et al., 2016). Given that older adults with hearing loss may experience a decline in cognitive function due to poor SRH, we hypothesized that SRH may be a mediating variable between hearing loss and cognitive function (H1).

Depression and anxiety are common in patients with cognitive impairment. The hazard ratios (HR) for conversion to dementia in older adults with MCI combined with anxiety or depression were 1.18 and 4.80, respectively, compared with older adults with MIC alone (Makizako et al., 2016; Li and Li, 2018). In addition, the link between hearing loss and mental health is clear. An American study found anxiety and depression in approximately one-fifth of older adults with hearing loss (Simning et al., 2019). However, existing studies have some limitations. When studying the connection between hearing loss and cognitive function, the majority of studies have mostly focused on the influence of depression rather than anxiety. For instance, a study of 8,094 older adults aged 65 years and older in China found that depression partially mediated the relationship between hearing loss and cognitive function, whereas the indirect effect of depression accounted for only 5.07% of the total effect (Cao et al., 2023), suggesting the existence of other important mediating variables. Depression and anxiety often coexist and interact with each other (Jacobson and Newman, 2017). Data suggest that approximately 85% of depressed patients experience significant symptoms of anxiety, and up to 90% of patients with anxiety have comorbid depressive symptoms, making it difficult to distinguish them (Hunt et al., 2002). This study fully considered the comorbidity of anxiety and depression. We employed latent variables, and the inclusion of both anxiety and depression, two observable factors, may provide a fuller picture of an individual's mental health. Therefore, we further hypothesized that depressive anxiety symptoms may mediate the relationship between hearing loss and cognitive function (H2).

Previous evidence suggests that SRH may have a complex bidirectional relationship with depressive anxiety symptoms. SRH can be used in general practice to further assess individuals with depression and anxiety (Östberg and Nordin, 2022). In turn, depression and anxiety are independent predictors of poor SRH over 7 years (Rouch et al., 2014). Previous studies have looked into the link between SRH and depressive anxiety symptoms and cognitive function in the fields of genetics, pathology, and epidemiology. For example, behavioral genetics studies suggest that the association between SRH and spatial reasoning and perceptual speed is mediated by genetic and nonshared environmental factors in individuals aged up to 67 years, whereas the association between SRH and overall cognitive function after age 67 is entirely due to genetic factors (Svedberg et al., 2009). Neuropathological studies have suggested that anxiety or depression interact synergistically with increased brain amyloid deposition to increase the risk of MCI (Pink et al.,

2022). Evidence from epidemiological studies suggests that patients with clinical depression and comorbid anxiety had deficits in multiple domains of cognitive functioning compared with those with clinical depression alone (Liu et al., 2020). Furthermore, compared with older adults with normal hearing, those with hearing loss had a 1.67-fold and 1.35-fold increased risk of poor SRH and depression, respectively (Yu and Liljas, 2019), and depressive anxiety symptoms is apt to occur in older adults with subpar SRH. However, the mechanisms by which SRH and depressive anxiety symptoms synergistically affect the link between hearing loss and cognitive function remain unclear. Considering SRH and depressive anxiety symptoms may be reciprocal, we employed two serial mediation models to test all combinations and analyze the mediating roles of SRH and depressive anxiety symptoms in the causal chain in specific flows. Therefore, we hypothesized that SRH and depressive anxiety symptoms serve as serial mediators in the link between hearing loss and cognitive function (H3).

To further investigate the relationship between hearing loss, SRH, depressive anxiety symptoms, and cognitive function, the current study proposed two serial mediation models (Figure 1). The hypothesized model can be used to elucidate the underlying mechanisms and enrich the prevention policy of cognitive impairment in older adults, which has important implications for public health.

2 Methods

2.1 Study design and participants

A cross-sectional study with a stratified whole-group random sampling method was conducted in Urumqi, Xinjiang, China. First, the nine municipal districts of Urumqi were divided into district stratification, and three municipal districts were randomly selected using the random number table method. Next, one community in each municipal district was randomly selected using the same method. Three communities were finally selected as representative residents in this study. Participants were recruited from community health centers between January and July 2022, and face-to-face interviews with participants and on-site data collection were conducted. As a result of the aging process, it is possible that older individuals experiencing hearing loss may encounter challenges in accurately responding to inquiries owing to their diminished auditory capabilities. Thus, all investigators were professionally trained. When participants had hearing difficulties, investigators minimized the effect of hearing difficulties on question answering by slowing down the speed of speech, increasing the volume of the voice, or using the text form so that the participants could understand the items of the questionnaires clearly and answer them accordingly. In addition, to avoid language

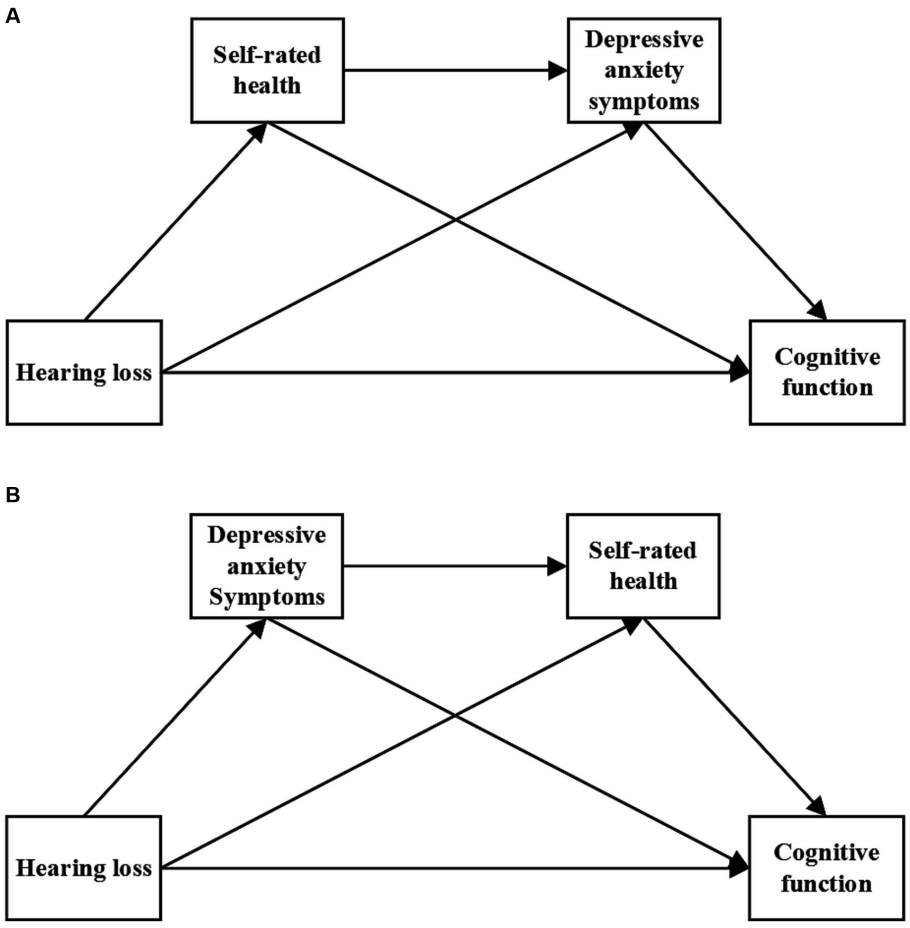

FIGURE 1
Hypothetical model. Panel **(A)** represents the serial mediation model 1 and Panel **(B)** represents the serial mediation model 2.

and cultural differences, the investigators included health workers and medical students who were familiar with the ethnic languages. Inclusion criteria were as follows: (1) current patients aged ≥65 years; (2) living in a community for >6 months; (3) volunteering to participate and providing informed consent for this study; and (4) clear consciousness and no language impairment. Exclusion criteria were as follows: (1) patients with physician-diagnosed dementia, mental or severe physical illness that prevents them from performing cognitive assessment tests; (2) hospitalized and elderly patients who are bedridden for long periods.

The N:q ratio is considered a simple and reliable rule to estimate the minimum sample size of a structural equation model because it takes into account the complexity of the model to be estimated, in which N is the number of samples and q is the parameter to be estimated in the model. Bentler and Chou (1987) state that a ratio of at least 5:1 between the sample size and the parameter being estimated is required to ensure that the estimate of the parameter is plausible, and a ratio of at least 10:1 is required to ensure the validity of the significance test (Bentler and Chou, 1987). Jackson (2003) suggests that 20:1 is a more desirable ratio (Jackson, 2003). In this study we used a ratio of 20:1 to determine the minimum sample size, where 22 parameters (coefficients of 6 paths, factor loadings between 5 observed and latent variables, measurement errors of 9 observable variables, and structural errors of 2 endogenous latent variables) needed to be estimated in this study, and a sample size of at least 440 is recommended. Recruiting a total of 646 participants, of whom 12 had dementia, 2 had missing data on both SRH and hearing function, 3 had missing data on SRH, 1 had missing data on hearing function, and 4 had missing data on cognitive function. By including 624 participants, the ultimate study sample met the minimum requirements for sample size.

2.2 Ethical statement

The Medical Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University approved this study (Ethics Approval No. K202009-05). All participants provided written informed consent.

2.3 Measures

2.3.1 Hearing loss

Hearing loss was measured by self-report (Valete-Rosalino and Rozenfeld, 2005). Participants examined their hearing status by answering the following question: "Do you have any difficulty hearing without the use of hearing aids?" "Difficulty" was coded as having a hearing loss, while "no difficulty" indicated no hearing loss.

2.3.2 SRH

SRH was determined based on the following question: "How do you think your health is? Is it very poor, poor, fair, good, or excellent?" SRH was measured using a 5-point scale, with 1 being very poor and 5 being excellent. The higher the score, the better the SRH.

2.3.3 Depressive anxiety symptoms

2.3.3.1 Depression

The 15-item Geriatric Depression Scale (GDS-15) is a 15-item assessment scale designed by Sheikh and Yesavage based on the 30-item Geriatric Depression Scale (GDS-30) developed by Brink and Yesavage in 1982 (Yesavage et al., 1982; Sheikh and Yesavage, 1986). The GDS-15 scale assesses older adults' negative thoughts, low mood, reduced activity level, and negative perceptions of their present and future lives. Participants answered questions based on how they felt the past week, with a total score ranging from 0 to 15, with higher scores indicating greater depressive symptoms, whereas scores ≥8 indicate depressive symptoms. The reliability and validity of the GDS-15 scale as a depression screening tool were demonstrated in a community-dwelling Asian elderly population (Nyunt et al., 2009). In this study, the Cronbach's alpha coefficient for the scale was 0.716.

2.3.3.2 Anxiety

The 7-item Generalized Anxiety Disorder scale (GAD-7) was used to assess anxiety symptoms (Spitzer et al., 2006). It consists of seven items that are used to assess how frequently participants experienced each symptom in the previous two weeks, and each item is scored from 0 to 3, equivalent to "none," "a few days," "over 50 % of the time," and "almost every day." The overall GAD-7 scale score has a range of 0 to 21, with a score of 5 and above indicating the presence of anxiety symptoms. In this study, the Cronbach's alpha coefficient for the scale was 0.910.

2.3.4 Cognitive function

Cognitive function was measured through the Mini-Mental State Examination (MMSE) (Folstein et al., 1975). The scale is one of the most extensively used tools in cognitive impairment evaluation, with its ratings being impacted by literacy. It contains 30 items with five dimensions: orientation (10 items), memory (3 items), attention and calculation (5 items), recall (3 items), and language capacity (9 items). The maximum score on the MMSE is 30, with lower scores indicating poorer cognitive function. The division boundaries for cognitive impairment were: illiteracy score ≤17, primary school score ≤20, and junior high school and above score ≤24. In this study, the Cronbach's alpha coefficient for the scale was 0.910.

2.3.5 Covariates

Participants' demographic information, lifestyle, fall history in the previous year, nutritional status, and somatic function were collected during the baseline study. Demographic information included age, gender, ethnicity, education level, living alone, and monthly household income. Lifestyle included a history of smoking and drinking. Fall history was determined by self-report. The Mini Nutritional Assessment Short Form (MNA-SF) was used to assess nutritional status; an MNA-SF score of ≤11 was defined as malnutrition (Rubenstein et al., 2001). For the evaluation of somatic function, the instrumental activities of daily living (IADL) scale was used, and an IADL score of <8 was defined as IADL impairment (Lawton and Brody, 1969).

