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Lifestyle and environmental influences on Alzheimer's disease: exploring the roles of diet, exercise, cognitive reserve, sleep, and air quality

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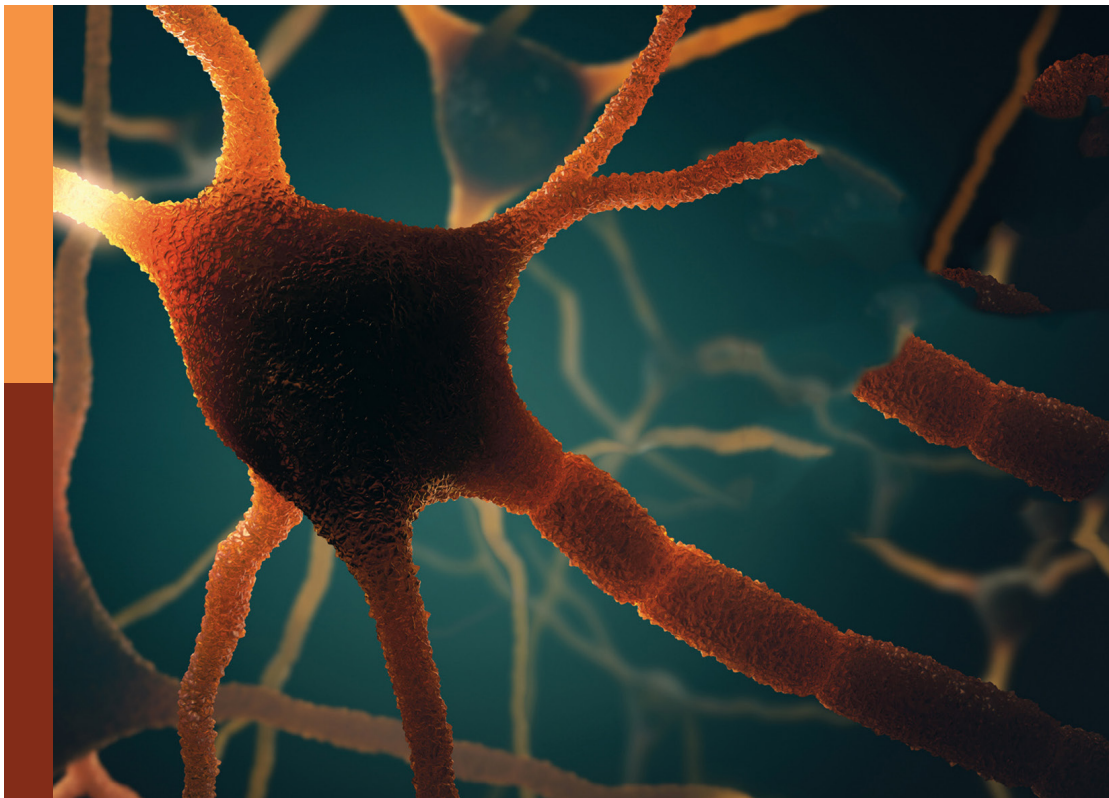

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Lifestyle and environmental influences on Alzheimer's disease: exploring the roles of diet, exercise, cognitive reserve, sleep, and air quality

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Table of contents

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Editorial: Lifestyle and environmental influences on Alzheimer's disease: exploring the roles of diet, exercise, cognitive reserve, sleep, and air quality

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Editorial on the Research Topic
Lifestyle and environmental influences on Alzheimer's disease: exploring the roles of diet, exercise, cognitive reserve, sleep, and air quality

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by a gradual onset and a protracted course, and it is the leading cause of dementia. The primary pathological features of AD include the accumulation of β-amyloid plaques and the hyperphosphorylation of Tau protein. In patients with AD, the accumulation of β-amyloid initially occurs in the preolfactory cortex. This deposition progressively extends to the entorhinal cortex and finally encompasses the associated cortical regions of the frontal, parietal, and temporal lobes. Further, the hyperphosphorylation of Tau protein significantly impairs the structural integrity of neurons. This leads to degeneration and subsequent loss of a large number of neurons, resulting in brain atrophy within the hippocampus and cortex, which gradually deteriorates as the disease progresses and the aging process. Currently, AD has become the most rapidly increasing neurodegenerative disorder in the world, imposing a huge burden on both families and society.

So far, the available treatment modalities for AD are still constrained. Previous research has demonstrated that conventional pharmacological agents, including cholinesterase inhibitors and NMDA receptor channel antagonists, can enhance the clinical manifestations of AD and mitigate its progression (Rijpma et al., 2014; Johnson and Kotermanski, 2006). Nevertheless, these therapeutic interventions cannot provide a cure for AD, exhibit minimal effect on the underlying pathological function of the

disease, and thus present challenges in managing the long-term progression of AD (Zhang et al., 2025). Furthermore, although the FDA has recently approved monoclonal antibodies aimed at β-amyloid for the treatment of early symptomatic AD, the current experience with anti-β-amyloid disease-modifying therapies (DMTs) is still limited. Consequently, further research is essential to evaluate both the clinical efficacy and the economic implications of these therapies.

Mild cognitive impairment (MCI) associated with AD represents an intermediary phase between cognitive health and the onset of AD (Hoang et al.) This stage serves as a "window period" for early diagnosis and prevention of AD. Neurobiologically, it is marked by reduced blood flow and metabolic activity in the temporoparietal cortex, atrophy of the medial temporal lobes—especially in the nasal cortex—elevated Tau protein levels in cerebrospinal fluid (CSF), diminished phosphorylation and $A\beta_{42}$ levels, as well as the deposition of $A\beta_{42}$ in the brain. Clinical manifestations of MCI include symptoms of depression as well as the utilization of avoidance coping strategies (Anderson, 2019). Delaying the progression of MCI to AD will effectively reduce the incidence of AD and result in substantial savings in medication expenses. This has prompted an examination of the influence of risk factors, such as lifestyle and environmental elements, on the progression of AD, as well as efforts to mitigate the risk of AD through multifaceted intervention strategies. In addition, it has a notable advantage that cannot be ignored compared to other drug therapies, as it is non-toxic and does not cause any negative side effects.

Advanced age has been widely recognized as the most important risk factor for the development of AD. At the same time, the other 12 modifiable factors, including cardiovascular health and poor dietary patterns, have been gradually demonstrated to be associated with an increased risk of AD. The combined rate of these potential risks of AD due to these factors is 40% globally, which is a significant number, suggesting that intervention with these pre-adjusted risk factors is crucial for preventing AD (Scheltens et al., 2021).

Despite this, there are few empirical studies on the use of non-pharmacological interventions for the prevention and treatment of AD worldwide. In this Research Topic, we focused on describing the lifestyle and environmental influences on AD, especially exploring the roles of diet, exercise, cognitive reserve, sleep, and air quality. A total of 19 articles on this topic have been published, primarily summarizing the potential impact of the intervention of lifestyle and environment on the progression of AD. Recent research has illuminated the intricate interplay between lifestyle and environmental factors in modulating AD risk and progression. Diet, particularly adherence to the Mediterranean diet, significantly reduces cardiovascular-related mortality among cognitively impaired individuals, suggesting a potential protective role in AD pathways (Li L. et al.; Wang et al.) Exercise is repeatedly shown to bolster cognitive resilience, with a frequency of $\geq$3 times/week, offering optimal benefits. Notably, combining physical activity with natural neuroprotective compounds, such as platycodin D, has synergistic effects in reducing amyloid burden and inflammation in AD mouse models (Liu et al.).

Cognitive reserve (CR), shaped by education and possibly enhanced by brain clearance systems like the glymphatic pathway, emerges as another critical factor (Zhou et al.) Higher education independently correlates to reduced risk of cognitive impairment, and glymphatic activity appears to mediate CR's benefits on cognition. Tools like nomograms incorporating CR, age, and genetic predispositions also show promise for early identification of MCI (Zhong et al.).

Sleep duration interacts with metabolic health to influence cognitive outcomes, especially in overweight and obese older adults, where a sleep window of 5–6 hours may be neuroprotective (Qiu et al.). Similarly, environmental exposures such as secondhand smoke (SHS) and pollutants like acrolein have been implicated in accelerating cognitive decline, particularly when combined with other vulnerabilities like vitamin D deficiency (Li Y. et al.). Acrolein's role in promoting oxidative stress and amyloid-beta toxicity underscores the impact of air quality on AD pathology (Jallow et al.).

Moreover, rural living and neighborhood disadvantages have been associated with distinct neuroanatomical changes, pointing to broader socioeconomic and environmental contributors to AD risk (Zhuang et al.). Additional insights highlight that metabolic factors such as high BMI and elevated cardiac metabolic index (CMI) are biomarkers of accelerated aging and potential contributors to AD (Sun and Bao.).

Finally, entertainment-based cognitive activity, such as computer use, shows a modest but significant protective association, reinforcing the value of sustained mental engagement (Lu et al.). As dementia continues to impose a significant global burden, this growing body of evidence emphasizes the multifactorial nature of AD and supports comprehensive prevention strategies targeting modifiable lifestyle and environmental factors (Zhong et al.; Sun et al.; Wen et al.).

In summary, based on our topic manuscripts, we propose that clinicians should be aware that AD can be prevented, and the progression of this incurable disease may be delayed through the modification of assorted risk factors, although the causal relationship between these non-pharmacological interventions and the progression of AD still needs to be confirmed in large-scale studies and national reports.

Author contributions

PS: Writing – original draft, Writing – review & editing, Validation, Supervision, Conceptualization. RC: Visualization, Conceptualization, Validation, Writing – review & editing, Writing – original draft. GW: Conceptualization, Writing – review & editing, Writing – original draft, Validation, Supervision. SQ: Writing – review & editing, Investigation, Writing – original draft. HW: Investigation, Visualization, Writing – original draft, Writing – review & editing. YL: Writing – original draft, Writing – review & editing, Investigation. ZW: Investigation, Writing – review & editing, Writing – original draft.

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Physical exercise frequency and cognition: a multicenter cross-sectional cohort study

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Background and aims: Dementia imposes a heavy burden on society and families, therefore, effective drug treatments, exploring and preventing factors associated with dementia, are paramount. To provide reference points for the best frequency of physical exercise (physical exercise), we investigated the association between frequency of PE and cognition in Chinese old adults.

Methods: 16,181 Chinese participants aged 65 years or older were included in this study. Associations between PE and cognition were estimated multivariate logistic and linear regression analyses. Associations were further investigated across dementia subtypes (Alzheimer dementia, vascular dementia, and other types of dementia). Subgroup analyses were performed in different age groups, in populations with and without stroke, and those with and without hypertension.

Results: PE associated with dementia after adjusting for full covariates (OR: 0.5414, 95% CI: 0.4536–0.6491, $p < 0.001$). Exercise performed at ≥3 times/week associated with lower risk of dementia (OR: 0.4794–0.6619, all p value <0.001). PE was associated with improved cognition (β: 12851, $p < 0.001$), and any PE frequency contributed to cognitive improvement (p values for exercise performed ≥1 time/week were <0.001). Similar conclusions were identified when we repeated analyses in different dementia subtypes and age groups. Subgroup analyses suggested that the cognition of individuals without hypertension also benefitted from exercising 1–2 times/week (OR: 0.6168, 95% CI: 0.4379–0.8668, $p = 0.005$).

Conclusion: The best exercise frequency is exercising ≥3 times/week for individuals from different dementia subtypes and age groups. While for those without hypertension, PE at 1–2 times /week is also beneficial.

KEYWORDS

physical exercise frequency, dementia, cognitive impairment, Alzheimer's disease, healthy guidance

Introduction

Dementia leads to a loss of independence thereby affecting families and the economy. In global terms, China has the largest population of individuals with dementia (Jia et al., 2020). In populations aged ≥65 years, the prevalence of all-cause dementia is 9.11%, while this prevalence is higher in rural areas when compared with urban areas (Hu et al., 2022). In 2050, the annual total cost of dementia will be approximately $1.89 trillion (Jia et al., 2020). Currently, no disease-modifying treatments are available for dementia. Therefore, exploring dementia prevention mechanisms and risk reduction approaches is paramount in China (Gao and Jia, 2023). Previous studies have shown that physical exercise (PE) is a potential cognition protective factor for individuals in early dementia stages (Liu et al., 2022), such as subjective cognitive decline (Wen et al., 2021) and mild cognitive impairment (Law et al., 2020). These findings suggest that PE interventions can affect cognition at an earlier stage than previously thought.