2.4 Statistical analysis

For data processing and statistical analysis, IBM SPSS 27.0 was used. Continuous variables were assessed for normality using the Kolmogorov-Sminov test. Normally distributed data are expressed as mean ± standard deviation(SD), whereas non-normally distributed data are expressed as median with an interquartile range of 25–75% in parentheses. Categorical variables were described using the number of cases and percentages. Chi-square tests and Fisher's exact tests were

used to compare sociodemographic and health-related characteristics between participants with and without cognitive impairment. Differences in MMSE scores across sociodemographic and health-related characteristics were compared using the Mann–Whitney test and the Kruskal-Wallis test. Spearman's correlations were conducted to test the relationships between hearing loss, SRH scores, depressive symptom scores, anxiety symptom scores, and cognitive function scores. Statistical significance was defined as a value of p of <0.05.

IBM AMOS version 26.0 was used to construct the structural equation model, and since the hearing function is a dichotomous variable, we processed it as a dummy variable before incorporating it into the study model, used the maximum likelihood method for parameter estimation, and evaluated the model fit using the goodness-of-fit test. The following criteria were used to judge the goodness of fit of the model: the chi-squared divided by the degrees of freedom (χ^2/df) ratio was less than 3, Goodness of Fit Index (GFI), Adjusted Goodness of Fit Index (AGFI), Comparative Fit Index (CFI), Normed Fit Index (NFI), and Tucker-Lewis Index (TLI) were greater than 0.90, and the root mean square error of approximation (RMSEA) was less than 0.08; The stability of the mediating effects and parameter estimates were examined using the Bootstrap method (Barber and Thompson, 2000). Bootstrapping is a type of repeated sampling in which a random sample of the same size is drawn with a return, and does not require the assumption of normality of the sampling distribution. We used 5,000 bootstrap resamples to calculate 95% bias-corrected confidence intervals (Preacher and Hayes, 2008). If the upper and lower limits did not include 0, it was statistically significant.

Robustness tests were conducted to determine the validity of the study model. The first method is, the alternative modeling method. Model 4 of the SPSS Macro Process was used to test for mediating effects (Hayes and Preacher, 2014), and variables that differed significantly in the chi-square test and Fisher's exact test were used as control variables. The second method, changing the sample composition. Expanding the sample size fills in missing data values through multiple interpolations. Reducing the sample size tested the male sample by stratifying for gender.

2.5 Common method biases

Data collected through participants' self-reports may be subject to common method bias, and this bias may lead to misinterpretation of the study results. To rule out common method bias, Harman's one-factor test was utilized (Podsakoff et al., 2003). This revealed that the amount of variance explained by the first common factor accounted for was 20.89% (<40%), indicating that there was no substantial common method bias in the study's data.

3 Results

3.1 Baseline characteristics

Participants were 624 community-dwelling older adults with a mean age of 72.42 ± 6.07 years were included, of which 151 (24.2%) had cognitive impairment and 249 (39.9%) had hearing loss. In addition, only 9 of 249 older adults with hearing loss wore hearing aids (3.61%), and 33.7% of all older adults with hearing loss had cognitive impairment. Sociodemographic and health-related characteristics of participants grouped by cognitive function are shown in Table 1. We found significant differences between the different cognitive function groups in terms of gender, age, number of falls, nutritional status, depressive symptoms, anxiety symptoms, SRH, and hearing function ($p < 0.05$), whereas the differences were not statistically significant regarding ethnicity, education level, living alone, monthly household income, smoking history, drinking history, and IADL condition ($p > 0.05$). A comparison of the MMSE scores of older adults with diverse characteristics revealed that differences in MMSE scores were statistically significant in terms of age, education level, living alone, monthly household income, nutritional status, number of falls in the previous year, hearing function, depressive symptoms, anxiety symptoms, and SRH ($p < 0.05$), whereas the differences were not statistically significant regarding gender, ethnicity, smoking history, drinking history, and IADL condition ($p > 0.05$) (Supplementary Table S1).

3.2 Correlation analysis of the main study variables

Descriptive statistics and Spearman's correlations for the main study variables are shown in Table 2. Hearing loss was found to have a positive connection with anxiety ($r = 0.167$, $p < 0.01$) and depression ($r = 0.195$, $p < 0.01$). SRH ($r = -0.350$, $p < 0.01$) and cognitive function ($r = -0.164$, $p < 0.01$) were both adversely linked with hearing loss.

3.3 Study model testing

The hypothesized models were tested for goodness-of-fit, and the results of the goodness-of-fit tests for the serial mediation model 1 and serial mediation model 2 were consistent with the following results: χ^2/df = 2.662, GFI = 0.979, AGFI = 0.958, CFI = 0.967, NFI = 0.949, TLI = 0.948, and RMSEA = 0.052, all of which met their respective criteria. Table 3 shows the standardized estimates of the paths in each serial mediation model. The results of the path analyses showed that hearing loss had a negative effect on SRH, cognitive function, and a positive effect on depressive anxiety symptoms. SRH had a negative effect on depressive anxiety symptoms (See Figure 2 for serial mediation model 1 and Figure 3 for serial mediation model 2).

3.4 Serial mediation model

The study examined the relationship between SRH, depressive anxiety symptoms, and cognitive function by analyzing two different causal orders. Table 4 shows the bootstrap results for indirect effects. The results of the serial mediation analysis showed that the total indirect effect of SRH and depressive anxiety symptoms was −0.115 (95% CI: −0.168 to −0.070), and the total effect of the model was −0.221 (95% CI: −0.307 to −0.132), with the total indirect effect accounting for 52.04% of the total effect of the model. In serial mediation model 1, the indirect effect path (HL → SRH → DAS → *CF*) had an indirect effect of −0.029 (SE = 0.013, 95%: −0.058 to −0.007). In the serial mediation model 2, the indirect effect paths (HL → DAS → SRH → *CF*) had an indirect effect of −0.016 (SE = 0.006,

10.3389/fnagi.2023.1297622

TABLE 1 Characteristics of study participants stratified by cognitive function (n = 624).

Variable	Categories	Cognitive function		$\chi 2$	*p*-value
		Normal *N* = 473 n (weighted %)	Impaired *N* = 151 n (weighted %)		
Gender	Male	189 (40.0%)	79 (52.3%)	7.137	0.008
	Female	284 (60.0%)	72 (47.7%)		
Age(years)	65–74	331 (70.0%)	80 (53.0%)	22.644	<0.001
	75–84	131 (27.7%)	57 (37.0%)		
	≥85	11 (2.3%)	14 (9.3%)		
Ethnicity	Han	392 (82.9%)	122 (80.8%)	0.341	0.559
	Ethnic minority	81 (17.1%)	29 (19.2%)		
Education level	Illiteracy	75 (15.9%)	24 (15.9%)	9.095	0.059
	Elementary school	145 (30.7%)	31 (20.5%)		
	Middle school	142 (30.0%)	49 (32.5%)		
	Senior high school	73 (15.4%)	36 (23.8%)		
	College and above	38 (8.0%)	11 (7.3%)		
Living alone	Yes	76 (16.1%)	34 (22.5%)	3.287	0.070
	No	397 (83.9%)	117 (77.5%)		
Monthly household income (CNY)	<1,000	25 (5.3%)	5 (3.3%)	6.656	0.155
	1,000–2,999	107 (22.6%)	33 (21.9%)		
	3,000–4,999	149 (31.5%)	40 (26.5%)		
	5,000–9,999	154 (32.6%)	65 (43.0%)		
	≥10,000	38 (8.0%)	8 (5.3%)		
Smoking history	Yes	58 (12.3%)	17 (11.3%)	0.109	0.741
	No	415 (87.7%)	134 (88.7%)		
Drinking history	Yes	84 (17.8%)	20 (13.2%)	1.679	0.195
	No	389 (82.8%)	131 (86.8%)		
Nutritional status	Malnutrition	32 (6.8%)	23 (15.2%)	10.208	0.001
	Normal	441 (93.2%)	128 (84.8%)		
IADL condition	Impaired	21 (4.4%)	3 (2.0%)	1.862	0.172
	Not impaired	452 (95.6%)	148 (98.0%)		
Number of falls	Never	389 (82.2%)	115 (76.2%)	8.653	0.013
	1–3	66 (14.0%)	21 (13.9%)		
	≥4	18 (3.8%)	15 (9.9%)		
Depressive symptoms	Yes	11 (2.3%)	11 (7.3%)	8.276	0.004
	No	462 (97.7%)	140 (92.7%)		
Anxiety symptoms	Yes	74 (15.6%)	44 (29.1%)	13.592	<0.001
	No	399 (84.4%)	107 (70.9%)		
SRH	Very poor	1 (0.2%)	0 (0.0%)	26.286	<0.001
	Poor	31 (6.6%)	30 (19.9%)		
	Fair	162 (34.2%)	51 (33.8%)		
	Good	212 (44.8%)	59 (39.1%)		
	Excellent	67 (14.2%)	11 (7.3%)		
Hearing function	Normal	308 (65.1%)	67 (44.4%)	20.542	<0.001
	Loss	165 (34.9%)	84 (55.6%)		

CNY, Chinese Yuan. IADL, Instrumental Activity of Daily Living; SRH, Self-rated health.

TABLE 2 Spearman correlation analysis between the main study variables.

Variable	M ± SD	Hearing loss	Depression	Anxiety	SRH	Cognitive function
Hearing loss	0.40 ± 0.49	1				
Depression	2.16 ± 2.13	0.195**	1			
Anxiety	2.31 ± 3.20	0.167**	0.414**	1		
SRH	3.58 ± 0.84	−0.350**	−0.305**	−0.274**	1	
Cognitive function	24.68 ± 5.41	−0.164**	−0.106**	−0.164**	0.212**	1

SRH, Self-rated health; **Correlation is significant at the 0.01 level (two-tailed).

TABLE 3 Path coefficients of the study model.

		Path		Standardized Regression Weights	SE	CR	*P*
Serial Mediation Model 1							
c	HL	→	*CF*	−0.106	0.118	−2.263	0.024
a1	HL	→	SRH	−0.361	0.064	−9.671	<0.001
a2	HL	→	DAS	0.126	0.217	2.596	0.009
b1	SRH	→	*CF*	0.165	0.077	3.175	0.001
b2	NE	→	*CF*	−0.210	0.035	−3.432	<0.001
d	SRH	→	DAS	−0.377	0.144	−6.844	<0.001
Serial Mediation Model 2							
c	HL	→	*CF*	−0.106	0.118	−2.263	0.024
a1	HL	→	DAS	0.263	0.225	5.201	<0.001
a2	HL	→	SRH	−0.269	0.065	−7.074	<0.001
b1	DAS	→	*CF*	−0.210	0.035	−3.432	<0.001
b2	SRH	→	*CF*	0.165	0.077	3.175	0.001
d	DAS	→	SRH	−0.352	0.019	−7.075	<0.001

HL, Hearing loss; SRH, Self-rated health; DAS, Depressive anxiety symptoms; CF, Cognitive function; SE, Standard error; CR, Critical ratio.

95%: −0.030 to −0.005). In the relationship between hearing loss and cognitive functions, SRH and depressive anxiety symptoms co-played a serial mediating role. This suggests that loss of hearing function leads to an increased risk of poor SRH or depressive anxiety symptoms, which in turn leads to a decline in cognitive function.

3.5 Robustness check

First, the alternative modeling approach. The independent mediating roles of SRH, depression, and anxiety between hearing loss and cognitive functioning were tested, controlling for gender, age, number of falls, and nutritional status variables. The results showed that the mediating effects of SRH, depression, and anxiety were all held after controlling for confounders (see Supplementary Table S2 and Figure 1). Second, the sample composition was changed. The model was retested using the new sample after filling in missing values (sample size = 634) and the male sample (sample size = 268). The results showed that the model fit was more favorable to the data, and the results of the mediation analyses were generally consistent with the original model (see Supplementary Table S3).

4 Discussion

The present study found a 24.2% prevalence of cognitive impairment in older adults from the Xinjiang community in northwestern China, which was somewhat higher than the general prevalence of 22.4% of cognitive impairment in China (Qin et al., 2022) and higher than the prevalence of 6.3% in the UK (Richardson et al., 2019). We also noted self-reported hearing loss among 39.9% of older adults, which was much higher than the 9.7% in Japan (Kawaguchi et al., 2023) and 23.2% in Korea (Lee and Chung, 2023). Given the high prevalence of cognitive impairment and hearing loss among community-dwelling older adults in northwestern China, local health organizations and relevant authorities should put a high premium on this situation. Furthermore, we found that hearing loss not only affects cognitive function directly but also indirectly through SRH and depressive anxiety symptoms. Moreover, SRH and depressive anxiety symptoms as mediators had a total mediating effect of 52.04%, greater than the direct effect of hearing loss on cognitive function, suggesting that our mediators are critical in explaining how hearing loss relates to cognitive function.

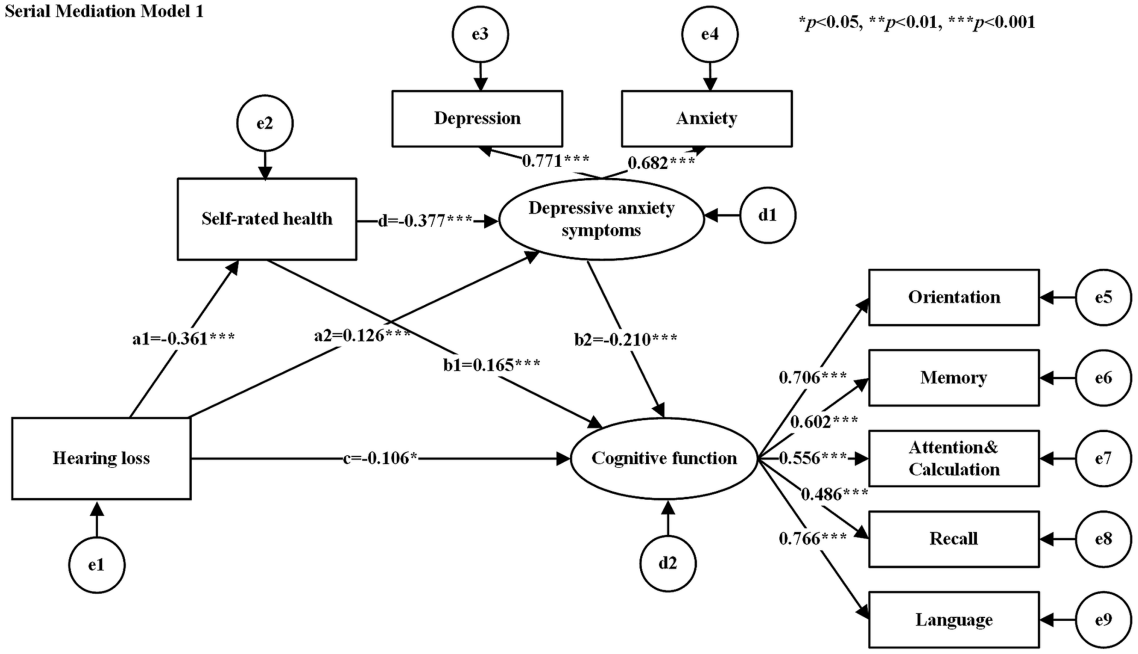

FIGURE 2
Serial mediation model 1. Rectangles for observed variables, ellipses for latent variables. e1–e9 denote measurement errors of the corresponding observed variables and d1–d2 denote structural errors of the corresponding endogenous variables. The values attached to the arrows are the direct effects of normalization. The numbers attached to the arrows between the latent and observed variables are the standardized factor loading values. Serial mediation model 2 same as above.

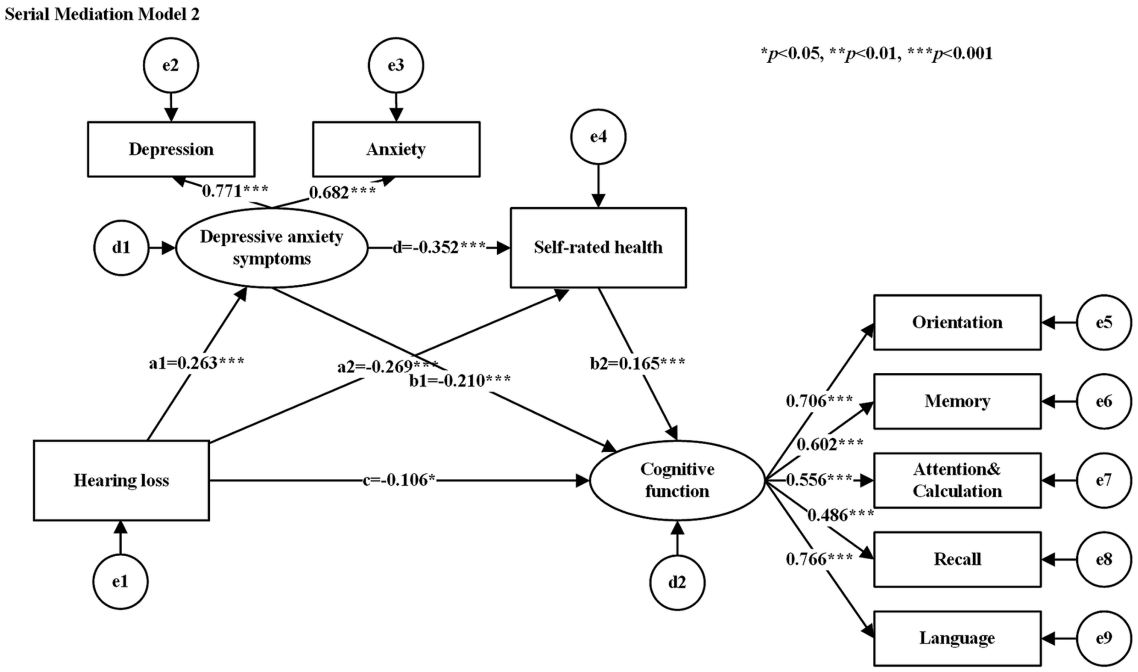

FIGURE 3
Serial mediation model 2.

4.1 Direct effect of hearing loss on cognitive function

Our findings showed that hearing loss significantly and negatively affected cognitive function in older adults. We also found that 33.7% of older adults with hearing loss suffered from cognitive impairment. This result indicates that hearing loss poses a serious threat to the cognitive health of older adults. Multiple hypotheses have been used to explain the mechanisms linking hearing loss and cognitive decline. For example, the common etiology hypothesis suggests that the

TABLE 4 Comparisons of the bootstrap results of the serial mediation models 1 and 2 (standardized coefficients).

Path	Estimate	SE	*p*	95%Bias-corrected confidence intervals		Percentage of Total Effects (%)
				Lower	Upper	
Total effect	−0.221	0.045	<0.001	−0.307	−0.132	100
Direct effect	−0.106	0.047	0.021	−0.201	−0.016	47.96
Total indirect effect	−0.115	0.025	<0.001	−0.168	−0.07	52.04
Serial Mediation Model 1						
Indirect effect (HL → SRH → *CF*)	−0.059	0.022	0.005	−0.103	−0.018	26.70
Indirect effect (HL → DAS → *CF*)	−0.027	0.015	0.013	−0.066	−0.005	12.22
Indirect effect (HL → SRH → DAS → *CF*)	−0.029	0.013	0.009	−0.058	−0.007	13.12
Serial Mediation Model 2						
Indirect effect (HL → DAS → *CF*)	−0.055	0.026	0.008	−0.155	−0.013	24.89
Indirect effect (HL → SRH → *CF*)	−0.044	0.017	0.005	−0.080	−0.013	19.91
Indirect effect (HL → DAS → SRH → *CF*)	−0.016	0.006	0.003	−0.030	−0.005	7.24

HL, Hearing loss; SRH, Self-rated health; DAS, Depressive anxiety symptoms; CF, Cognitive function; SE, Standard error.

association between hearing loss and cognitive decline may be due to common neurodegenerative disorders and there is no clear causal relationship between the two (Uchida et al., 2019). According to the sensory deprivation hypothesis, auditory decline leads to a reduction in the transmission of auditory information to the brain and a long-term lack of a sufficient amount of perceptual stimulation, causing atrophy in areas of the auditory system, resulting in the onset of cognitive decline (Slade et al., 2020). According to the information degradation hypothesis, patients with hearing loss tend to listen hard, which can overconsume the brain's cognitive resources to offset the absence of auditory information, and in the long term, cognitive resources will be over-utilized, leading to cognitive decline (Powell et al., 2021). Although the exact underlying mechanism between hearing loss and cognitive decline remains unclear, current research suggests that restoring auditory input improves auditory neural function and cognitive function in hearing loss patients (Karawani et al., 2018). Hearing loss interventions can prevent or delay 8% of dementia (Livingston et al., 2020). Therefore, the management of hearing in older adults should be enhanced to improve hearing function and reduce cognitive deterioration and other adverse effects.

4.2 Mediating role of SRH

To the best of our knowledge, few studies to date have used SRH as a mediator to investigate the relationship between hearing loss and cognitive function. Our study demonstrated that hearing loss can indirectly affect cognitive function in older adults through SRH. Although there is a high prevalence of poor SRH in older adults with hearing loss, the underlying mechanisms remain unclear. Most studies support that the nature of hearing loss (congenital or acquired) and the degree to which hearing loss causes limitations in daily activities affect SRH (Anderle et al., 2023). Hearing loss in older adults not only affects their daily communication and interactions but also leads to other health problems such as impaired lower limb function, frailty syndrome, and IADL disability (Yévenes-Briones et al., 2021). Thus, older people with hearing loss may perceive significant changes in their lifestyle, activities, and social life due to physical limitations, and they may be aware of their health decline compared to their past or peers, thus making a poor evaluation of their health (Pinto et al., 2016). Hogan et al. (2015) argues that when an individual's coping mechanisms are not well-suited to the demands of their environment, they are more likely to experience increased stress and diminished well-being, ultimately leading to a lower SRH (Hogan et al., 2015). Whitmore et al.'s (2023) study suggests that SRH may initially decrease when individuals experience a disease adversity, such as a new diagnosis. However, as resources are activated and older adults recover or adapt to adversity, SRH may return to its original levels or even increase Furthermore, Whitmore's study indicates that individuals with congenital hearing impairment are not necessarily associated with poor SRH. This is because they develop alternative communication mechanisms apart from speaking and hearing. Moreover, after receiving hearing aids and/or rehabilitation, they develop coping strategies, such as sign language and oral-facial reading, to integrate into the community (Anderle et al., 2023). All of this evidence suggests that individuals who are unable to cope with the changes brought about by hearing loss and lack appropriate coping strategies, such as seeking professional help or using hearing aids, are more likely to experience poor SRH. Working memory refers to an individual's ability to temporarily store and manipulate information while performing a cognitive task, and a poor SRH is associated with poorer overall cognition and working memory, which leads to decreased cognitive function (Aguiñaga et al., 2023). Thus, more emphasis should be placed on improving the poor SRH in older adults, which could be a novel approach to preventing or delaying cognitive decline.

4.3 Mediating role of depressive anxiety symptoms

Results from our study imply that older adults suffering from hearing loss are more likely to experience depression and anxiety,

which raises the likelihood of cognitive deterioration. Hearing loss has historically been related to poor mental health (Bigelow et al., 2020). 1hearing loss and depressive anxiety symptoms. For instance, reduced auditory input leads to dysfunctional emotional processing circuits that are dysfunctional key limbic structures responsible for emotion and behavior, which can lead to impaired perception and misclassification of emotional responses (Zinchenko et al., 2018). Decreased amygdala and hippocampal responsivity to emotional sounds in patients with hearing loss is another potential mechanism, which can contribute to the occurrence of depression (Husain et al., 2014). Disrupted connections in the amygdala also exacerbate anxiety associated with hearing loss (Tang et al., 2020). Behavioral mechanisms have also been used to explain the relationship between hearing loss and depressive anxiety symptoms. Due to the negative impacts of hearing loss, such as social isolation, loneliness, and limited mobility, it can raise the risk of depressive anxiety symptoms (Sharma et al., 2021). Evidence suggests that anxiety and depression have severely adverse consequences on the transient memory domain of cognitive capability in patients with hearing loss, thereby accelerating cognitive decline (Andries et al., 2023). Additionally, anxiety and depression accelerate the rate of atrophy in the frontal and temporal lobes of the brain, respectively, facilitating the progression of MCI toward Alzheimer's disease (Mah et al., 2015; Sacuiu et al., 2016). Thus, reducing anxiety and depressive symptoms in older adults with hearing loss possibly protects their cognitive function to some extent, which warrants further exploration in the future.