Physical inactivity is a modifiable risk factor associated with the reduced age-specific incidence of dementia (Tarassova et al., 2020; Alshagrawi and Abidi, 2023). Data from 7,000 individuals over a 2 years follow-up period showed that PE prevented or delayed cognitive impairment progression (He et al., 2021). PE increases cerebral blood flow (CBF) and nervous system plasticity (Farì and Lunetti, 2021). PE also reduces the neuroinflammation, oxidative stress, and amyloid β-protein (Aβ) deposition (Zhang et al., 2019). However, some studies have also shown inconsistent results; after a 5 years exercise intervention, older individuals showed no significant improvements in cognition (Zotcheva et al., 2022). Meanwhile, the most effective PE modalities for different population subgroups remain limited (Bull et al., 2020). Thus, there is a need for large sample studies to confirm such associations and provide evidence for the best PE intervention modality (Cha, 2022). To address this, we assessed the effects of PE on dementia and provided evidence showing the best PE interventions in China.

Materials and methods

Participants

This study is our second multicenter, cross-sectional epidemiological survey, from April to October 2019, of dementia in elderly Chinese participants aged 65 years or older.

We collected data from 13 provinces, metropolitan areas, and autonomous areas which represented different geographical regions, urbanization levels, and economic development status in China. These areas included: Beijing, Tianjin, Chongqing, Fujian, Guizhou, Heilongjiang, Hubei, Hebei, Henan, Hunan, Liaoning, Shanxi, and Xinjiang. The detailed multistage, stratified cluster-sampling procedure was described in our previous study (Chen et al., 2022). A total of 23,382 individuals were interviewed, while only 21,745 individuals were eligible. All eligible individuals were aged 65 years or older and had lived in the same community or village for at least 1 year preceding the survey date. Among the eligible population, 301 refused to participate; 353 were untraceable; 72 had life-threatening illness; 78 were severe disability; 86 were deceased. Therefore, information from 20,855 individuals were collected. After excluding individuals with incomplete data and hearing or vision deficit, we included 16,181 individuals in our study (Figure 1).

Screening interview

This cross-sectional, door-to-door, questionnaire-based survey was conducted by senior neurologists and medical staff. All interviewers and experts received the same training on collecting information, neuropsychological assessments, and diagnosis, and retrained every 2 months. Participants' findings were recorded from physical and neurological examinations.

During interviews, participants completed a self-designed questionnaire using help from reliable informants (participant's spouse, children, other relatives or close friends, in descending order). Informants provided information if participants were unable to do so. The average interview lasted 30 min. Information collected from questionnaire included demographic factors (age, sex, and education years), lifestyle factors (smoking, drinking, PE status and PE frequency), and comorbidities (hypertension, diabetes, cerebrovascular disease etc). PE was defined as performing physical exercise that lasted 30 min or more and was evaluated with reference to a health survey (Kurtze et al., 2008). Participants were thought to perform PE if they answered "yes" for the question "Do you perform physical exercise that lasted 30 min or more?" PE frequency was collected by asking "How often do you perform physical exercise?" The answer was selected from the following choice:: 0 times/week (never), 1–2 times/week, 3 times/week, 4–5 times/week, and >5 times/week. The answers would be confirmed by reliable informants.

Comorbidities, including stroke, hypertension, diabetes mellitus (DM), and coronary heart disease (CHD) history, were recorded from medical registers, and then confirmed with senior neurologists and medical staff to ensure accuracy. Stroke was defined as having a diagnosed or a known history of hemorrhagic or ischemic stroke. Hypertension was defined as having an average systolic blood pressure ≥ 140 mmHg or an average diastolic blood pressure ≥ 90 mmHg on ≥ three occasions or patients taking antihypertensive drugs. DM was defined as having a fasting serum glucose level ≥ 7 mmol/L, a non-fasting serum glucose level ≥ 11.1 mmol/L, or using hypoglycemic agents. CHD was defined as coronary atherosclerotic heart disease, which meant heart disease caused by coronary artery stenosis or occlusion.

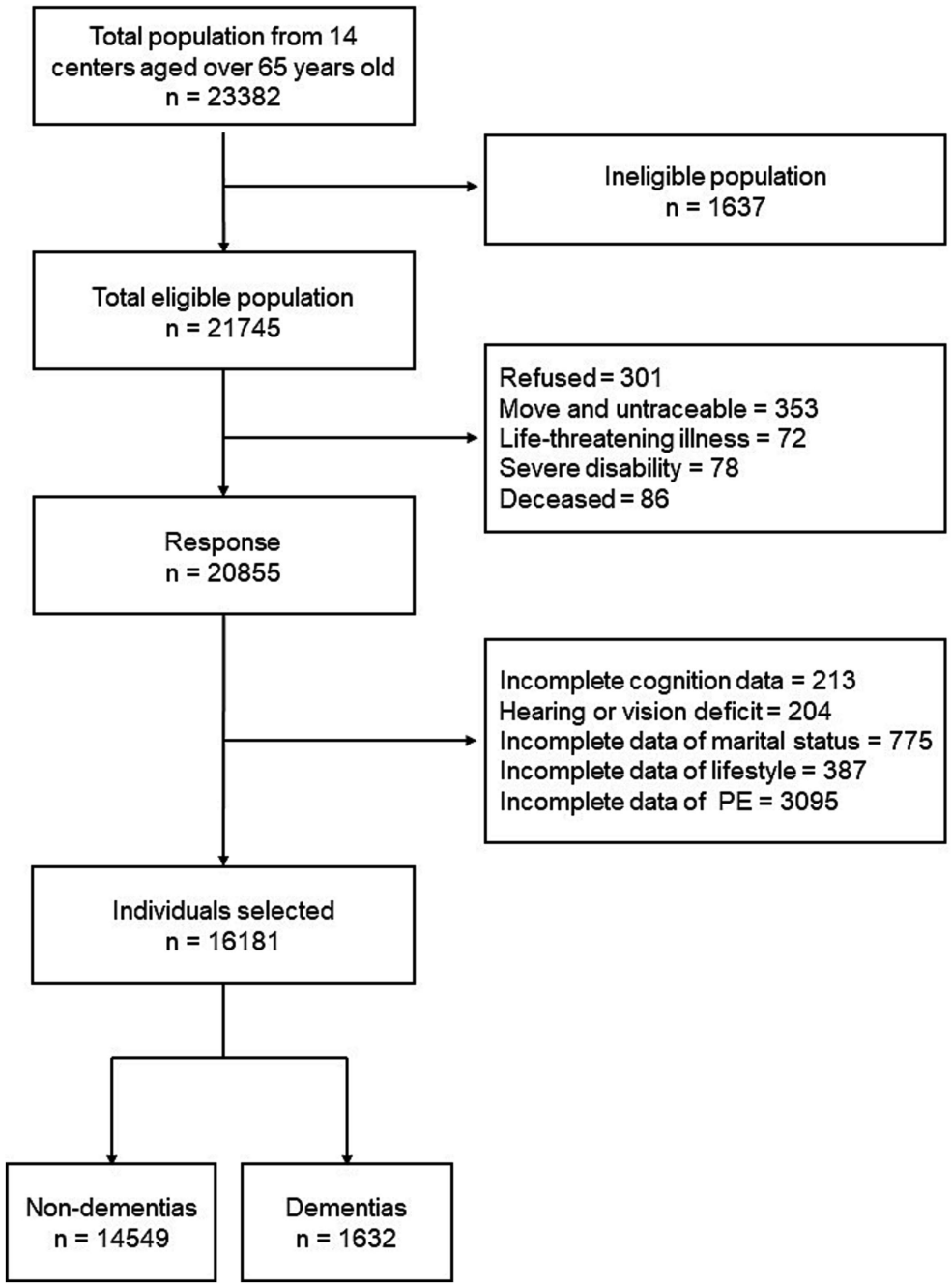

FIGURE 1
Flowchart.

Cognitive evaluation and dementia criteria

The Chinese Mini-Mental State Examination (C-MMSE) (Arevalo-Rodriguez et al., 2015), the Clinical Dementia Rating (CDR) scale (Morris, 1993), and Activities of Daily Living (ADL) scale (Eto et al., 1992; Chen et al., 1995) were administered by qualified and experienced specialists in neurology. Interviewers at each site included four junior neurologists and four neurologists from the local cooperative hospital. An expert panel and interviewers reviewed all the gathered information, and primary diagnoses were made at the end of each workday. If consensus was not reached, an expert returned to the participant's residence the following day to reexamine and reevaluate the participant and provide a final, definitive diagnosis. Data were stored on a secure server accessible by authorized personnel only.

In our survey, a non-dementia status was assigned when participants scored 0 on global CDR and ≥27 on the C-MMSE. When the C-MMSE test score was ≤ the cutoff point (≤17 for illiterate persons, ≤20 for persons with 1–6 years of education, and ≤24 for persons with ≥7 years of education), dementia was defined based on clinical criteria from the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV edition). DSM-IV criteria for dementia required

an impairment in memory and at least one additional cognitive domain; an impairment that resulted in a significant decline from a previous functioning, a gradual onset and progressive course, and not due to any other process. An Alzheimer's disease (AD) diagnosis was based on The National Institute of Neurological and Communicative Disorders-AD and Related Disorders Association criteria (McKhann et al., 2011). We used diagnostic criteria for vascular dementia (VD) as proposed by the Neuroepidemiology Branch of the National Institute of Neurological Disorders and Stroke (Román et al., 1993). Other types of dementia (mixed dementia, frontotemporal dementia, dementia with Lewy bodies, Parkinson's disease, alcoholic dementia, hydrocephalus dementia, and posttraumatic dementia) were defined by globally accepted criteria (McKeith et al., 2017).

Ethical considerations

The study was approved by the ethics committee of Tianjin Huanhu Hospital (ID:2019-40). Written informed consent was obtained from participants or their guardians. The procedures were performed in accordance with the ethical standards of the Committee on Human Experimentation. Study data were anonymous.

Statistical analysis

We used Kolmogorov–Smirnov normality tests and Quantile-Quantile plots to assess data normality. Variables were transformed using the "car" package in R software (Xu et al., 2020) to generate approximate normal distributions (Supplementary Figure S1). Statistical analyses were conducted on transformed values. Differences in categorical variables between two groups were analyzed using Chi-square tests, and numerical variables were analyzed using Wilcoxon tests. Difference comparisons between two groups involved multiple comparisons, which may have generated uncontrolled type I error rates (the rate of rejecting the null hypothesis when it should not be rejected) (Cabral, 2008). We used the false discovery rate (FDR) to adjust for multiple comparisons (threshold $q < 0.05$).

Model building and covariate selection

Statistically significant indicators in univariate analysis (age, sex, education years, and stroke, Supplementary Tables S1, S2) were included in multivariate analysis. Although no significance was identified for hypertension, DM, CHD, smoking, and drinking, they were previously considered risk factors for dementia (Baumgart et al., 2015) and were also included in multivariate analysis and categorized. M2 was adjusted for demographic factors (age, sex, and education years). M3 was additionally adjusted for comorbidities and lifestyle indicators (stroke, hypertension, DM, CHD, smoking, and drinking).

First, associations between PE (status and frequency) and dementia were estimated using a univariate logistic regression model (M1). Then, associations were further confirmed using a multivariate logistic regression model (M2). Finally, indicators were added to the multivariate logistic regression model as covariates to assess the robustness of results (M3).

Considering the fact that PE could affect cognition, we investigated if PE (status and frequency) was associated with C-MMSE scores. Associations between PE and cognition were estimated using linear regression models M1–M3, which adjusted for the same aforementioned factors. We also conducted an association study in different dementia subtypes, in participants with AD, VD, and other dementia types.