4.4 Serial mediation effect of SRH and depressive anxiety symptoms

A series of mediating effects of SRH and depressive anxiety symptoms provide new perspectives on the mechanisms through which hearing loss affects cognitive function. In serial mediation model 1, hearing loss initially caused poor SRH and subsequently increased the risk of depressive anxiety symptoms, which may have led to a more rapid cognitive decline. In addition to the high burden of hearing loss and its adverse influence on the quality of life, hearing loss affects patients' SRH and psychosocial (Jayakody et al., 2022). Patients with hearing loss may have poor SRH due to limited social participation and disability in daily activities in the absence of hearing aids (Anderle et al., 2021). A Brazilian study found that the odds of reporting poor SRH in peers who perceived hearing loss as a health problem were 3.72 times higher compared with peers who failed to perceive hearing loss as a health problem (Guia et al., 2018). Poor SRH can lead to a lack of perceived self-worth and meaning in an individual's life (Vogel et al., 2021). Therefore, patients with hearing loss are more likely to exhibit 'disengaged coping' to escape the stress and exhaustion related to social interactions, as well as the embarrassment of displaying hearing difficulties before other people, which implies avoiding addressing hearing loss by opting out or withdrawing, for instance, withdrawing from social gatherings or pretending to hear during conversations (Heffernan et al., 2016). This negative coping can exacerbate mental tension, undermine mental health, and lead to the onset of anxiety and depression. Depression and anxiety are clinical markers that can help identify early signs of cognitive decline (Perin et al., 2022).

In serial mediation model 2, hearing loss initially leads to depressive anxiety symptoms and subsequently increases the risk of poor SRH, which can lead to a decline in cognitive function. If individuals with hearing loss adopt appropriate coping mechanisms (e.g., care-seeking behaviors, hearing rehabilitation training, wearing hearing aids, and seeking social support), the negative psychosocial and health consequences of hearing loss can be mitigated (Wells et al., 2020). In this case, hearing loss patients have a low risk of depression and anxiety and tend to make a positive assessment of their health. Moreover, individuals with good SRH perform better in executive function, working memory, and global cognition than individuals with poor or fair SRH (Aguiñaga et al., 2023). This study found that SRH and depressive anxiety symptoms are interrelated, regardless of the direction in which they flow between hearing loss and cognitive function, both of which have a serial mediation effect, shedding light on the mechanisms through which hearing loss impacts cognition. These findings suggest that older individuals should prioritize not only the management of hearing loss but also the management of SRH and mental health.

4.5 Implications and limitations

This study innovatively used SRH and depressive anxiety symptoms as mediating variables and confirmed that both SRH and depressive anxiety symptoms partially mediated the relationship between hearing loss and cognitive function in community-dwelling older adults. These findings may help identify people at high risk of cognitive impairment and ultimately prevent and treat this disease through the management of SRH and depressive anxiety symptoms in older adults with hearing loss. According to the data, the prevalence of hearing loss among Chinese adults over 60 years old is 58.85%, but the rate of hearing aid acquisition is only 6.5% (Gong et al., 2018), which is lower than the 10% in Japan and 17.4% in South Korea (Moon et al., 2015; Sugiura et al., 2022). Reliable evidence suggests that the use of hearing aid devices in patients with hearing loss reduces the risk of cognitive decline by 19% (Yeo et al., 2023). In this study, only 3.61% of older adults with hearing loss had access to hearing aids, well below the national level and in other Asian countries. We suggest that older adults with hearing loss should be promptly identified and managed to improve the utilization of hearing aid devices. Future studies should also develop cognitive function assessment tools that are more applicable to older adults with hearing loss. Community and medical personnel should regularly assess SRH and the mental health of older adults, especially those with hearing loss, which may facilitate the early detection of cognitive problems. Previous research found that the number and quality of social networks can buffer the adverse impacts of poor SRH on mental health (Windsor et al., 2016), and therefore older adults should be encouraged to engage in more social group activities regularly to build a good social support system.

Although this study has some theoretical and practical implications, some limitations exist. First, this cross-sectional study did not fully elucidate the causal relationships among hearing loss, SRH, depressive anxiety symptoms, and cognitive function. Longitudinal studies with large sample sizes are needed to comprehensively explore the causal relationships among the investigated variables. Second, hearing loss was determined by self-report in this study. Although self-reported hearing loss is a brief and

highly effective indicator in epidemiological studies, there is a need to jointly use self-reported hearing loss with hearing status measured by pure-tone audiometry for screening and research (Louw et al., 2018). Finally, the study variables in this study were surveyed by questionnaire and may be subject to reporting bias.

5 Conclusion

In summary, this study investigated the relationships among hearing loss, SRH, depressive anxiety symptoms, and cognitive function. The pathway analysis revealed that hearing loss can affect cognitive function directly as well as indirectly through the serial mediation effects of SRH and depressive anxiety symptoms. These findings may help to identify and manage cognitive problems in older adults on time. Additionally, focusing on enhanced management of hearing loss — complemented by the management of SRH and mental health — may be another effective public health strategy to protect cognitive function in older adults.

Data availability statement

The datasets presented in this article are not readily available because the data are available from the corresponding author upon reasonable request. Requests to access the datasets should be directed to FC, 1152065261@qq.com.

Ethics statement

The studies involving humans were approved by Medical Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University (Ethics Approval No. K202009-05). 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

FC: Funding acquisition, Investigation, Supervision, Writing – review & editing. YC: Conceptualization, Formal analysis, Writing – original draft. XJ: Investigation, Visualization, Writing – review & editing. XL: Formal analysis, Writing – review & editing. HN: Methodology, Writing – review & editing. MH: Validation, Writing – review & editing. WJ: Writing – review & editing, Data curation. NZ: Writing – review & editing. HF: Conceptualization, Project administration, Supervision, Writing – review & editing. PY: Conceptualization, Funding acquisition, Investigation, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by the National Key Research and Development Program of China [Grant No. 2020YFC2008603], the Science and Technology Aid to Xinjiang Project [Grant No. 2022E02119], and the Innovation and Entrepreneurship Training Program for College students in Xinjiang Uygur Autonomous Region [Grant No. S202210760071].

Acknowledgments

The authors are grateful to all the participants who contributed to this study.

Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2023.1297622/full#supplementary-material

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frontiers | Frontiers in Aging Neuroscience

TYPE Original Research
PUBLISHED 26 June 2024
DOI 10.3389/fnagi.2024.1341227

OPEN ACCESS

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RECEIVED 20 November 2023
ACCEPTED 13 June 2024
PUBLISHED 26 June 2024

CITATION
Qin Y, Zhang H, Qing L, Liu Q, Jiang H, Xu S, Liu Y and He X (2024) Machine vision-based gait scan method for identifying cognitive impairment in older adults.
Front. Aging Neurosci. 16:1341227.
doi: 10.3389/fnagi.2024.1341227

Machine vision-based gait scan method for identifying cognitive impairment in older adults

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Objective: Early identification of cognitive impairment in older adults could reduce the burden of age-related disabilities. Gait parameters are associated with and predictive of cognitive decline. Although a variety of sensors and machine learning analysis methods have been used in cognitive studies, a deep optimized machine vision-based method for analyzing gait to identify cognitive decline is needed.

Methods: This study used a walking footage dataset of 158 adults named West China Hospital Elderly Gait, which was labelled by performance on the Short Portable Mental Status Questionnaire. We proposed a novel recognition network, Deep Optimized GaitPart (DO-GaitPart), based on silhouette and skeleton gait images. Three improvements were applied: short-term temporal template generator (STTG) in the template generation stage to decrease computational cost and minimize loss of temporal information; depth-wise spatial feature extractor (DSFE) to extract both global and local fine-grained spatial features from gait images; and multi-scale temporal aggregation (MTA), a temporal modeling method based on attention mechanism, to improve the distinguishability of gait patterns.

Results: An ablation test showed that each component of DO-GaitPart was essential. DO-GaitPart excels in backpack walking scene on CASIA-B dataset, outperforming comparison methods, which were GaitSet, GaitPart, MT3D, 3D Local, TransGait, CSTL, GLN, GaitGL and SMPLGait on Gait3D dataset. The proposed machine vision gait feature identification method achieved a receiver operating characteristic/area under the curve (ROCAUC) of 0.876 (0.852–0.900) on the cognitive state classification task.

Conclusion: The proposed method performed well identifying cognitive decline from the gait video datasets, making it a prospective prototype tool in cognitive assessment.

KEYWORDS

gait, gait recognition, cognitive impairment, machine vision, CNN, BiLSTM

1 Introduction

Cognitive impairment, characterized by altered performance in specific cognitive tasks such as orientation, attention, comprehension, memory, reasoning, problem-solving, organizational skills, processing speed, perseverance, and motivation (Allain et al., 2007), can affect multiple domains of cognition simultaneously or consecutively, either gradually or abruptly. Cognitive impairment and dementia are the primary causes of disability in older adults, and promoting healthy brain aging is considered a critical element in reducing the burden of age-related disabilities (Lisko et al., 2021). It is estimated that 40% of dementia might be prevented or delayed by modifying its risk factors, improving activities of daily living (Livingston et al., 2020; Yun and Ryu, 2022). Routine, non-cognitive evaluations alone are insufficient for physicians to accurately predict patients' cognitive function. Therefore, cognitive assessment facilitates the diagnosis and potential intervention of disorders that impair thinking (Woodford and George, 2007).

The association between motor function and cognition can be understood, in part, in the context of the evolution of human bipedalism (Leisman et al., 2016). Bipedalism served as a significant basis for the evolution of the human neocortex as it is among the most complex and sophisticated of all movements. Gait pattern is no longer regarded as a purely motor task but is considered a complex set of sensorimotor behaviors that are heavily affected by cognitive and affective aspects (Horst et al., 2019). This may partially explain the sensitivity of gait to subtle neuronal dysfunction, and why gait and postural control is associated with global cognitive function in very old people, and can predict the development of disease such as diabetes, dementia, or Parkinson's disease years before they are diagnosed clinically (Ohlin et al., 2020).

Previous studies reported that slower walking speeds and a greater decline in speed over time are correlated with a greater risk of developing dementia independent of changes in cognition, supporting the role of gait speed as a possible subclinical marker of cognitive impairment (Hackett et al., 2018). Furthermore, spatial, temporal, and spatiotemporal measures of gait and greater variability of gait parameters are associated with and predictive of both global and domain-specific cognitive decline (Savica et al., 2017).

A variety of sensors and machine learning analysis methods have been used in cognitive studies. Chen et al. (2020), for example, used a portable gait analysis system and collected gait parameters that were used in a machine learning classification model based on support vector machine and principal component analysis. Zhou et al. (2022) collected 23 dynamic gait variables using three-dimensional (3D) accelerometer data and used random forest and artificial neural network to classify cognitive impairment.

The purpose of this study was to develop a machine vision-based gait identification method for geriatric diseases without using contact sensors or indexes, and to explore its potential as a cognitive impairment screening tool that is convenient, objective, rapid, and non-contact. To this end, a series of hyperparameters in machine vision networks for gait feature extraction and identification were deeply optimized to produce a method called Deep Optimized GaitPart (DO-GaitPart), and the optimized components and DO-GaitPart were evaluated. The performance for dementia and mild cognitive impairment (MCI) evaluation was evaluated by receiver operating characteristic/area under the curve (ROCAUC). These methods may be suitable for community screening and generalize to any gait-related approach to disease identification.