Variables in multivariate regression analyses were selected for interaction analyses. Accordingly, we conducted subgroup analyses stratified by age (65–74, or ≥75), hypertension (yes or no), and stroke (yes or no). Variance inflation factors were used to assess multicollinearity, which we found no evidence of in our analyses.

Two-tailed $p < 0.05$ values were considered statistically significant. Analyses were conducted in R software (version 3.6.1).

Results

Participant characteristics

Participant characteristics are shown (Table 1). In total, 16,181 participants (14,549 with non-dementia and 1,632 with dementia) were included. In the population, the average age was 74.35 years (±6.31 years) and the average education duration was 7.07 years (±4.73 years). We used FDR values (q values) to adjust false positive results in multiple comparisons. When compared with non-dementia, participants with dementia were older (73.92 ± 6.03 vs. 78.11 ± 7.389, q value <0.001), less educated (education years 7.21 ± 4.75 vs. 5.89 ± 4.43, q value <0.001), had a larger percentage of females (55.62% vs. 62.81%, q value <0.001), a larger percentage of stroke (13.29% vs. 18.08%, q value <0.001) and worse cognitive performance (C-MMSE score = 26.90 ± 3.17 vs. 15.93 ± 4.93, q value <0.001). Participants with dementia performed less PE and had lower PE frequencies (q value <0.001). No significant differences were identified for hypertension, DM, CHD, smoking, and drinking (q value >0.05).

Associations between physical exercise and dementia

From univariate logistic regression analysis (Figure 2 and Supplementary Table S3), PE was associated with dementia (odds ratio (OR): 0.4212, 95% confidence interval (CI): 0.3569–0.4994, $p < 0.001$) regardless of the frequency (1–2 times/week: OR: 0.7336, 95% CI: 0.5838–0.9212, $p = 0.008$; 3 times/week: OR: 0.5591, 95% CI: 0.4531–0.6906, $p < 0.001$; 4–5 times/week: OR: 0.3727, 95% CI: 0.3118–0.4470, $p < 0.001$; and >5 times/week: OR: 0.3778, 95% CI: 0.3142–0.4556, $p < 0.001$). After adjusting for age, sex, and education duration (years) in M2, PE appeared to protect participants from dementia (OR: 0.5379, 95% CI: 0.4512–0.6441, $p < 0.001$), especially for PE at ≥3 times/week (3 times/week: OR: 0.6497, 95% CI: 0.5217–0.8099, $p < 0.001$; 4–5 times/week: OR: 0.4772, 95% CI: 0.3956–0.5778, $p < 0.001$; and >5 times/week: OR: 0.5044, 95% CI: 0.4150–0.6150, $p < 0.001$). However, performing PE 1–2 times/week did not make any difference (OR: 0.7927, 95% CI: 0.6244–1.0059, $p = 0.056$). In M3 the association between PE and dementia remained significant (OR:

TABLE 1 Characteristic of participants.

Characteristics	Non-dementia (n = 14,549)	Dementia (n = 1,632)	Total (n = 16,181)	p value	q value
Age (years)	73.92 ± 6.03	78.11 ± 7.389	74.35 ± 6.31	<0.001	<0.001
Sex (female)	8,092 (55.62%)	1,025 (62.81%)	9,117 (56.34%)	<0.001	<0.001
Education (years)	7.21 ± 4.75	5.89 ± 4.43	7.07 ± 4.73	<0.001	<0.001
C-MMSE score	26.90 ± 3.17	15.93 ± 4.93	25.79 ± 4.74	<0.001	<0.001
Hypertension (yes)	7,263 (49.92%)	816 (50.00%)	8,079 (49.93%)	0.973	0.990
DM (yes)	2,184 (15.01%)	239 (14.64%)	2,423 (14.97%)	0.721	0.865
CHD (yes)	2,129 (14.63%)	250 (15.32%)	2,379 (14.70%)	0.481	0.642
Stroke (yes)	1,933 (13.29%)	295 (18.08%)	2,228 (13.77%)	<0.001	<0.001
Smoking (yes)	3,781 (25.99%)	451 (27.63%)	4,232 (26.15%)	0.160	0.240
Drinking (yes)	3,354 (23.05%)	377 (23.10%)	3,731 (23.06%)	0.990	0.990
Physical exercise (yes)	13,784 (94.74%)	1,442 (88.36%)	15,226 (94.10%)	<0.001	<0.001
Frequency of physical exercise				<0.001	<0.001
Never	765 (5.26%)	190 (11.64%)	955 (5.90%)		
1–2 times/week	933 (6.41%)	170 (10.42%)	1,103 (6.82%)		
3 times/week	1,649 (11.33%)	229 (14.03%)	1,878(11.61%)		
4–5 times/week	6,342 (43.59%)	587 (35.97%)	6,929(42.82%)		
>5 times/week	4,860 (33.40%)	456 (27.94%)	5,316(32.85%)		

Continuous variables were represented as mean ± SD. Categorical variables were represented as numbers (proportion). Differences in categorical variables between two groups were analyzed using Chi-square tests, and numerical variables were analyzed using Wilcoxon tests. q value: significance after false discovery rate (FDR) correction. C-MMSE, Chinese Mini-Mental State Examination; DM, diabetes mellitus; CHD, coronary heart disease.

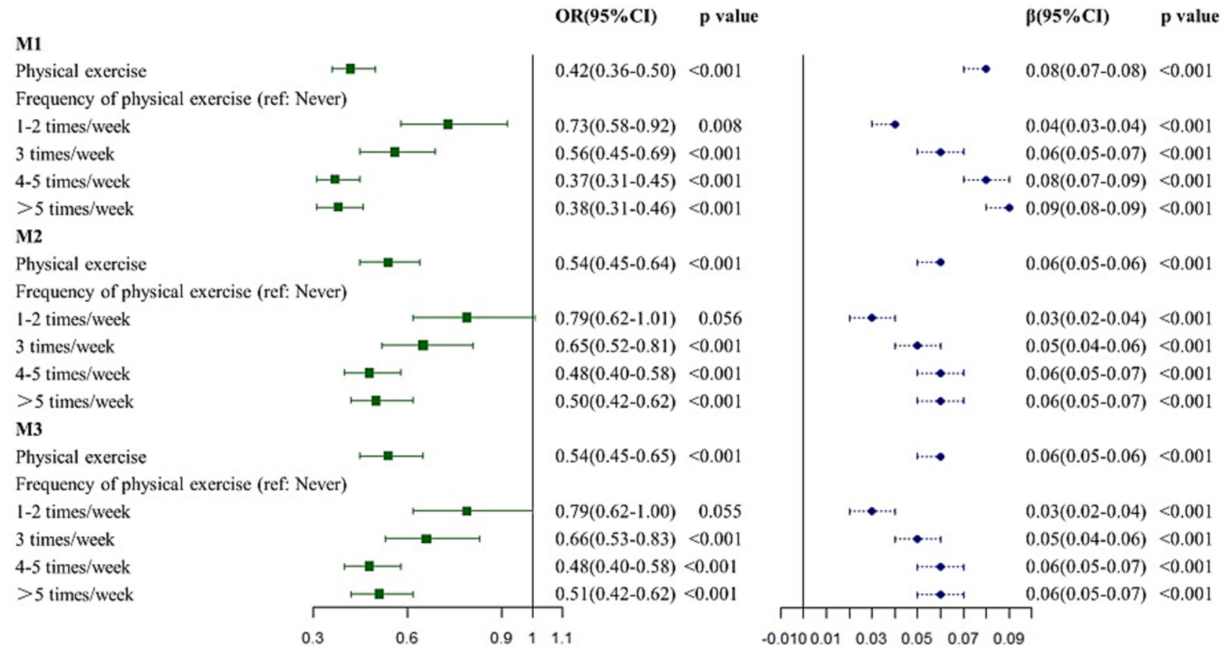

FIGURE 2
Association between physical exercise and dementia. M1: the univariate regression analysis. M2: the multivariate analysis adjusted for age, sex, and education years. M3: the multivariate analysis adjusted for age, sex and education years, hypertension, DM, CHD, stroke, smoking and drinking.

0.5414, 95% CI: 0.4536–0.6491, $p < 0.001$). When compared with inactivity, performing PE ≥ 3 times/week was a protective factor for dementia (3 times/week: OR: 0.6619, 95% CI: 0.5310–0.8259, $p < 0.001$; 4–5 times/week: OR: 0.4794, 95% CI: 0.3969–0.5811, $p < 0.001$; and >5 times/week: OR: 0.5053, 95% CI: 0.4152–0.6170, $p < 0.001$).

Association between physical exercise and cognition

PE was positively associated with cognition in unadjusted model (β: 26944, $p < 0.001$, Figure 1 and Supplementary Table S4). The association remained significant after adjusting for age, sex, and education years (M2, β: 13013, $p < 0.001$) and full covariate adjustment (M3, β: 12851, $p < 0.001$). In terms of PE frequency, performing PE ≥ 1 time/week had a positive effect on cognition in univariate linear regression analysis M1 (1–2 times/week: β: 9259, $p < 0.001$; 3 times/week: β: 18463, $p < 0.001$; 4–5 times/week: β: 26858, $p < 0.001$; and >5 times/week: β: 33721, $p < 0.001$). Consistent with M1, performing PE ≥ 1 time/week was positively associated with cognition in M2 (1–2 times/week: β: 6675, $p < 0.001$; 3 times/week: β: 12823, $p < 0.001$; 4–5 times/week: β: 13395, $p < 0.001$; and >5 times/week: β: 14222, $p < 0.001$), and M3 (1–2 times/week: β: 6788, $p < 0.001$; 3 times/week: β: 12648, $p < 0.001$; 4–5 times/week: β: 13221, $p < 0.001$; and >5 times/week: β: 14036, $p < 0.001$).

Association between physical exercise and dementia subtype

The results for different dementia subtypes were largely similar to the above analyses (Figure 3 and Supplementary Table S5). PE (M3: OR: 0.5708, 95% CI: 0.4578–0.7178, $p < 0.001$) and performing PE ≥ 3 times/week (M3: 3 times/week: OR: 0.6741, 95% CI: 0.5115–0.8906, $p = 0.005$; 4–5 times/week: OR: 0.5055, 95% CI: 0.3996–0.6439, $p < 0.001$; and >5 times/week: OR: 0.5450, 95% CI: 0.4276–0.6992, $p < 0.001$) was associated with AD, while no association was observed between AD and performing PE 1–2 times/week ($p = 0.259$). When compared with inactivity, PE (M3: β: 10406, $p < 0.001$) and performing PE ≥ 1 time/week (M3: 1–2 times/week: β: 5219, $p = 0.013$; 3 times/week: β: 11134, $p < 0.001$; 4–5 times/week: β: 10464, $p < 0.001$; and >5 times/week: β: 11325, $p < 0.001$) improved cognition in AD participants.

VD was associated with PE (M3: OR: 0.3864, 95% CI: 0.2536–0.6052, $p < 0.001$). Performing PE ≥ 3 times/week indicated the most beneficial frequency for VD (M3: 3 times/week: OR: 0.5216, 95% CI: 0.3044–0.8981, $p = 0.018$; 4–5 times/week: OR: 0.3328, 95% CI: 0.2101–0.5383, $p < 0.001$; and >5 times/week: OR: 0.3239, 95% CI: 0.1994–0.5346, $p < 0.001$). Cognitive improvement in VD participants was associated with PE (M3: β: 8806, $p < 0.001$) and performing PE ≥ 1 time/week (M3: 1–2 times/week: β: 5907, $p = 0.003$; 3 times/week: β: 9987, $p < 0.001$; 4–5 times/week: β: 8334, $p < 0.001$; and >5 times/week: β: 9694, $p < 0.001$).