2 Methods

2.1 Participants

The current research was a cross-sectional designed analysis that included collecting part of baseline data in the West China Health and Aging Trend study, an observational study designed to evaluate factors associated with healthy aging among community-dwelling adults aged 50 years and older in western China. In 2019, we included a subset of 158 participants in Sichuan province. All participants (or their proxy respondents) were recruited by convenience and provided written informed consent to the researchers, and our institutional ethics review boards approved the study. All researchers followed the local law and protocol to protect the rights of privacy and likeness and other interests of participants in this study.

2.2 Definition of cognitive impairment

The Short Portable Mental Status Questionnaire (SPMSQ), a widely employed cognitive assessment tool that encompasses location, character orientation, and calculation, was applied. The established cutoff point for differentiating between healthy participants and those with mild to more severe cognitive impairment was set at a level of exceeding 3 errors in 10 questions (Pfeiffer, 1975).

2.3 Recording of walking video

The set of recordings was similar to that used in our previous research (Liu et al., 2021). Gait videos were shot in spacious, warm, level, well-lit indoor environments. A complete recording of each participant included six 4 m walking sequences, with three synchronized video segments shot using three different cameras (F = 4 mm, DS-IPC-B12V2-I, Hikvison, Zhejiang, China) for each sequence. The height from ground to cameras was approximately 1.3 m, and their angles were adjusted to ensure that the participant's whole body could be filmed for the entire gait process between benchmarks. Data were stored by the recorder (DS-7816N-R2/8P, Hikvison, Zhejiang, China) in MP4 format at 1080p resolution.

Abbreviations: BiLSTM, Bi-directional long short-term memory; Conv2d, Two-dimensional convolutional network; HP, Horizontal pooling; DO-GaitPart, Deep Optimized GaitPart; DSFE, Depth-wise spatial feature extractor; DS-Conv2d, Depth-wise spatial two-dimensional convolutional network; DW-Conv2d, Depth-wise two-dimensional convolutional network; DW-D-Conv2d, Depth-wise dilated two-dimensional convolutional network; FConv, Focal convolutional network; GEI, Fait energy image; HP, Horizontal pooling; LSTM, Long short-term memory; LeakyReLU, Leaky rectified linear unit; MCI, Mild cognitive impairment; MTA, Multi-scale temporal aggregation; MTM, Multi-scale temporal module; ROCAUC, Receiver operating characteristic/area under the curve; SPMSQ, Short Portable Mental Status Questionnaire; STTG, Short-term temporal template generator; WCHEG, West China Hospital Elderly Gait;.

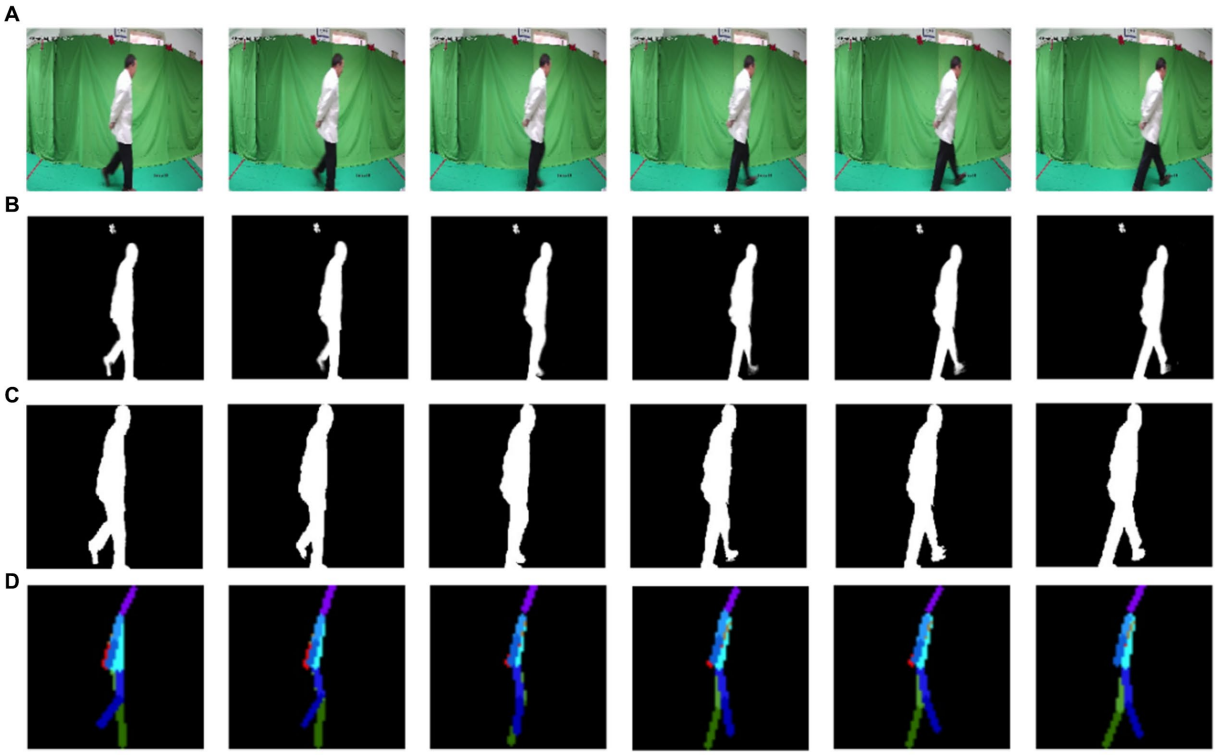

FIGURE 1
Flow of pretreatment: **(A)** static image sequence, **(B)** raw silhouette sequence, **(C)** gait silhouette sequence, and **(D)** gait skeleton sequence.

2.4 Pretreatment of recording footage and data set

Then video files of each walking sequence were converted into static image frames (Figure 1A). The raw silhouette of walking participants was obtained through the RobustVideoMatting method (Figure 1B) (Lin et al., 2022). The FindContours function of the OpenCV library in Python was used to segment the minimum external rectangle of the maximum silhouette for the more refined silhouettes, after the participant image was centralized and normalized to 256 × 256, the gait silhouette sequence was generated (Figure 1C). The measure for spatial information extraction of skeleton points from the gait silhouette sequence was HRNet (Figure 1D) (Sun et al., 2019). Our dataset, named West China Hospital Elderly Gait (WCHEG), was used to validate the model along with two open gait video databases: CASIA-B and Gait3D. CASIA-B (Yu et al., 2006), includes data from 124 participants, with 6 normal walking sequences, 2 long clothing sequences, and 2 backpacking sequences per participant. Gait3D (Zhu et al., 2021) includes a large-scale outdoor dataset of 5,000 participants, with 1,090 total hours of gait video. The WCHEG dataset was used to test the effectiveness of the model in recognizing cognitive impairment. Each dataset uses gait skeleton images and silhouette images as model inputs, both of which have a size of 128 × 128.

2.5 Machine vision approach and analysis

Our gait dataset WCHEG included more than 400,000 frames of raw static images and corresponding silhouette and skeleton gait images. The main purpose of our optimized design was to balance computational power consumption and accuracy of the model classification. A temporal part-based module, GaitPart (Fan et al., 2020), which was designed based on the idea that the local short-range spatiotemporal features (micro-motion patterns) are the most discriminative characteristics for human gait, was applied as the original analysis work frame in the current study. To better adapt this method to the mission of cognitive impairment assessment, three novel components were designed in our analysis pipeline to achieve the proposed DO-GaitPart (Figure 2): short-term temporal template generator (STTG), depth-wise spatial feature extractor (DSFE), and multi-scale temporal aggregation (MTA).

2.6 STTG

To ensure that the input gait sequence contains a complete gait cycle with less computational cost and minimal loss of temporal information, we designed an STTG. We grouped the input dual-channel gait sequence X_{in} into M per frame and created a short-term temporal template using systematic random sampling. Most of the previous work (Fan et al., 2020; Huang X. et al., 2021; Kaur et al., 2023) directly input gait sequences into the network frame by frame, with each input gait sequence including at least one gait cycle, which meant that the sequence mean size was usually 30 frames, equivalent to more than 1 s. Because part of our participant data has the feature of cognitive impairment as well as a low stride frequency, a gait cycle often contained far more than 30 frames. As shown in Figure 3A, adjacent frames are highly similar, which generates a large amount of

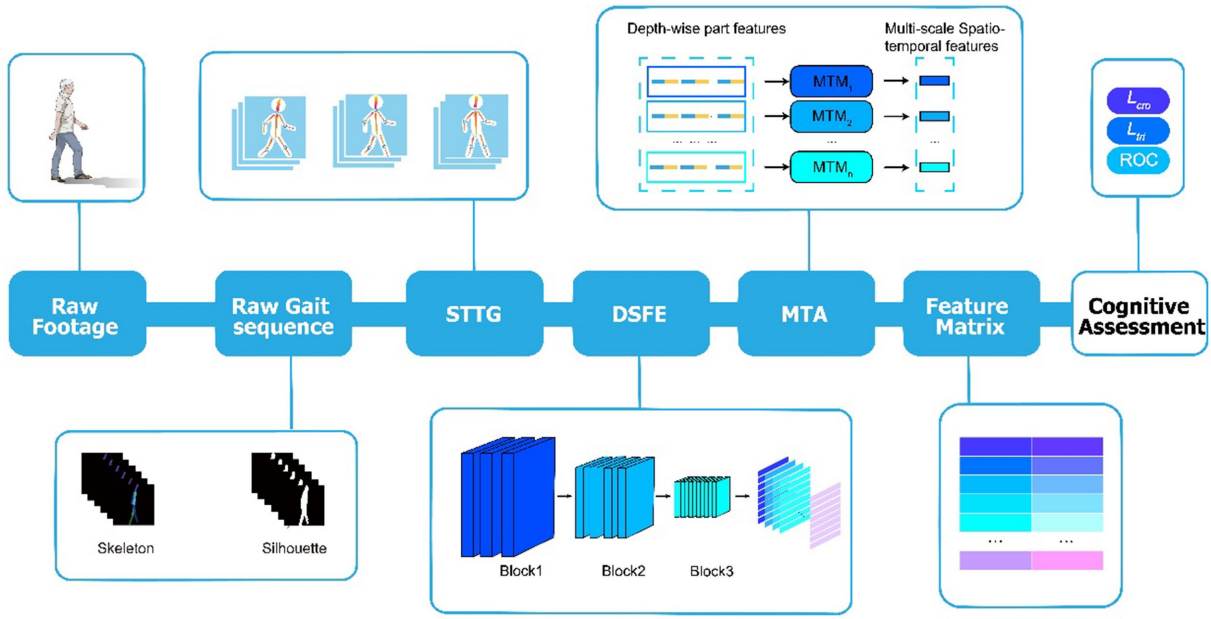

FIGURE 2
Overview of proposed gait analysis model. Extract the original gait sequence from the raw gait footage, which includes silhouette and skeleton gait images. Then, input the gait sequence into STTG to generate the template sequence, and input it into DSFE to extract depth-wise spatial features. Then, horizontally cut the output into n parts to obtain depth-wise part features. Furthermore, input each part into MTM separately to obtain the output multi-scale spatial–temporal features. Obtain the feature matrix through full connection and batch normalization, train the model through a series of loss functions such as triplet loss and cross entropy loss, and test through evaluation indicators such as ROC to achieve cognitive assessment.