PE (M3: OR: 0.4749, 95% CI: 0.2536–0.5295, $p < 0.001$) and performing PE ≥ 3 times/week (M3: 3 times/week: OR: 0.6148, 95% CI: 0.4004–0.9462, $p = 0.026$; 4–5 times/week: OR: 0.4361, 95% CI: 0.3029–0.6369, $p < 0.001$; and >5 times/week: OR: 0.4033, 95% CI: 0.2707–0.6057, $p < 0.001$) appeared to associated with lower risk of other dementia types. Consistent with aforementioned analyses, PE (M3: β: 9043, $p = 0.001$) and performing PE ≥ 1 time/week (M3: 1–2 times/week: β: 6407, $p < 0.001$; 3 times/week: β: 10458, $p < 0.001$; 4–5 times/week: β: 8525, $p < 0.001$; and >5 times/week: β: 9839, $p < 0.001$, Supplementary Table S6) had positive effects on cognitive improvement in individuals with other dementia types. No multicollinearity was identified in our analyses (Supplementary Table S7).

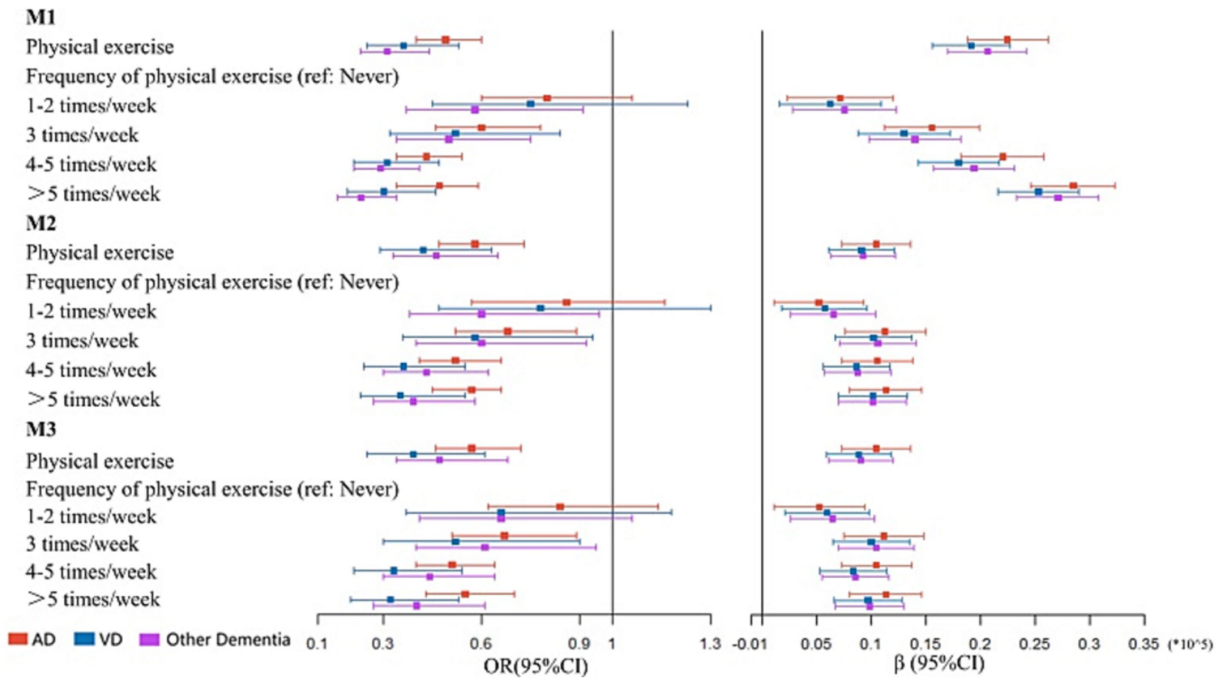

FIGURE 3
Association between physical exercise and dementia subtype. M1: the univariate regression analysis. M2: the multivariate analysis adjusted for age, sex, and education years. M3: the multivariate analysis adjusted for age, sex and education years, hypertension, DM, CHD, stroke, smoking and drinking.

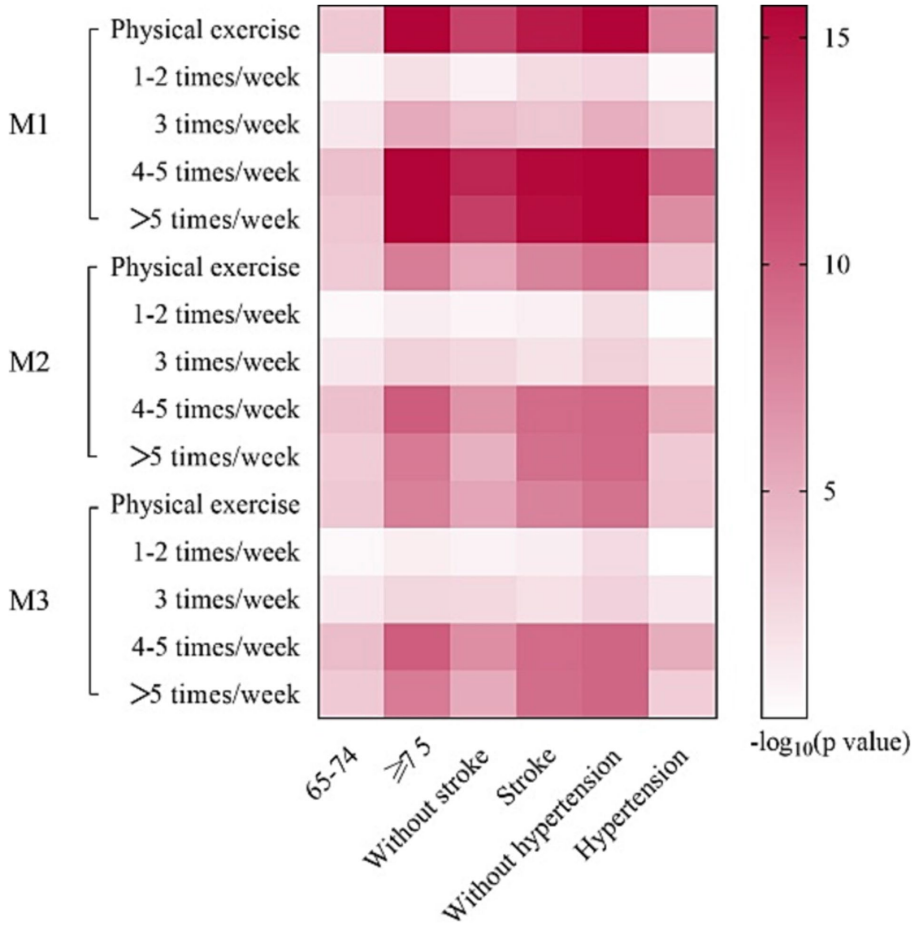

FIGURE 4
Logistic regression analyses of subgroup. M1: the univariate logistic regression analysis. M2: the multivariate logistic regression analysis adjusted for age, sex and education years. M3: the multivariate logistic regression analysis adjusted for age, sex and education years, hypertension, DM, CHD, stroke, smoking and drinking.

Subgroup analyses

Interaction analyses demonstrated that associations between PE frequency and dementia were possibly affected by age, hypertension status, and stroke status (Supplementary Table S8). Therefore, subgroup analyses were conducted at different ages (65–74, and ≥75 years, Supplementary Table S9), stroke status (yes and no, Supplementary Table S10) and hypertension status (yes and no, Supplementary Table S11).

Subgroup analysis results were largely consistent with aforementioned analyses (Figure 4). However, some inconsistencies were identified. Participants without hypertension appeared to benefit from performing PE 1–2 times/week (M1: OR: 0.6094, 95% CI: 0.4404–0.8409, $p = 0.003$). This association remained significant in M2 (OR: 0.6255, 95% CI: 0.4446–0.8782, $p = 0.007$) and M3 (OR: 0.6168, 95% CI: 0.4379–0.8668, $p = 0.005$).

Discussion

In a large sample cohort from China, we assessed associations between PE frequency and dementia. PE exerted positive effects on cognition in our cohort. When compared with inactivity and having a lower PE frequency (1–2 times/week), performing PE ≥ 3 times/week was better for improving cognition. Further findings, based on stratified analyses by age, hypertension, and stroke status, consistently and significantly showed the protective role of PE and performing PE ≥ 3 times/week. Of note, participants without hypertension might benefit from performing PE 1–2 times/week. Our findings strengthen the evidence showing the protective effects of PE frequency on dementia, and provide insights on PE for dementia prevention.

In our study, PE was a protective factor for dementia, regardless of age and comorbidity. These observations were consistent with previous studies; in a 10 years follow-up study, PE was inversely associated with cognitive impairment onset (Jedrziewski et al., 2010). Similarly, a systematic review involving 5,606 individuals from 73 articles concluded that all types of PE protected individuals from decreased global cognition (Huang et al., 2022). However, recent studies have also reported inconsistent results. A multicenter trial randomized 494 individuals, followed them for 4 months, and showed that moderate to high-intensity PE did not slow cognitive impairment in individuals with mild to moderate dementia (Lamb et al., 2018). A recent systematic review reported that neither a combination of strength and aerobic exercise, nor aerobic exercise alone, exerted

beneficial effects toward cognition and dementia (Steichele et al., 2022). PE exposure and sample size heterogeneity could account for some of these inconsistencies. Other covariates potentially affecting cognition, such as lifestyle factors and comorbidity, may also contribute to this heterogeneity.

Different PE levels can generate different effects, but few studies have quantified PE interventions for dementia (López-Ortiz et al., 2021; Liu et al., 2022). Previous studies also confirmed a dose–response relationship between exercise and cognition (Gallardo-Gómez et al., 2022). Higher PE frequency appeared to contribute to better cognitive results, while specific PE thresholds require clarification (Jia et al., 2019). Our analyses indicated that performing PE ≥ 3 times/week was associated with dementia. Of note, performing PE 1–2 times/week was a protective factor for dementia in individuals without hypertension. This finding supported a previous study showing that low-frequency PE exerted positive effects on cognitive function in individuals with chronic diseases (Cai et al., 2017).

Although recommendations for PE levels and types for particular groups have been reported, the evidence for the best PE modality for individuals with different cognitive states remains uncertain (Ding et al., 2020; Steichele et al., 2022). In our study, we analyzed different dementia types, including AD, VD, and other dementias. Consistent with previous studies, we confirmed that PE was a protective factor against AD and benefited cognition (Norton et al., 2014). Regular PE protects non-dementia individuals from AD pathological changes in cerebrospinal fluid (CSF) (Zhong et al., 2022). Also, PE was associated with VD in our study. This finding supports previous studies showing that PE exerted beneficial effects toward VD and putatively prevented VD development (Aarsland et al., 2010). This association may relate to the fact that PE increases oligodendrocyte precursor cell populations in the sub ventricular zone of the brain (Ohtomo et al., 2020).

Animal model and human studies have explored underlying mechanisms at multiple levels (Stillman et al., 2020; Tarassova et al., 2020). Firstly, PE may increase cerebral perfusion by increasing cerebral blood flow (CBF) (Huang et al., 2022). Such increases during PE could meet the energy demands related to cognition in the brain and improve cognitive function (Buxton, 2021; Yamada et al., 2021). Results of the researches on the association between PE and cognition were inconsistent. Some studies have pointed out that high-intensity exercises were associated with hyperventilation and hypoxia, which constricted blood vessels and reduced CBF (Verges et al., 2012). This observation may explain a decline in cognition after high-intensity PE (Gallardo-Gómez et al., 2022). However, a study has pointed out that cognitive impairment caused by high-intensity exercise was not related to CBF (Komiyama et al., 2020). Our study explored the relationship between PE frequency and cognition in a large sample size. Secondly, PE improved cognition by promoting neuroplasticity and neuroprotection (Soshi et al., 1991; Farì and Lunetti, 2021). These processes were directly mediated by increased brain-derived neurotrophic factor (BDNF) levels induced by PE (Wheeler et al., 2020). BDNF activates multiple intracellular signaling pathways, including phospholipase C-γ1/protein kinase C, Ras-mitogen-activated protein kinases, and phosphoinositide 3-kinase/seronine protein kinase, to regulate cerebral cortex thickness and synaptic density, thus increasing brain plasticity (Wang and Holsinger, 2018). At peripheral levels, PE promoted fibronectin type III domain-containing 5 cleavage into irisin, which may have activated the brain cyclic adenosine phosphate/Protein Kinase A/cAMP-response element binding protein and enhanced BDNF levels (Madhu et al., 2022). PE also stimulated the ketone body D-β-hydroxybutyrate and cathepsin B to activate BDNF expression. Also, serotonin (Pietrelli et al., 2018) and several growth factors, including insulin growth factor-1 and vascular endothelial growth factor, were also induced by PE and exerted synergistic effects with BDNF in terms of neuroplasticity and neuroprotection (Jachim et al., 2020). Finally, neuroinflammation increases with aging and contributes to cognition decline, whereas PE was shown to attenuate this process (Huang et al., 2021). PE appeared to regulate micro-RNA expression (Hu et al., 2015), and significantly decreased pro-inflammatory markers, including interleukin-1β (IL-1β), IL-6, and tumor necrosis factor-α (TNF-α) (Qin et al., 2022). Proinflammatory microglia and astrocytes were suppressed by PE (Nakanishi et al., 2021). Additionally, PE was positively associated with CSF Aβ42 levels (Zhong et al., 2022), which may be mediated by activating lysosomal function (Wang et al., 2022) and promoting microglial Aβ clearance (Liang et al., 2022).

Our subgroup analysis showed that performing PE 1–2 times/week was associated with a lower risk of dementia in patients without hypertension. In participants with hypertension, performing PE ≥3 times/week was beneficial. Chronic hypertension had detrimental effects on cognition via mechanisms underpinning cerebral small vessel disease, reduced white matter integrity, and impaired autoregulation in the brain (Claassen et al., 2021; Triposkiadis and Xanthopoulos, 2023). Thus, hypertension may reduce or negate the benefits of low-frequency PE.

A major advantage of our study is its large sample size which provides considerable data reliability and robustness. Also, cognition-related covariate adjustments highlighted the independence of PE as a protective factor for dementia and cognition. Our dementia subtype analyses could help us understand the effects of PE on different dementia types. However, our study had notable limitations.

As a cross-sectional study, we did not provide causation information similar to other prospective cohorts. Objective measurements for PE, such as pulse oximetry or the calculation of "mets," and some PE-related indicators (types, intensity, or duration) were unavailable. Information about the consistent length of comorbidities was not collected. Additionally, participants were primarily elderly Chinese individuals, thus diversity across ages, races, and regions was not confirmed, and so populations should be expanded to identify more generalizable findings. Finally, our study was limited to dementia population and cognitively normal population. More studies should be performed in individuals at pre-clinical dementia stages so appropriate PE interventions can be implemented for these individuals.

Conclusion

In conclusion, PE was associated with cognitive decline when different adjustments were applied, regardless of dementia subtype. Performing PE ≥ 3 times/week was most effective in preventing dementia, whereas cognition appeared to benefit from any PE frequency. Moreover, the protective effects of PE were consistently observed in subgroups. Our findings underscore the importance of PE as a non-pharmaceutical therapy for delaying cognitive decline and preventing dementia in China.

Data availability statement

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

Ethics statement

The studies involving humans were approved by the ethics committee of Tianjin Huanhu Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

CW: Formal analysis, Investigation, Software, Writing – original draft, Writing – review & editing. J-HG: Formal analysis, Investigation, Writing – review & editing. G-WH: Investigation, Resources, Writing – review & editing. X-DW: Investigation, Writing – review & editing. YLü: Investigation, Validation, Writing – review & editing. J-PN: Investigation, Visualization, Writing – review & editing. X-LM: Investigation, Writing – review & editing. PC: Investigation, Writing – review & editing. YLi: Investigation, Writing – review & editing. B-ZG: Investigation, Writing – review & editing. YY: Investigation, Writing – review & editing. YLv: Investigation, Writing – review & editing. Z-HR: Investigation, Writing – review & editing. SL: Data curation, Investigation, Supervision, Writing – review & editing. YZ: Investigation, Resources, Visualization, Writing – review & editing. YJ: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Validation, Writing – review & editing.

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Conflict of interest

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

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2024.1381692/full#supplementary-material

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Moderating effect of education on glymphatic function and cognitive performance in mild cognitive impairment

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Objective: This research aims to investigate putative mechanisms between glymphatic activity and cognition in mild cognitive impairment (MCI) and analyzes whether the relationship between cognitive reserve (CR) and cognition was mediated by glymphatic activity.

Methods: 54 MCI patients and 31 NCs were enrolled to evaluate the bilateral diffusivity along the perivascular spaces and to acquire an index for diffusivity along the perivascular space (ALPS-index) on diffusion tensor imaging (DTI). The year of education was used as a proxy for CR. The ALPS-index was compared between two groups and correlation analyses among the ALPS-index, cognitive function, and CR were conducted. Mediation analyses were applied to investigate the correlations among CR, glymphatic activity and cognition.

Results: MCI group had a significantly lower right ALPS-index and whole brain ALPS-index, but higher bilateral diffusivity along the y-axis in projection fiber area (Dyproj) than NCs. In MCI group, the left Dyproj was negatively related to cognitive test scores and CR, the whole brain ALPS-index was positively correlated with cognitive test scores and CR. Mediation analysis demonstrated that glymphatic activity partially mediated the correlations between CR and cognitive function.

Conclusion: MCI exhibited decreased glymphatic activity compared to NCs. CR has a protective effect against cognitive decline in MCI, and this effect may be partially mediated by changes in glymphatic activity.

KEYWORDS

cognitive reserve, glymphatic function, cognitive function, mild cognitive impairment, diffusion tensor image

Introduction

The glymphatic system is a highly polarized convective system of cerebrospinal fluid (CSF) and interstitial fluid exchange along the periarterial space (Nedergaard and Goldman, 2020). It is similar to the lymphatic system of the surrounding tissue and plays an important role in protein clearance and reduction of abnormal aggregation, such as

the amyloid-β protein (Aβ) and Tau proteins. As mentioned in the literature review, the impairment of glymphatic system is a part of the pathophysiological mechanisms that mediate and accelerate the progression of neurodegenerative diseases, which is closely correlated to the cognition, executive function and memory in Alzheimer's disease (AD) and AD-related dementia (Bah et al., 2023). In recent years, researchers have gradually used the non-invasive diffusion tensor imaging along the perivascular space (DTI-ALPS) to evaluate the function of glymphatic system (van der Thiel et al., 2023). DTI-ALPS can calculate the difference of diffusion rate of water molecules in different directions of diffusion in brain without contrast enhancement (Taoka et al., 2017). Although the ALPS-index reveals the diffusivity of perivascular spatial orientation in the periventricular white matter (WM), it is considered an indirect measure of the state of glymphatic function (Carlstrom et al., 2022). Studies have shown a positive relation between the ALPS-index and Mini-Mental State Examination (MMSE) scores, suggesting that the completeness of glymphatic function may play a role in cognitive prediction. Several reports involving patients with AD and mild cognitive impairment (MCI) have shown that the ALPS-index was related to Aβ protein in the CSF, fluorodeoxyglucose metabolism and cognitive function (Kamagata et al., 2022; Hsu et al., 2023; Zhang et al., 2023). The results of current studies on DTI-ALPS in MCI are inconsistent, with most studies finding a reduced ALPS-index in MCI compared to normal controls (NCs) (Steward et al., 2021; Liang et al., 2023), but some research have shown that there is no difference on ALPS-index between MCI and NCs after adjusting for education level (Kamagata et al., 2022).

Cognitive reserve (CR) is a proposed concept to elucidate the discrepancy between pathological changes and functional alterations in the brain. It is believed to act as a potential protective factor for preventing AD, enabling some individuals to maintain cognitive abilities and decelerate the progression of dementia (Stern and Barulli, 2019). Studies have demonstrated that individuals with MCI who possess higher CR levels are more likely to revert to normal rather than progress to dementia (Iraniparast et al., 2022) and have a beneficial impact on ameliorating cognitive impairment (Berezuk et al., 2021; Corbo et al., 2023). The level of education is commonly utilized as a proxy for CR in current researches and exhibits a strong correlation to dementia (Livingston et al., 2020). Enhancing educational attainment has been linked to a decreased risk of MCI and a postponement in the onset of clinical symptoms and disease progression (Liu et al., 2013). Neuroimaging researches have indicated that CR is linked to enhanced connectivity within cognitive control networks, particularly between the left frontal cortex and the dorsal attentional network in MCI (Franzmeier et al., 2017a,b). Additionally, it has been demonstrated that CR could modify cortical architecture and WM macromolecular volume, enhance cerebral blood flow, which may alleviate cognitive decline in MCI (Fingerhut et al., 2022; Serra et al., 2022; Brenner et al., 2023; Zhou et al., 2024).

To date, very little attention has been paid to the role of CR on glymphatic activity, and the relationship between glymphatic activity and CR in MCI is unclear. Therefore, in this study, we aimed to investigate glymphatic activity in MCI by the DTI-ALPS method and to explore the association between CR and glymphatic activity.

Materials and methods

Participants

Eighty-five subjects were included from the memory disorder clinic at the Department of Neurology in Lanzhou University Second Hospital and the local community, including 54 individuals with MCI and 31 NCs. The MCI subjects were classified according to the diagnostic criteria (Albert et al., 2011), and the Clinical Dementia Rating Scale (CDR) score was less than 0.5. Subjects met criteria for NCs based on: (1) over 50 years of age; (2) normal physical health; (3) have normal cognition, with a minimum score of 27–30 points on the MMSE; (4) CDR score of 0 point; (5) have no history of memory decline; and (6) right-handed. This research has received approval from the Ethics Committee of Lanzhou University Second Hospital, and all participants have provided written informed consent.

Cognitive and cognitive reserve assessment

We used the Montreal Cognitive Assessment (MoCA) and the MMSE to assess general cognition. Memory recall was assessed using the Auditory Verbal Learning Test (AVLT, Chinese version), while verbal fluency was measured using the verbal fluency test (VFT). The activity of daily living (ADL) and instrumental activity of daily living (IADL) were used to assess subject's ability in daily life. The years of education attained by an individual, as well as any vocational training completed, were used as proxy for CR, and training courses lasting at least 6 months were accounted for as 0.5 points.

MRI imaging

All participants underwent brain scanning using an MRI-3 T machine (Ingenia CX, Philips Healthcare, Netherlands) equipped with a 32-channel head coil. The parameters for T1-weighted images of the whole brain were as followed: TR = 5.9 ms, TE = 3.7 ms, flip angle = 8°, FOV = 256 × 256 mm^2, and voxel size = 1 × 1 × 1 mm. The parameters of the DTI sequence were as follows: TR = 5,000 ms, TE = 102 ms, spatial resolution = 2 × 2 × 2 mm^3, b-value =1,000 s/mm^2 along 120 gradient directions. A high-resolution 3D-T2 weighted image was also conducted to rule out brain disorders such as strokes or tumors with parameters: TR = 3,000 ms, TE = 250 ms, FOV = 256 × 256 mm^2, and voxel size = 1 × 1 × 1 mm. Total intracranial volume was processed from the whole-brain T1-weighted images segmentation using the Computational Anatomy Toolbox 12(CAT-12), a toolbox of Statistical Parametric Mapping version 12 software package (SPM-12, https://www.fil.ion.ucl.ac.uk/spm/software/spm12/). The ALPS-index was calculated from DTI by FMRIB's Software Library (FSL) 6.0.3 software package (Smith et al., 2004) and to estimate the glymphatic activity in each subject in accordance with previous studies (Taoka et al., 2017; Yokota et al., 2019). Diffusivity maps along the x, y-axis in projection fiber area and the diffusivity along the z-axis in association fiber area were performed by the color-coded 1st

eigenvector maps on FSLEyes.[1] At the level of the lateral ventricle body, two 5-mm-diameter spherical regions of interests (ROIs) were placed in the area of the projection fibers and association fibers on Mango software.[2] The ALPS-index is defined by the ratio of mean of the diffusivity along the x-axis in projection fiber area (Dxproj) and diffusivity along the x-axis in association fibers area (Dxassoc) to the mean of diffusivity along the y-axis in projection fiber area (Dyproj) and diffusivity along the z-axis in association fibers area (Dzaccoc) as following formula: ALPS-index = mean (Dxproj, Dxassoc)/mean (Dyproj, Dzassoc). A larger ALPS-index indicates a larger rate of water diffusion along the perivascular space, while a value close to 1 suggests that the effect of water diffusion along the perivascular space is minimized.