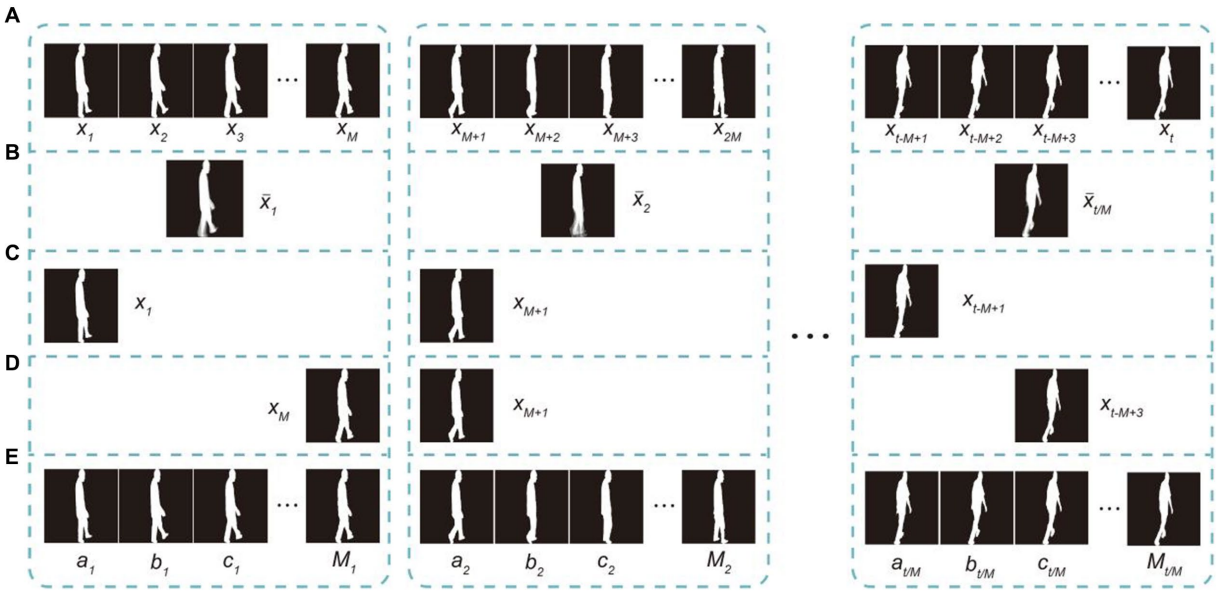

FIGURE 3
Different temporal template generating methods, with $M=4$: **(A)** raw image sequence $X=\{x_i|_{,,,}i=1|_{,,,}2|_{,,,}\ldots|_{,,,}t\}$, **(B)** gait energy image method, **(C)** equidistant sampling method sampling the image with equal $M-1$ spacers from the beginning, **(D)** simple random sampling every M images, and **(E)** short-term temporal template generator, which divides the whole gait sequence into M sets and randomly selects a set at a time.

information redundancy and increases unnecessary computational costs. Creating the template with the gait energy image (GEI) method (Han and Bhanu, 2006), as shown in Figure 3B, leads to the loss of temporal information, because the template is based on the average of each group image. Generating the template though equidistant sampling (Figure 3C), in which fixed positions in each group are picked up and only 1 / M gait images are retained in the dataset, causes a lot of waste. Generating the template using simple random sampling (Figure 3D) picks up some adjacent frames at the same time, resulting in information redundancy. STTG extracts the kth frame in each

TABLE 1 Detailed parameters for depth-wise part feature extractor.

Block	Layer	In C	Out C	Kernel	Dilation	Padding
Block1	Conv2d	2	32	5	1	2
	DS-Conv2d	32	32	3	2	1
	MaxPool2d, kernel size = 2, stride = 2					
Block2	Conv2d	32	64	3	1	1
	Conv2d	64	64	3	1	1
	MaxPool2d, kernel size = 2, stride = 2					
Block3	Conv2d	64	192	3	1	1
	Conv2d	192	192	3	1	1
	MaxPool2d, kernel size = 2, stride = 2					

Conv2d, two-dimensional convolutional network; In C, input channels; Out C, output channels; kernel, kernel size; dilation, dilation rate; padding, zero padding.

group, where k is a random value from the set $\{1,2,\ldots,M\}$ with the equivalent probability, and in every training epoch k revalues (Figure 3E), which can avoid all the disadvantages of the above methods. In the current study, we compared the situation of $M = 2,3,4,5$ and found that the best results were achieved at $M = 4$.

2.7 DSFE

We develop a DSFE to extract both global and local fine-grained spatial features from gait images. Many previous models (Huang X. et al., 2021; Li et al., 2023) used only basic convolutional neural network (CNN) modules to extract spatial features from gait images, which leads to failure of capture all the gait details. Some networks, such as GaitPart (Fan et al., 2020) developed a component focal convolutional network (FConv) to extract part features, but then just combined those part features, and as a result ignored the connections between part features. However, the DSFE extracts partial spatial features and keeps the relation between part features. The DSFE consists of three blocks. The first block contains one two-dimensional convolutional network (Conv2d) layer and one depth-wise spatial Conv2d (DS-Conv2d) layer. The following two blocks contain two Conv2d layers each. The specific network structure is shown in Table 1. For the DSFE module, we compared the location and quantity of replacing Conv2d with DS-Conv2d in Block 1, Block 2, and Block 3, respectively. We found that using DS-Conv2d in the second layer of Block1 had the best performance.

The structure of the DS-Conv2d module is shown in Figure 4 and can be expressed as Equation (1):

$$\begin{aligned} \mathrm{DS-Conv2d}(\cdot) = \mathrm{Conv2d}(\cdot) \oplus \mathrm{DW-D-} \\ \mathrm{Conv2d}\left(\mathrm{DW-Conv2d}(\cdot)\right) \end{aligned} \tag{1}$$

where depth-wise two-dimensional convolutional network (DW-Conv2d) represents depth-wise convolution (Guo et al., 2023). As shown in Figure 4, depth-wise convolution is the extraction of local features from a single-channel spatial feature map. Each convolutional kernel only performs convolution operations on a single channel. Depth-wise dilated two-dimensional convolutional network (DW-D-Conv2d) is a special type of depth-wise convolution that introduces dilated convolution to increase the model's receptive field and extract long-range features from a single spatial feature map. The combination of the two parts takes into account local contextual information, enlarges the receptive field, and enables the extraction of richer spatial information from the gait sequence. Leaky rectified linear unit (LeakyReLU) is the activation function, which can be expressed as Equation (2):

$$\mathrm{LeakyReLU}(x) = \begin{cases} x, x \geq 0 \\ ax, x < 0, 0 < a < 1 \end{cases} \tag{2}$$

2.8 MTA

MTA is composed of multiple parallel multi-scale temporal modules (MTMs), each of which is responsible for extracting features from the corresponding part of the gait sequence, acquiring multi-scale temporal features. The input to the DSFE module passes through the horizontal pooling (HP) module to obtain $F_{\mathrm{HP}} \in \mathbb{R}^{\frac{t}{M} \times c_1 \times p}$, expressed as $F_{\mathrm{HP}} = \left\{ f_{\mathrm{HP}}^j | , , j = 1 | , , 2 | , , \ldots | , , p \right\}$, where $f_{\mathrm{HP}}^j \in \mathbb{R}^{\frac{t}{M} \times c_1}$ represents the temporal features of the jth horizontal part. Then, the part is input into the MTM, as shown in Figure 5, extracting both frame-level $F_{\mathrm{f}} = \left\{ f_{\mathrm{f}}^j | , , j = 1 | , , 2 | , , \ldots | , , p \right\}$ and long short-term temporal features $F_{\mathrm{ls}} = \left\{ f_{\mathrm{ls}}^j | , , j = 1 | , , 2 | , , \ldots | , , p \right\}$, which are then aggregated into multi-scale temporal features $F_{\mathrm{MTA}} = \left\{ f_{\mathrm{MTA}}^j | , , j = 1 | , , 2 | , , \ldots | , , p \right\}$, expressed as Equation (3):

$$\begin{aligned} f_{\mathrm{f}}^j &= \mathrm{BatchNorm}\left(f_{\mathrm{HP}}^j \right) \\ f_{\mathrm{ls}}^j &= \mathrm{BatchNorm}\left(f_{\mathrm{f}}^j + \mathrm{BiLSTM}\left(f_{\mathrm{HP}}^j \right) \right) \\ f^j{}_{\mathrm{MTA}} &= \mathrm{TP}\left(\mathrm{Attention}\left(\mathrm{Concat}\left(f_{\mathrm{f}}^j, f_{\mathrm{ls}}^j \right) \right) \right) \\ \mathrm{Attention}(\cdot) &= \mathrm{LeakyReLU} \\ &\left(\mathrm{Conv1d}\left(\mathrm{Dropout}\left(\begin{matrix} \mathrm{LeakyReLU} \\ (\mathrm{Conv1d}(\cdot)) \end{matrix} \right) \right) \right) \end{aligned} \tag{3}$$

where f_{f}^j, f_{ls}^j and f_{MTA}^j represent the frame-level time characteristics, long short-term time features, and multi-scale time characteristics of the jth horizontal part, respectively, and for now

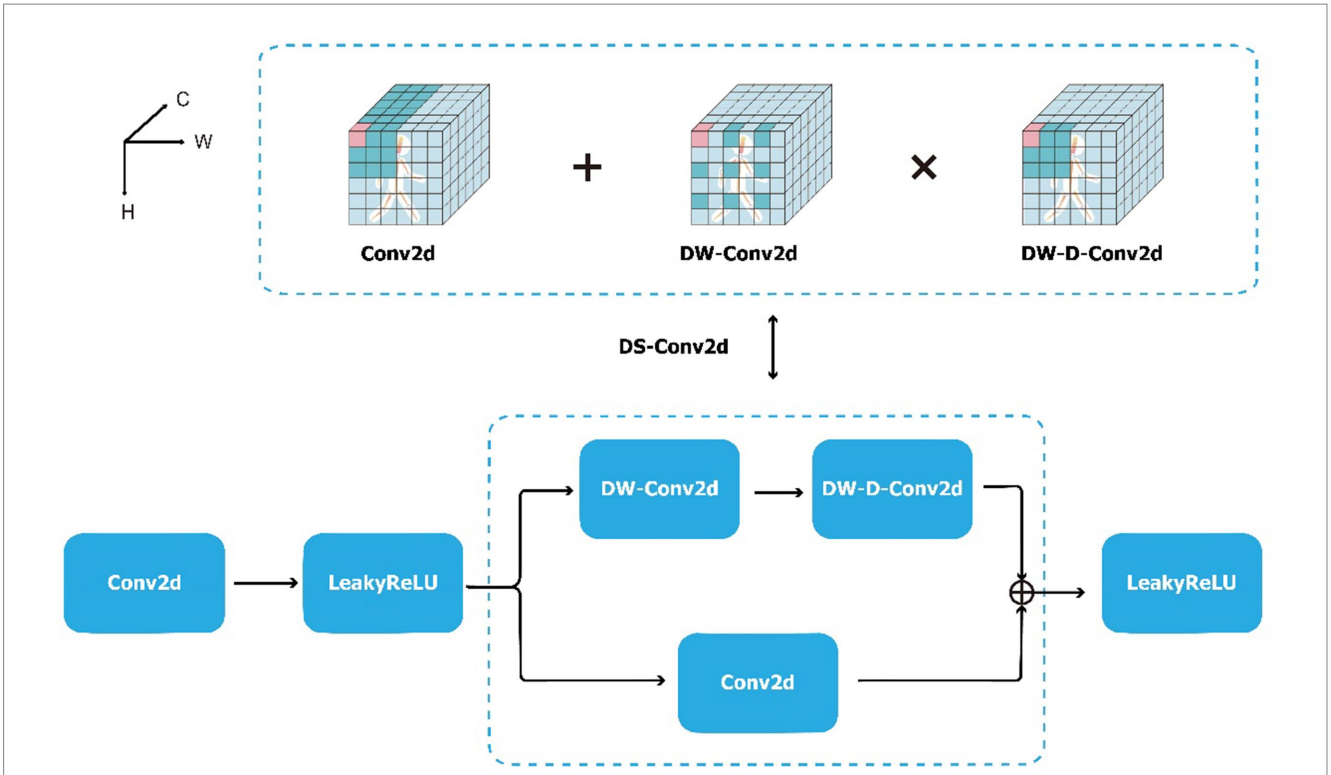

FIGURE 4
The convolution part of Block 1 in frame of DSFE, including Conv2d, DS-Conv2d and LeakyReLU. The DS-Conv2d's convolution operation process of a pixel (pink cube) of a three-dimensional feature map of a single frame (the whole cube). The information (all color cubes) contained in the receptive field is weighted and aggregated into the pink cube. The H, W, and C of cube represent the height, width, and channel dimensions of the feature map. The dark cubes indicate the position of the convolution kernel. The convolution core size of Conv2d, DW-Conv2d, and DW-D-Conv2d are all 3 × 3, and the dilation rate of DW-Conv2d is 2. Note: The operation process has omitted the zero filling.