Statistical analyses

Group comparisons of clinical and cognitive function, and diffusivities, as well as correlation analysis between differential diffusivity and ALPS-index with CR, were performed using SPSS 22 software. We used the independent sample t-test for normal distribution data, while the Mann–Whitney U test was used for non-normal distribution data. Pearson's correlation and Spearman correlation values were calculated to assess the correlation among the glymphatic activity, CR, and cognitive function. Mediation analysis was conducted using a SPSS plugin called "Process" (version 4.1), with age considered as an exposure variable, education as a predictor, glymphatic activity as a mediator, and cognitive test scores as outcomes. A p-value of less than 0.05 represents a significant difference.

Results

Demographic data and cognitive function

As presented in Table 1, age, sex, ADL, IADL, and geriatric depression scale (GDS) did not differ between MCI and NCs. The MCI group showed lower cognitive performance and total intracranial volume (TIV) than NCs group ($p < 0.001$), and had a significantly lower education level on average than the NCs group.

TABLE 1 Demographic characteristics.

	NCs (n = 31)	MCI (n = 54)	p
Age (y)	61.61 (5.8)	64 (60–68)	0.103
Gender (m/f)	9/22	17/37	0.814
Education (y)	11.32 (2.4)	8.5 (5.75–10.25)	<0.001*
MoCA	26 (26–27)	21 (17.75–23)	<0.001*
MMSE	28 (27–29)	25 (23–26)	<0.001*
AVLT-delay	9 (9–11)	4 (3–5)	<0.001*
VFT	15 (18–20)	13.5 (11.75–15)	<0.001*
ADL	8 (8–8)	8 (8–8)	0.601
IADL	12 (12–12)	12 (12–13)	0.11
GDS	2 (1–6)	1 (1–5.25)	0.481
TIV (cm^3)	1366.26 (113.89)	1353.21 (1279.95–1501.24)	0.024*

Normal distribution data are presented as mean (SD); non-normal distribution data are presented as median (interquartile range); NCs, normal controls; MCI, mild cognitive impairment; MMSE, mini-mental state examination; MoCA, Montreal cognitive assessment; AVLT, auditory verbal learning test; VFT, verbal fluency test; ADL, activity of daily living; IADL, instrumental activity of daily living; GDS, geriatric depression scale; TIV, total intracranial volume, * p<0.05.

Comparison of the diffusivities between two groups

Table 2 showed the comparison of the diffusivities between MCI groups and NCs, adjusting for age, gender and TIV, the MCI group had significantly lower right ALPS-index and whole brain right ALPS-index, but higher bilateral diffusivity along the y-axis in projection fiber area (Dyproj) than the NCs group (Figure 1). There was no significant difference in bilateral Dxassoc, Dzassoc, and Dxproj between the two groups.

TABLE 2 Comparison of the diffusivities between MCI patients and NCs.

Diffusivity	NCs	MCI	p
Left Dxproj	0.29 (0.03)	0.3 (0.27–0.32)	0.055
Left Dyproj	0.26 (0.05)	0.28 (0.05)	0.033*
Left Dxassoc	0.41 (0.04)	0.4 (0.04)	0.677
Left Dzassoc	0.21 (0.05)	0.21 (0.19–0.26)	0.322
Right Dyproj	0.25 (0.04)	0.29 (0.05)	0.002*
Right Dxproj	0.3 (0.27–0.3)	0.29 (0.27–0.33)	0.503
Right Dxassoc	0.39(0.05)	0.39 (0.04)	0.787
Right Dzassoc	0.2 (0.04)	0.21 (0.19–0.24)	0.274
Left ALPS-index	1.49 (0.22)	1.38 (1.29–1.58)	0.097
Right ALPS-index	1.51 (0.2)	1.38 (0.15)	0.001*
ALPS-index	1.5 (0.2)	1.4 (0.16)	0.011*

Normal distribution data are presented as mean (SD); non-normal distribution data are presented as median (interquartile range); NCs, normal controls; MCI, mild cognitive impairment; Dxassoc/Dzassoc, diffusivity along the x-axis/z-axis in association fiber area; Dyproj/Dxproj, diffusivity along the y-axis/x-axis in projection fiber area; diffusivity was presented as apparent diffusion coefficient values ($\times 10^{-3}$ mm^2/s); * p<0.05.

Correlation between the DTI-ALPS and cognition

Adjusting for age, gender, and TIV, the ALPS-index was positively related to general cognition (MoCA, $r = 0.274$, $p = 0.045$; MMSE, $r = 0.293$, $p = 0.031$) (Figure 2A), verbal fluency ($r = 0.273$, $p = 0.046$) and memory ($r = 0.327$, $p = 0.016$) (Figure 2B), but the left Dyproj was negatively related to general cognition (MoCA, $r = -0.362$, $p = 0.007$; MMSE, $r = -0.317$, $p = 0.02$) (Figure 2C), memory ($r = -0.369$, $p = 0.006$) and verbal fluency ($r = -0.344$, $p = 0.011$) (Figure 2D). The results of the correlation analysis indicate a higher ALPS-index is associated with higher cognitive function in MCI, and a higher left Dyproj is associated with lower

1 https://zenodo.org/record/3937147

2 https://rii.uthscsa.edu/mango/mango.html

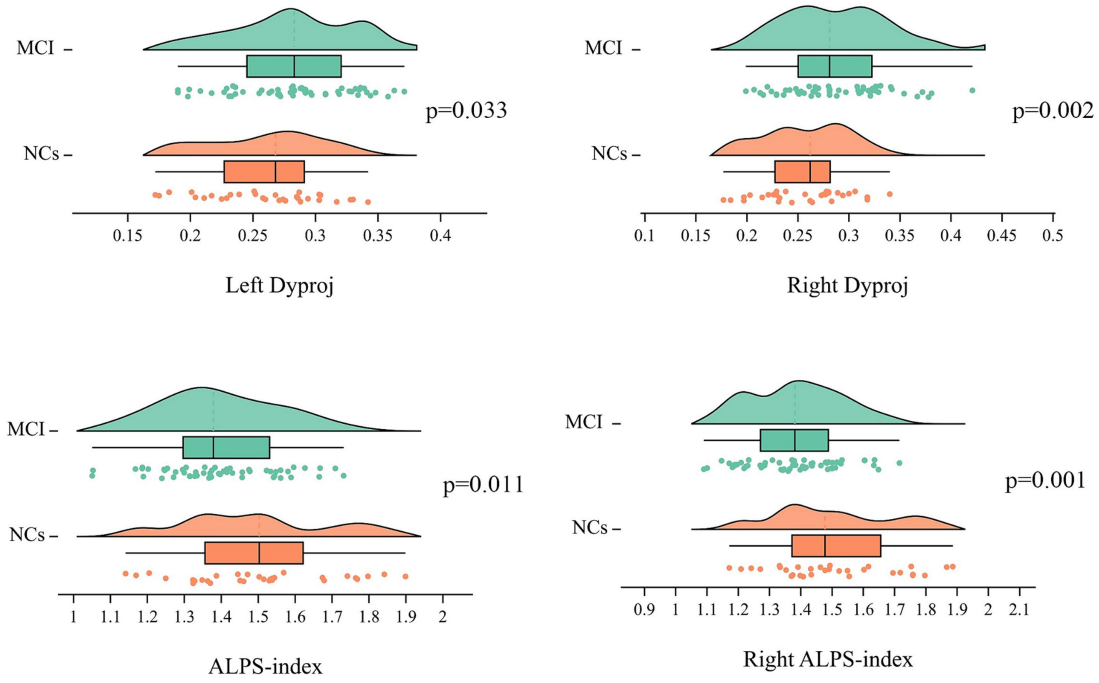

FIGURE 1
Distribution of the ALPS-index and bilateral Dyproj in MCI and HCs group. ALPS, diffusion tensor imaging along the perivascular space; Dyproj, diffusivity along the y-axis in projection fiber area; diffusivity was presented as apparent diffusion coefficient values ($\times 10^{-3}$ mm^2/s). P, *p*-value.

cognitive function. It is proposed that glymphatic function plays a protective role in cognition.

Relationship among glymphatic activity, CR and cognitive function

As shown in Figure 3, a significant positive relationship was found between the ALPS-index and CR ($r = 0.292$, $p = 0.032$), while a negative correlation was found between the left Dyproj and CR ($r = -0.317$, $p = 0.02$) in MCI. These findings indicate that there is an association between CR and glymphatic activity in MCI. To test this possibility, mediation analyses were conducted with cognitive score as the dependent variable, years of education (CR) as the independent variable, and glymphatic activity as the mediation variable. According to mediation analysis, the left Dyproj and ALPS-index partially mediated the effect of the relationship between education and cognitive performance. As described in Figure 4, an increase in ALPS-index was related to an increase in the cognitive score (path b). Moreover, changes in education affected glymphatic activity (path a). The mediation effect was assessed by path $a \times b = c\text{-}c'$ and the mediation effect size was assessed by $a \times b / c$. A positive relationship was found between the education and cognitive function, ALPS-index significantly explained 13.3, 10, and 17.4% of the overall effect of the link between the CR and MMSE, MoCA and AVLT score, respectively. An increased left Dyproj was related to a decreased cognitive score, and left Dyproj significantly explained 10, 12.5, and 17.4% of the overall effect of the link between CR and MMSE, MoCA and AVLT, respectively. The results further confirm the protective effect of CR on cognitive function, and suggest that this effect is partially achieved through the preservation of glymphatic activity.

Discussion

In this study, we assessed the glymphatic activity in MCI and NCs by using DTI-ALPS and explored the relationship among glymphatic activity, CR, and cognitive performance. We found that MCI exhibited decreased glymphatic activity compared to NCs and CR has a protective effect against cognitive decline in MCI, and this effect may be partially mediated by changes in glymphatic activity.

Consistent with previous results (Steward et al., 2021), we found that lower ALPS-index was related to lower cognitive test scores in MCI patients. Recent evidences have suggested that compared with the NCs group, the volume and density of virchow-robin space (VRS) in MCI patients were significantly increased (Niazi et al., 2018) and increased VRS was related to the changes in CSF flow and decline of the waste clearance system (Sepehrband et al., 2021). A possible explanation for this might be that the enlargement of VRS could lead to expansion of impaired glymphatic flow, which reduce the removal of metabolic wastes and increase the concentration of Aβ and Tau protein (Rasmussen et al., 2018). As mentioned in the positron emission tomography (PET) study, ALPS-index was negatively related to the deposition of amyloid protein and microtubule-associated protein tau, and was positively correlated with cognitive scores in several AD-related brain regions (Hsu et al., 2023). Besides, lower ALPS-index was correlated with lower deposition of Aβ42 in CSF and fluorodeoxyglucose-18 uptake, and worse multiple cognitive impairment in MCI (Kamagata et al., 2022).

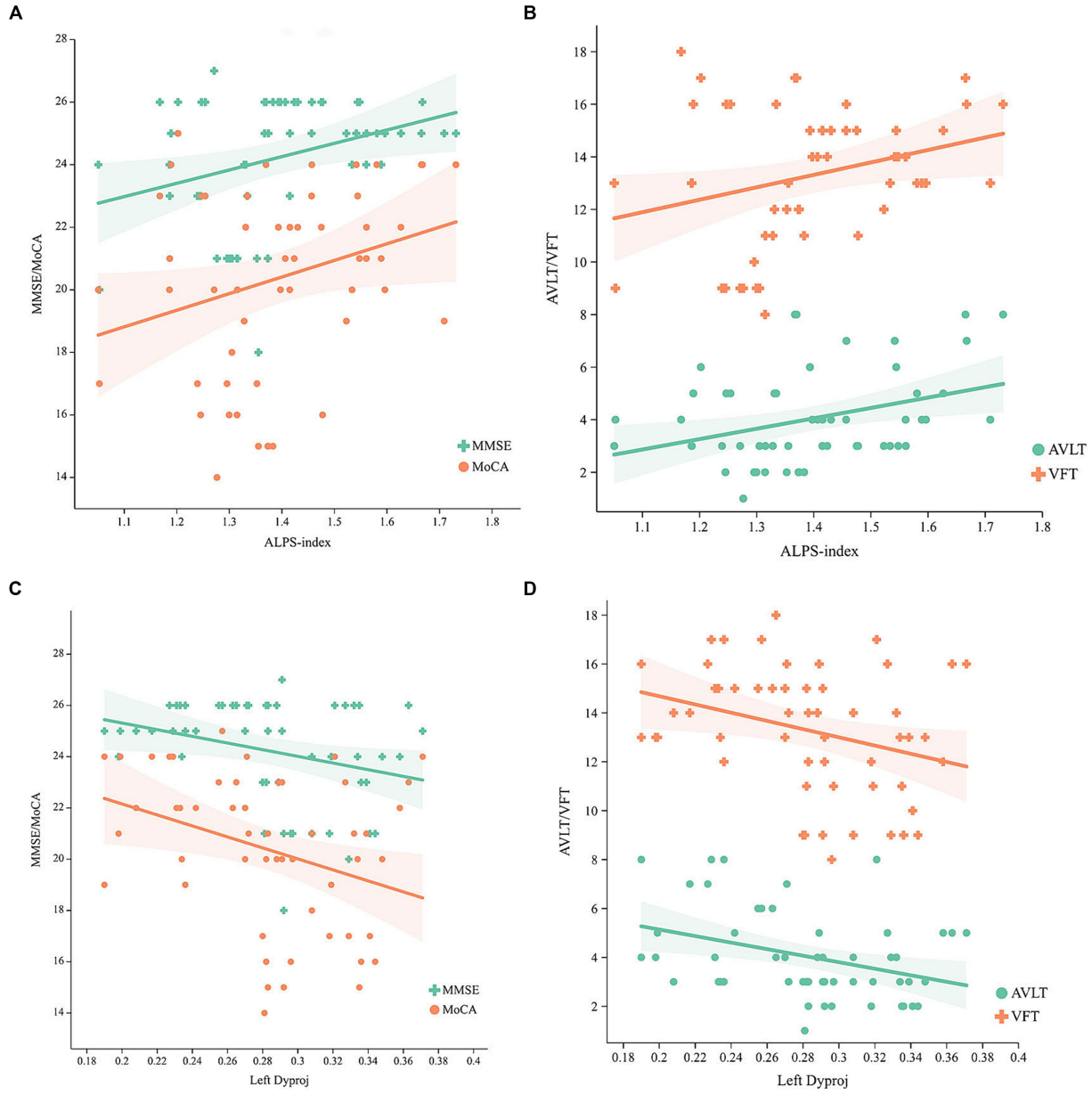

FIGURE 2
Correlation between the ALPS-index, left Dyproj and cognitive function in MCI. **(A)** Correlation between the ALPS-index and MMSE, MoCA scores. **(B)** Correlation between the ALPS-index and AVLT, VFT scores. **(C)** Correlation between the left Dyproj and MMSE, MoCA scores. **(D)** Correlation between the left Dyproj and AVLT, VFT scores. ALPS, diffusion tensor imaging along the perivascular space; Dyproj, diffusivity along the y-axis in projection fiber area; Diffusivity was presented as apparent diffusion coefficient values ($\times 10^{-3}$ mm^2/s); MMSE, mini mental state examinations; MoCA, Montreal cognitive assessment; AVLT, auditory verbal learning test; VFT, verbal fluency test.

We also found that bilateral Dyproj values in MCI group were increased compared to the NCs group, and were negatively correlated with cognitive test scores. This finding was also reported by Taoka et al. (2017) which may be associated with the degeneration of WM in the projection fibers as a result of MCI (Fellgiebel and Yakushev, 2011). A study on DTI mapping also showed increased axial and radial diffusivity of projection fiber in patients with AD, which may be related to a reduced tissue density of the fiber (Huang et al., 2012). Similar results were found in a previous study, they found that Dzassoc and Dyproj were significantly increased in AD patients when compared with the NCs, revealing increased water diffusion perpendicular to association and projection fibers, respectively (Kamagata et al., 2022). The absence of significant changes in Dxxassoc and Dxxproj values reflect that the increase in water diffusion perpendicular to the WM tracts is offset by a decrease in water diffusion along the perivascular spaces (PVS). These findings demonstrated that the degeneration of these fibers in AD and glymphatic activity in MCI stage of pre-AD may be impaired, and the ALPS-index may reflect the glymphatic function which is influenced by the extracellular microenvironment.

As expected, we further found that a significant positive relationship between the ALPS-index and CR, while a negative

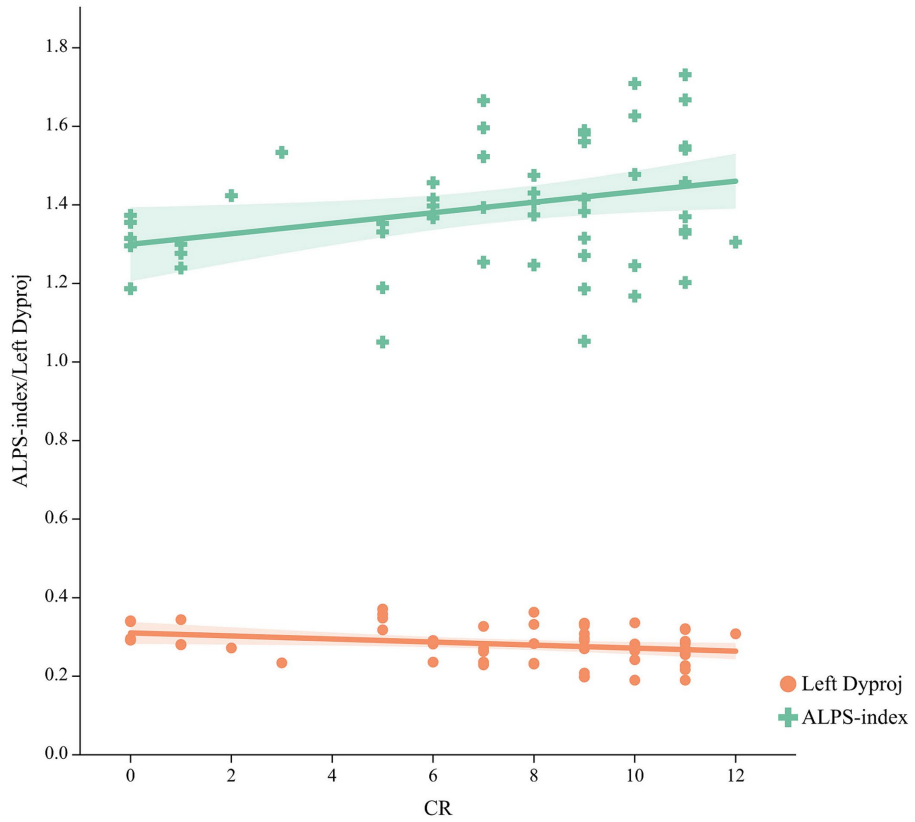

FIGURE 3
Correlation between the CR and ALPS-index, left Dyproj in the MCI group. CR, cognitive reserve; ALPS, diffusion tensor imaging along the perivascular space; Dyproj, diffusivity along the y-axis in projection fiber area; Diffusivity was measured with apparent diffusion coefficient values (× 10^{-3} mm^2/s).

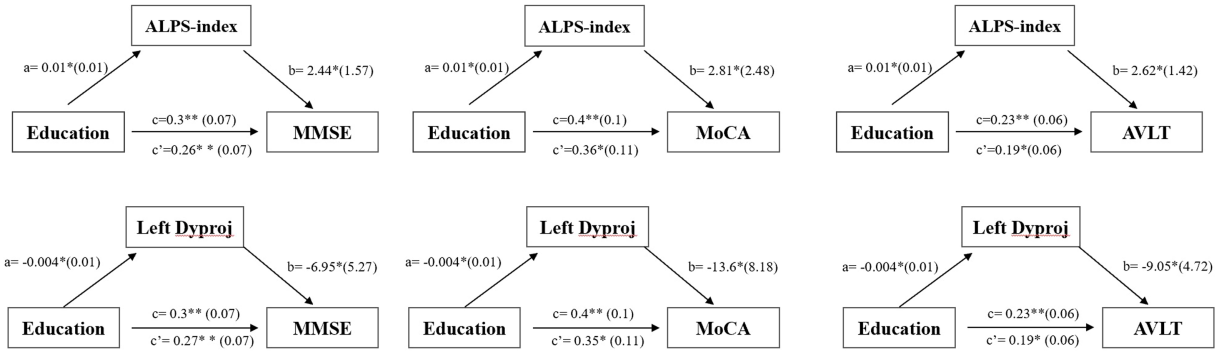

FIGURE 4
Simple mediation results of the effects of left diffusivity along the y-axis in projection fiber area/ALPS-index on the relationship between education and cognitive function in the MCI group; a, b, c, and c' are path coefficients representing unstandardized regression weights and standard errors (in parentheses). The c path coefficient represents the total effect. The c' path coefficient refers to the direct effect. All analyzed a, b, c and c' paths were significant, *$p < 0.05$, **$p < 0.001$. ALPS, diffusion tensor imaging along the perivascular space; Dyproj, diffusivity along the y-axis in projection fiber area; CR, cognitive reserve; MMSE, mini mental state examinations; MoCA, Montreal cognitive assessment.

relationship was observed between the left Dyproj and CR in MCI group, and glymphatic activity mediated the effect of the relationship between CR and cognition. This finding broadly supports that the CR was not directly related to cognition, but rather that its influence on cognitive function was partially mediated by glymphatic activity. It also further confirms that CR can not only modulate brain structure and functional network in MCI, but also has an effect on glymphatic activity. In accordance with the present results, previous studies demonstrated that the higher CR may moderate the negative impact of cerebral small vessel disease on cognitive function (Durrani et al., 2021) and the correlation between cerebral blood flow and category fluency is influenced by CR in MCI (Brenner et al., 2023). Early studies also indicated that the protective role in education against cognitive decline in MCI is mediated at least partially by changes on

cerebral blood flow in right hippocampus (Zhu et al., 2023). This finding was also reported in experiments on young-onset AD to show that the relationship between the ALPS-index and cognitive function was significantly mediated by gray matter reserve (Chang et al., 2023). Similarly, Hisao et al. found that a higher ALPS-index suggested a stronger cortical reserve in areas that align with the default mode network, lower ALPS-index and cortical atrophy in specific regions were related to decreased mental manipulation and short-term memory among older individuals (Hsiao et al., 2023). It is somewhat surprising that we only found MCI groups had significantly lower right ALPS-index, and a negative correlation between the left Dyproj and CR, there is no difference on left ALPS-index between two groups and no correlation between right Dyproj and CR. It seems possible that these results are due to the relatively small sample size may not accurately reflect the correlation. Another possible explanation is that the ROI was manually placed, which could introduce subjectivity into our measurements and account for the observed differences.

These findings may be somewhat limited by the relatively small number of subjects, the relationships between CR, ALPS-index, and cognitive function may be different in more diverse individuals. Another potential limitation is the CR only used education as a proxy, but CR was also associated with other factors such as occupational attainment and cognitive activity. Therefore, future studies should take more CR proxies into account for a more accurate analysis. Finally, the ALPS-index was calculated from the whole brain average, which did not reveal regional glymphatic impairment, further studies evaluating regional glymphatic dysfunction in MCI-related brain regions are needed.