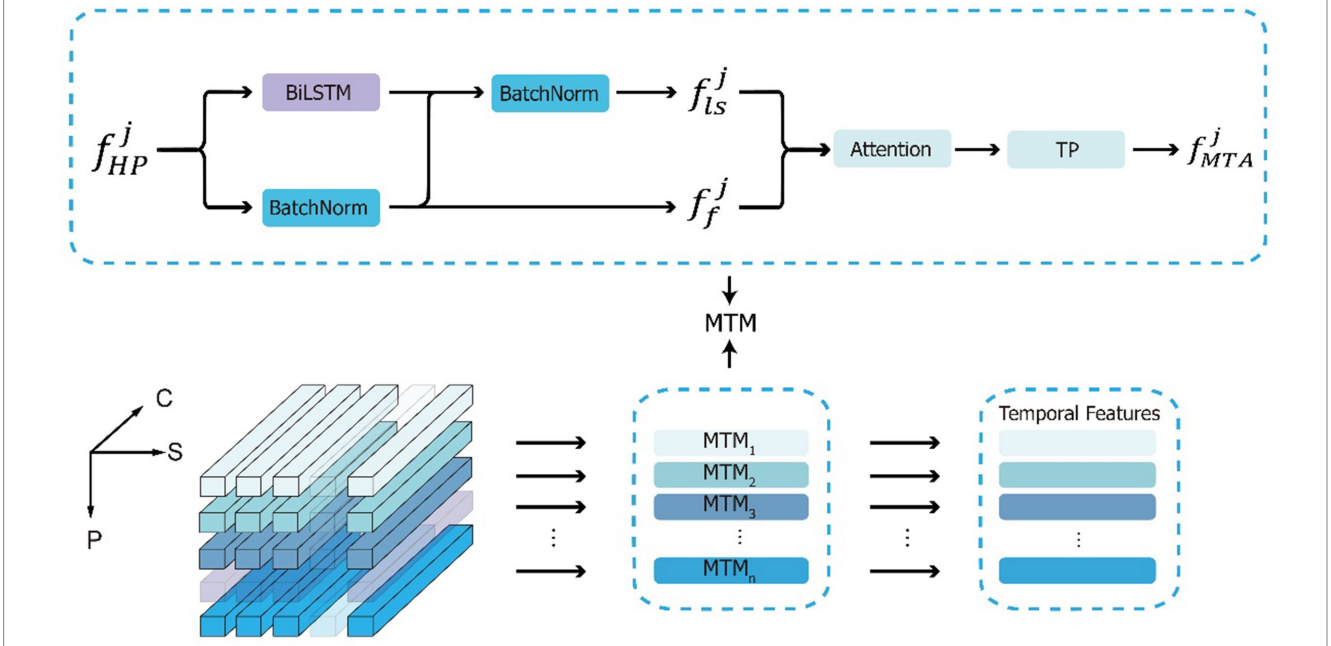

FIGURE 5
The calculation process of MTA and the details of MTM. The input is the three-dimensional gait feature maps, where P represents the component dimension, S represents the time dimension, C represents the channel dimension, and a semi transparent cube represents the omission of the feature maps. Along the component dimensions, input F_{HP} into the MTMs module to obtain multi-scale time features.

TABLE 2 Accuracy comparison (%) with different addition of the three components of our model on CASIA-B and WCHEG.

Group	STTG	DSFE	MTA	CASIA-B			WCHEG
				NM	BG	CL	
A	x	x	x	97.4	92.8	74.9	74.9
B	✓	x	x	97.6	93.1	76.2	76.5
C	x	✓	x	97.4	92.9	77.7	78.8
D	x	x	✓	97.8	93.2	80.3	77.7
E	✓	✓	x	97.9	93.4	79.9	79.1
F	x	✓	✓	98.0	94.7	82.8	78.2
G	✓	x	✓	97.8	94.1	83.5	77.3
H	✓	✓	✓	**98.1**	**95.4**	**84.6**	**82.5**

NM, normal walking; BG, carrying bags; CL, wearing coats or jackets. Bold values mean best performance method, model, module or algorithm in comparison.

$F_f, F_{ls}, F_{MTA} \in \mathbb{R}^{c_2 \times p}$. $\mathrm{BatchNorm}(\cdot)$ indicates normalized data to mean of 0 and standard deviation of 1 by Batch. $\mathrm{BiLSTM}(\cdot)$ is a special type of long short-term memory (LSTM) (Hochreiter and Schmidhuber, 1997) known as bi-directional LSTM (BiLSTM), which is capable of accessing both past and future information in a time series, introducing more contextual dependencies and performing well in extracting short-term and long-term relationships. $\mathrm{Concat}(\cdot)$ represents the concatenation operation, connecting the frame-level time feature F_f with the long short-term feature F_{ls} along the channel dimension. $\mathrm{Attention}(\cdot)$ represents using the attention mechanism of SENet (Hu et al., 2018), which introduces the attention mechanism to focus on the relationships between channels and performs feature weighting on the channel dimension; the greater the weight equivalent the higher the correlation between the channel and key temporal information. Meanwhile, we introduce the Dropout (Srivastava et al., 2014) technique in $\mathrm{Attention}(\cdot)$, which can mitigate the overfitting phenomenon and enhance the model's ability to generalize to new data. $\mathrm{TP}(\cdot)$ represents temporal pooling, and according to previous research (Fan et al., 2020), selecting $\mathrm{TP}(\cdot) = \max(\cdot)$ yields better results.

We compared the classification results of frame-level feature, long short-term feature, and multi-scale aggregated feature. We found that long short-term feature performed better than frame level feature and multi-scale aggregated feature achieved the best classification results. By extracting frame-level and long short-term temporal features, it captures abstract features at different scale levels in the gait sequence, and then uses an attention mechanism to aggregate more distinctive temporal information.

2.9 Loss function and sample

During the training stage, both the separate batch all (BA+) triplet loss (Hermans et al., 2017) and the label smoothing cross entropy loss (Szegedy et al., 2016) were used to achieve more effective training results. The multiply loss function L_{mul} can be defined as $L_{mul} = \lambda_{tri} L_{tri} + \lambda_{cro} L_{cro}$, where L_{tri} and L_{cro} represent the BA+ triplet loss and the label smoothing cross entropy loss, respectively. λ_{tri} and λ_{cro} represent the weight coefficients of the loss functions. Here, $\lambda_{tri} = 1.0$ = and $\lambda_{cro} = 0.2$. The batch size was set to $(p,k) = (4,6)$, which represents that every batch includes p participants, and k gait image sequences will be picked up in every participant's footage. The length of the analyzing sequence is 80 frames. If the length of the original sequence is less than 15 frames, it is discarded; if the length is between 15 and 80 frames, it is repeatedly sampled.

2.10 Comparison, ablation, and classification

CASIA-B and Gait3D was used in the comparison of individual recognition accuracy among previous gait analysis methods and DO-GaitPart. To determine which component in our model led to better adaptation for the gait analysis mission, components were removed from the total pipeline in a process known as ablation. We set eight groups of different hyperparameters for experiments and compared accuracy with that of GaitPart (composed of three Block + HP + temporal pooling modules, where each layer includes two convolutional layers and one maximum pooling layer), as baseline, in the individual recognition task. A two-class classification for mild or worse cognitive impairment gait and healthy gait features was designed to evaluate the performance of models as cognitive classifiers for the WCHEG dataset. The ground truth state for all gait features in this experiment was labelled using a previously performed SPMSQ assessment.

3 Results

The hardware environment is CPU, Intel i7-8700, 3.20 GHz, GPU, GeForce RTX 2080 Ti + GeForce RTX 1080 Ti. And the software development environment is Python 3.7.1, Pytorch 1.8.1.

3.1 Ablation study

We found that each component of our model is essential, and the addition of each component provides a positive gain in the identification results of both datasets. The best performance of the model was achieved when the three components were deployed simultaneously (Table 2). Furthermore, we conduct ablation studies on specific parameters of each module.

3.1.1 Analysis of different *M* numbers of STTG

The ablation experiments were designed to demonstrate the most appropriate choice of parameters for the STTG (Table 3), where the

TABLE 3 Accuracy comparison (%) with different *M* numbers of STTG on CASIA-B and WCHEG.

M	CASIA-B			WCHEG
	NM	BG	CL	
2	97.8	94.9	83.4	79.9
3	97.5	95.1	84.4	80.1
4	**98.1**	**95.4**	**84.6**	**82.5**
5	97.6	95.0	84.0	78.9

Bold values mean best performance method, model, module or algorithm in comparison.

TABLE 4 Accuracy comparison (%) with replacing Conv with DS-Conv in different blocks of DSFE on CASIA-B and WCHEG.

Block 1	Block 2	Block 3	CASIA-B			WCHEG
			NM	BG	CL	
✓	x	x	**98.1**	**95.4**	**84.6**	82.5
✓	✓	x	97.5	93.9	83.1	78.1
✓	✓	✓	97.1	94.3	83.7	79.2
x	✓	x	96.8	94.0	83.2	78.2
x	x	✓	95.2	89.1	72.6	71.1

Bold values mean best performance method, model, module or algorithm in comparison.

TABLE 5 Accuracy comparison (%) with different algorithms used by MTA on CASIA-B and WCHEG.

F_f	$F1s$	Attention	CASIA-B			WCHEG
			NM	BG	CL	
x	LSTM	x	97.5	93.1	79.2	78.9
✓	LSTM	✓	97.8	94.2	82.8	81.1
x	BiLSTM	x	97.7	93.7	81.2	81.3
✓	BiLSTM	✓	**98.1**	**95.4**	**84.6**	**82.5**

Bold values mean best performance method, model, module or algorithm in comparison.

inter-frame similarity of the gait sequence decreases as the value of *M* increases, and the same number of frames can contain more gait information, reaching an optimum at $M = 4$. Whereas, when the value of M is too large, it leads to a decrease in the continuity between frames and affects the learning of the complete action of the gait. Meanwhile in the WCHEG dataset, the introduction of STTG shows a more significant performance improvement because STTG allows the input to contain more complete gait cycles.

3.1.2 Analysis of different insertion positions of DS-Conv in DSFE

We conducted the ablation study by replacing the second Conv layer with DS-Conv in three different Blocks of DSFE, respectively, (Table 4). By comparison, it can be found that adding DS-Conv in Block1 has the best performance, because no pooling operation has been performed at this time, which can avoid the effects of input distortion and information loss, and better fuse contextual information and large receptive field information. Meanwhile, too much use of this module can lead to the loss of fine-grained information, which in turn leads to poorer model performance.

3.1.3 Effectiveness of MTA

In order to validate the effectiveness of MTA, we set up ablation experiments (Table 5). It can be found that BiLSTM will obtain better results compared to LSTM for extracting long and short-term features, because BiLSTM has the characteristic of bidirectional computation, which acquires more comprehensive temporal features. Meanwhile, the use of Attention better fuses the multi-scale features and reduces the risk of overfitting by dropout method.

3.2 Comparison in gait identification task

As shown in Table 6, the accuracy of the proposed method on CASIA-B dataset was compared with several previous gait identification methods, including GaitSet (Chao et al., 2019), GaitPart (Fan et al., 2020), MT3D (Lin et al., 2020), 3D Local (Huang Z. et al., 2021), TransGait (Han and Bhanu, 2006), CSTL (Lin et al., 2020), GLN (Huang Z. et al., 2021), GaitGL (Liang et al., 2022), SMPLGait (Zhu et al., 2021). The results show that DO-GaitPart has excellent gait recognition on the CASIA-B dataset, and is superior to the comparison methods in the BG walking scene. Meanwhile, DO-GaitPart has the best performance on the Gait3D dataset compared to the comparison methods.

3.3 Characterization of participants

We compared the background information of participants between the training/validation and test sets (Table 7). We found no

TABLE 6 Accuracy in comparison with previous gait identification methods on CASIA-B and Gait3D.

Method	CASIA-B			Gait3D			
	NM (%)	BG (%)	CL (%)	R-1 (%)	R-5 (%)	mAP (%)	mINP
GaitSet (Hermans et al., 2017)	95.0	87.2	70.4	42.6	63.1	33.7	19.7
GaitPart (Fan et al., 2020)	96.2	91.5	78.7	29.9	50.6	23.3	13.2
MT3D (Szegedy et al., 2016)	96.7	93.1	81.5	—	—	—	—
3D Local (Chao et al., 2019)	97.5	94.3	83.7	—	—	—	—
TransGait (Han and Bhanu, 2006)	98.1	94.9	85.8	—	—	—	—
CSTL (Lin et al., 2020)	**98.7**	94.8	**88.7**	12.2	21.7	6.44	3.28
GLN (Huang et al., 2021)	96.9	94.0	77.5	42.2	64.5	33.1	19.6
GaitGL (Liang et al., 2022)	97.4	94.5	83.6	23.5	38.5	16.4	9.2
SMPLGait w/o 3D (Zhu et al., 2021)	—	—	—	47.7	67.2	37.6	22.2
DO-GaitPart	98.1	**95.4**	84.6	**49.2**	**68.2**	**39.1**	**24.1**

NM, normal walking; BG, carrying bags; CL, wearing coats or jackets. Bold values mean best performance method, model, module or algorithm in comparison.

TABLE 7 Characterization and cognitive status of participants among 158 older adults.

Characteristic	Prevalence, *n* (%)	Within cognitive status, *n* (%)		Within analysis set, n (%)	
		Healthy	MCI or Worse	Training and validation	Test
All participants	158 (100.0)	66 (41.1)	92 (58.3)	110 (69.6)	48 (30.4)
Age, years (Mean ± SD)	65.4 ± 8.2	64.5 ± 1.0	66.0 ± 0.9	65.5 ± 0.8	65.3 ± 1.2
Gender					
Male	30 (19.0)	18 (27.3)	12 (13.0)	20 (18.2)	10 (20.8)
Female	128 (81.0)	48 (72.7)	80 (87.0)	90 (81.8)	38 (79.2)
Cognitive status					
Healthy	66 (41.8)	—	—	46 (41.8)	20 (41.7)
MCI or Worse	92 (58.2)	—	—	64 (58.2)	28 (58.3)
Education level					
Primary or illiterate	130 (82.3)	39 (59.1)	91 (98.9)	91 (82.7)	39 (81.3)
Junior high	22 (13.9)	21 (31.8)	1 (1.1)	14 (12.7)	8 (16.7)
Senior high or higher	6 (3.8)	6 (9.1)	0 (0.0)	5 (4.5)	1 (2.1)
Marital status					
Married	130 (82.3)	55 (83.3)	75 (81.5)	91 (82.7)	39 (81.3)
Others	28 (17.7)	11 (16.7)	17 (18.5)	19 (17.3)	9 (18.8)
Body and cognitive measurement (mean ± SD)					
BMI, kg/m^2	25.5 ± 3.7	25.2 ± 0.4	25.8 ± 0.4	25.6 ± 0.4	25.5 ± 0.5
Time of 4 m walking, s	7.2 ± 2.0	6.6 ± 0.2	7.7 ± 0.2	7.2 ± 0.2	7.2 ± 0.2
Wrong answers in SPMSQ	2.9 ± 2.0	0.9 ± 0.1	4.3 ± 0.1	2.9 ± 0.2	2.8 ± 0.3

MCI, mild cognitive impairment; BMI, body mass index.

significant differences in age, gender, education level, or cognitive status prevalence between the training/validation and test sets.

3.4 Classification

Table 8 presents a comparison of predictive performance among various methods for cognitive state classification, with a focus on gait features. Machine vision-based classification techniques, specifically DO-GaitPart, GaitSet, and GaitPart, exhibit notably superior performance when compared to approaches considering age, grip strength, and walking time characteristics. The significance levels for all methods, except for age and 3 m re-entry time, are less than 0.001, providing statistical evidence for the potential of these methods in identifying cognitive impairment. Notably, among these gait-based methods, DO-GaitPart achieves the highest ROCAUC value (0.876, Figure 6) with a 95% confidence interval of 0.852–0.900, indicating its robust predictive capability for cognitive impairment. This

TABLE 8 Predictive performance of cognitive state classification via different method.

Method	ROCAUC (0.95 confidence)	Significance	Gink coefficient	Max K-S
GaitSet (Hermans et al., 2017)	0.821 (0.793–0.849)	<0.001	0.642	0.496
GaitPart (Zhu et al., 2021)	0.850 (0.824–0.875)	<0.001	0.699	0.581
TransGait (Han and Bhanu, 2006)	0.864 (0.839–0.890)	<0.001	0.729	0.626
DO-GaitPart	**0.876 (0.852–0.900)**	**<0.001**	**0.752**	**0.656**
Age	0.531 (0.429–0.623)	0.508	0.062	0.113
Grip strength	0.663 (0.576–0.750)	<0.001	0.327	0.269
4 m walking time	0.696 (0.613–0.779)	<0.001	0.392	0.288
3 m re-entry time	0.646 (0.558–0.734)	0.001	0.292	0.261

ROCAUC, receiver operating characteristic/area under the curve. Bold values mean best performance method, model, module or algorithm in comparison.

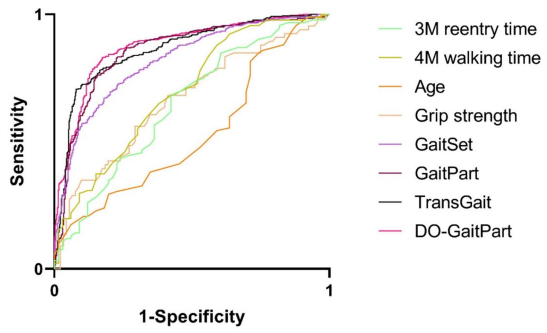

FIGURE 6
Receiver operating characteristic/area under the curve (ROCAUC) of test set via DO-GaitPart, GaitPart, GaitSet, Grip strength, age, 4M walking time, 3M reentry time.

performance stands significantly ahead of other methods, as evidenced by the substantially lower significance values. Moreover, DO-GaitPart operates with remarkable efficiency, consuming a mere 0.013 s per gait sequence, ensuring swift response to gait-related information. Conversely, methods relying on age and grip strength exhibit comparatively lower ROCAUC values, signaling their limited effectiveness in cognitive state classification. In summary, these result underscores the efficacy of machine vision-based gait feature classification methods, particularly highlighting DO-GaitPart, in predicting cognitive impairment.

4 Discussion

In the current study, a machine vision method based on visible light camera footage of walking was implemented to identify mild and worse cognitive impairment among older adults. First, walking video dataset labelled using a cutoff of three errors on the SPMSQ consisting of 158 participants aged 50 and older was created. All images of gait sequences were segmented, normalized, and refined. Skeleton point information was extracted from sequences by HRNet application. Gait skeleton points and silhouette information were used in a trained recognition network, DO-GaitPart. To decrease computational cost and minimize the loss of time information, STTG was applied in the template generation stage. DSFE was used to extract more spatial features and keep the relation between features. Attention mechanism-based MTA extracted more multi-scale temporal features, including frame-level and long short-term temporal features, and aggregated more characteristic features.

After training, machine vision methods achieved better predictive performance globally than age, grip strength, or 4 m walking time in the healthy and cognitive impairment classification task. Although silhouettes contain information regarding variation in walking appearance and movement, long clothing and carrying a backpack could mislead the feature extrication process in silhouette-only methods. Here, both skeleton points and silhouette information were used to generate gait features, as skeleton points characterize human joint movement and decrease the impact of clothing and carried objects. The data input into the analysis model should contain a full gait cycle, which has a large computational cost. Compared with the previous sampling method, random sampling, STTG greatly increases the information entropy that the input sequence contains and maintains the same computational cost. GaitPart developed FConv to extract part features, but it ignored the connection between part features. With the applied depth-wise dilation convolution and depth-wise dilation convolution, DSFE comprehensively extracted contextual information and long-range features. GaitPart considered long-range features to have little effect, and provided a micro-motion capture module to extract short-range features. In our experiments, long-range features also have unique advantages in gait recognition, compared with short-range features. Therefore, we design an MTA module to aggregate multi-scale temporal features, including frame-level features, short-term features, and long-term features. Although DO-GaitPart exhibited good performance in cognitive identification task, long clothing that covered the participant's body could decrease the precision of skeleton point identification and segmentation, thus influencing the performance of the overall method. Like most nonlinear regression algorithms, part of the analysis process in the current study was not interpretable, understandable, and straightforward (Liang et al., 2022).

Research on cognitive MCI and Alzheimer's disease increasingly emphasizes the application of machine vision and modal fusion algorithms. Key techniques, including prior-guided adversarial learning, brain structure–function fusion, and multimodal representation learning, are being actively explored to improve diagnostic precision and enable earlier predictions of cognitive decline

(Zuo et al., 2021, 2023, 2024). As these techniques evolve, they are poised to significantly advance our comprehension and treatment of neurodegenerative conditions. However, its performance in cognitive impairment classification tasks is still limited by the dataset size and the uncertainty of cognitive impairment labels. In future work, expanding the dataset and incorporating additional cognitive function screening scales, such as MMSE and MoCA, will ensure more accurate and stable data labeling. Additionally, the analysis of gait features should be extended to improve the model's ability to recognize different levels of cognitive impairment.

5 Conclusion

This study introduces DO-GaitPart, a machine vision method for identifying cognitive impairment in the elderly from walking videos, featuring three key advancements: STTG, DSFE, and MTA. Addressing the global challenge of managing progressive cognitive decline (Jia et al., 2021), this non-invasive, cost-effective tool optimizes elder healthcare by conserving manpower and broadening its scope (Newey et al., 2015; Reynolds et al., 2022). Utilizing affordable cameras, it enables high-frequency, long-term cognitive assessments, potentially inspiring self-reporting tests and telemedicine for cognitive health (Charalambous et al., 2020; Hernandez et al., 2022). The method's machine learning algorithms also show promise for detecting other geriatric conditions, enhancing the toolkit for geriatric care.

Data availability statement

The datasets presented in this article are not readily available because their containing information that could compromise the privacy of research participants. Requests to access the datasets should be directed to YL, liuyixin@wchscu.cn.

Ethics statement

The studies involving humans were approved by Biomedical Ethics Committee of West China Hospital, Sichuan 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

YQ: Methodology, Writing – original draft, Validation. HZ: Visualization, Writing – original draft. LQ: Writing – review & editing, Supervision. QL: Data curation, Writing – original draft. HJ: Funding acquisition, Writing – review & editing, Data curation. SX: Funding acquisition, Writing – review & editing, Data curation. YL: Conceptualization, Data curation, Funding acquisition, Writing – original draft, Writing – review & editing. XH: Funding acquisition, Supervision, Validation, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by the Science & Technology Department of Sichuan Province (Grant No. 2022YFH0014); Chengdu Municipal Science and Technology Program (Grant No. 2019-YF09-00120-SN); the National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University (Grant No. Z2023LC004); and the Scientific Research of Sichuan Medical Association (Grant No. S22016).

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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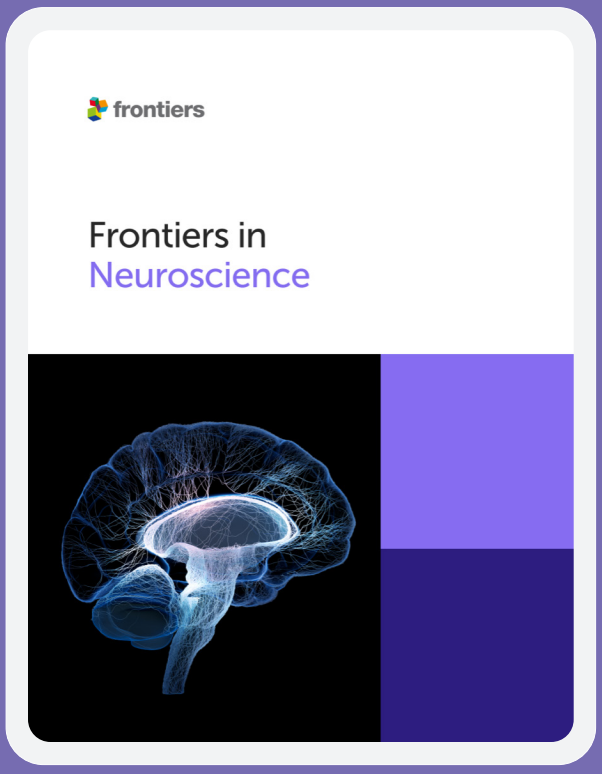

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