Conclusion

The results of this research support the idea that glymphatic activity in MCI patients was lower than NCs and suggest a role for CR in moderating the associations between glymphatic activity and cognition. Further modeling work will need to be conducted to expand the sample size and assess the regional glymphatic activity using more CR proxies.

Data availability statement

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

Ethics statement

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

Author contributions

LZ: Conceptualization, Formal analysis, Writing – original draft. WY: Data curation, Investigation, Writing – review & editing. YL: Data curation, Investigation, Writing – review & editing. YZ: Investigation, Methodology, Writing – review & editing. XG: Data curation, Formal analysis, Writing – review & editing. KA: Software, Writing – review & editing. GL: Supervision, Writing – review & editing. JZ: Funding acquisition, Supervision, Validation, Writing – review & editing.

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Conflict of interest

KA was employed by Philips Healthcare.

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A comprehensive bibliometric analysis of global research on the role of acrolein in Alzheimer's disease pathogenesis: involvement of amyloid-beta

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Background: Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive and behavioral decline. Acrolein, an environmental pollutant and endogenous compound, is implicated in AD development. This research employs bibliometric analysis to assess current trends and key areas concerning acrolein-AD interaction.

Methods: The Web of Science was used to extensively review literature on acrolein and AD. Relevant data were systematically gathered and analyzed using VOSviewer, CiteSpace, and an online bibliometric tool.

Results: We identified 120 English publications in this specialized field across 19 journals. The Journal of Alzheimer's Disease was the most prominent. The primary contributors, both in terms of scientific output and influence, were the USA, the University of Kentucky, and Ramassamy C, representing countries/regions, institutions, and authors, respectively. In this field, the primary focus was on thoroughly studying acrolein, its roles, and its mechanisms in AD utilizing both *in vivo* and *in vitro* approaches. A significant portion of the research was based on proteomics, revealing complex molecular processes. The main focuses in the field were "oxidative stress," "lipid peroxidation," "amyloid-beta," and "cognitive impairment." Anticipated future research trajectories focus on the involvement of the internalization pathway, covering key areas such as synaptic dysfunction, metabolism, mechanisms, associations, neuroinflammation, inhibitors, tau phosphorylation, acrolein toxicity, brain infarction, antioxidants, chemistry, drug delivery, and dementia. Our analysis also supported our previous hypothesis that acrolein can interact with amyloid-beta to form a protein adduct leading to AD-like pathology and altering natural immune responses.

Conclusion: This study provides a broad and all-encompassing view of the topic, offering valuable insights and guidance to fellow researchers. These emerging directions underscore the continuous exploration of the complexities associated with AD. The analyses and findings aim to enhance our understanding of the intricate relationship between acrolein and AD for future research.

KEYWORDS

Alzheimer's disease, acrolein, oxidative stress, bibliometrics, amyloid-beta, Web of Science

Introduction

Alzheimer's disease (AD) is a complex and progressive neurodegenerative disorder that primarily affects the brain, leading to cognitive decline and behavioral changes. It is the most common cause of dementia, a general term for a decline in cognitive ability severe enough to interfere with daily life (Alzheimer's Association, 2013; Morató et al., 2022). The hallmark features of AD include the accumulation of abnormal proteins aggregates in the brain, namely amyloid plaques and tau tangles. These aggregates interfere with the normal functioning of neurons and disrupt communication between brain cells. This results in the gradual loss of memory, thinking skills, and eventually the ability to carry out basic tasks (Querfurth and LaFerla, 2010; Selkoe and Hardy, 2016). The exact cause of AD is not fully understood, but age, genetic, lifestyle and environmental factors are known to be major risk factors. While there is currently no cure for AD, there are treatments and interventions available that can help manage some of the symptoms and improve the quality of life for both individuals with the disease and their caregivers.

Acrolein is an alpha, beta-unsaturated aldehyde, considered both an environmental pollutant and an endogenous substance. It is highly reactive, volatile, and toxic, characterized by a pungent odor. Exogenously, it can be produced during the incomplete combustion of organic materials, including cigarette smoke, automobile exhaust, and emissions from industrial processes. Additionally, acrolein can be formed during certain cooking processes, such as frying or grilling, especially when oils and fats are heated to high temperatures (Stevens and Maier, 2008; Kassem et al., 2018). Within the body, it can be produced as the end product of lipid peroxidation, threonine degradation, anticancer drug metabolism, and polyamine catabolism (Chang et al., 2022).

Alzheimer's disease is characterized by a complex interplay of pathological factors. Nevertheless, a prevailing hypothesis suggests that the progressive neuronal degeneration observed in AD may be attributed to the accumulation of extracellular amyloid plaques primarily composed of amyloid-ß (Aß). These plaques are believed to originate from the proteolytic cleavage of amyloid precursor protein (APP) mediated by ß- and γ-secretases (Wolfe, 2003; Sanotra et al., 2023). There is evidence suggesting that acrolein plays a significant role in the pathogenesis of various neurodegenerative diseases, including AD (Chang et al., 2022). In AD, acrolein levels are notably elevated in the hippocampus and temporal cortex regions of the brain. This increase in acrolein contributes to AD by elevating oxidative stress, damaging neurons, and affecting various biological pathways. The detrimental effects of acrolein encompass DNA damage, disruption of mitochondrial function, initiation of endoplasmic reticulum stress, protein adduction, promotion of inflammation, impairment of cell membranes, formation of reactive oxygen species (ROS), and tau phosphorylation, thereby influencing the pathophysiology of AD (Dang et al., 2010; Moghe et al., 2015). Notably, a research study has highlighted the development of a straightforward sporadic AD animal model through acrolein administration. This model exhibited classic AD pathologies, including increased levels of amyloid-beta (Aβ) and tau phosphorylation, proliferation of astrocytes and microglia, reduced synaptic proteins, and cognitive impairments (Huang et al., 2013; Chen et al., 2022). The model proved to be useful for studying the mechanisms underlying the onset of AD and the potential development of anti-AD drugs. Moreover, research has investigated the alterations in acrolein metabolism in AD. It is suggested that deregulated acrolein metabolism may be correlated with neuronal damage in AD patients, providing potential insights into the disease progression and early diagnosis of AD (Sexton et al., 2021; Sanotra et al., 2023). Acrolein has been implicated in the development of AD following traumatic brain injury (TBI) or as a secondary factor in TBI-related AD. Recent research has shown that acrolein, acting as a diffusive factor in secondary injury, plays a crucial and self-sufficient role in promoting inflammation (TNF-α) and Aβ42 aggregation, key contributors to AD pathology (Rogers et al., 2023). However, the exact interaction between acrolein and AD remains unclear.

Bibliometric analysis serves as a valuable tool for assessing the influence of publications and research collectives within their respective fields (Ho and Kahn, 2014). Moreover, it offers an effective means of quantifying the caliber of published output for entities such as countries, institutions, and authors (Zhang and Wang, 2012). Presently, the utilization of the Science Citation Index Expanded or Social Science Citation Index has become indispensable in gauging the research achievements of countries, institutions, and authors across multiple dimensions (Jallow et al., 2021). Recent times have witnessed the execution of bibliometric analyses within the Web of Science (WoS) categories, including psychology (Berta et al., 2022), neurosciences (Wilson et al., 2021; Fei et al., 2022), cardiology (Wang et al., 2022), and cancer (Fresno-Alba et al., 2023; Xu et al., 2023). These analyses have played a

Abbreviations: Aβ, amyloid-beta; AD, Alzheimer's disease; APP, amyloid precursor protein; ROS, reactive oxygen species; SCI, Science Citation Index.

crucial role in evaluating research achievements and productivity across countries, institutions, and authors. In a similar vein, this study will center its focus on dissecting research papers concerning the role of acrolein in the genesis of AD.

Keyword search plays a pivotal role in bibliometric analysis for multiple reasons. It enables researchers to focus their investigation on specific topics, thus enhancing the accuracy and relevance of their findings. Keywords serve as gateways to the vast realm of scholarly literature, allowing researchers to efficiently identify and retrieve relevant publications. By using the right keywords, researchers can reduce noise, pinpoint key articles, and gain valuable insights into research trends, impact, and collaborations (Ellegaard and Wallin, 2015). Using precise keywords and targeted databases to investigate the correlation between acrolein and the pathogenesis of AD can provide valuable insights into the condition, enabling the identification of potential protective strategies.

This study covers research papers published up to the current date, which is 31 July 2023. The primary aim is to investigate the impact of acrolein exposure on the pathogenesis of AD. The results of this research have the potential to enhance the understanding of the role of acrolein in the development of AD, thereby promoting the creation of novel therapeutic interventions.

Materials and methods

Data source

The bibliometric information for research reports was obtained from the Science Citation Index (SCI) Expanded database within the Web of Science Core Collection of Clarivate Analytics. This database is a rich collection of citation indexes that represents the connections between scholarly research articles from various fields, including sciences, social sciences, and arts and humanities (Poly et al., 2023).

Search strategy

In this study, we utilized the search keywords "Acrolein*" and "Alzheimer's *" OR "Alzheimer's type dementia *" OR "Senile dementia*" to conduct a topic search across various fields, including title, abstract, author keywords, and KeyWords Plus. The objective of this search was to identify research papers related to the pathogenesis of AD and the role of acrolein in this context. No time limitation was set for the search, thereby encompassing a wide range of relevant literature. To ensure the consistency and reliability of the search results, two different researchers independently performed the search process. This approach aimed to minimize any potential biases or discrepancies in the selection of research papers. The researchers completed the search process on 31 July 2023. After identifying the relevant research papers, they were exported to Excel for further analysis and investigation. A complete representation of literature search and bibliometric analysis process is shown in **Figure 1**.

Our retrieval formula:

$$((((ALL = (Alzheimer's\ disease\ ^*))$$
$$OR\ ALL = (Alzheimer's\ type\ dementia\ ^*))$$
$$OR\ ALL = (Senile\ dementia^*))\ AND\ ALL = (Acrolein^*))$$

Data collection and bibliometric index statistics

In the research process, the relevant data from all the searched documents were exported, and various bibliometric indicators were identified and computed using Microsoft Excel. These indicators encompassed crucial aspects of the publications, including the following: annual number of publications, citation frequency, average citation frequency, journal name, journal impact factor, publication country/region, publication institution, and author. By employing Excel, the researchers were able to efficiently organize and analyze the bibliometric data. This analysis provides valuable insights into research performance, citation patterns, and the impact of scholarly works across various fields of study.

Visualization analysis

In our study, we made use of three powerful bibliometric analytic tools to conduct a comprehensive analysis of scholarly data. These tools were VOSviewer (Version 1.6.16), CiteSpace (version 6.2.R6), and an online bibliometric tool available at https://bibliometric.com/. VOSviewer, which is a versatile software tool, played a key role in mapping institutions' cooperation, authors' cooperation, co-authorship, citation, co-citation, and bibliographic coupling (van Eck and Waltman, 2010). With VOSviewer, we were able to visualize and explore complex networks of collaborations and relationships within the scholarly landscape, gaining valuable insights into the interconnections between authors, institutions, and publications. For a deeper understanding of emerging trends and research hotspots within our field of study, we used VOSviewer for keyword co-occurrence analysis and the CiteSpace software tool for clustering analysis and keyword burst detection. Additionally, to map country/region and institution cooperation, we employed an online bibliometric tool, which offered unique features complementing the analyses conducted with VOSviewer.

Analysis of KeyWords Plus

KeyWords Plus is a specialized application used for citation indexing, which involves extracting relevant terms from the titles of publications cited by authors in the ISI (now Clarivate Analytics) database. The primary goal of KeyWords Plus is to enhance the citation indexing process, improving its accuracy and efficiency, as mentioned by Garfield in his works (Bose and Sarma, 1975; Makar et al., 1975). Analysis of keyword in article title also serve as useful tool for identification of research hotspots and frontiers in a certain filed. In the present study, we utilized the VOSviewer analytic tool to extract keywords from the 120 articles. To identify

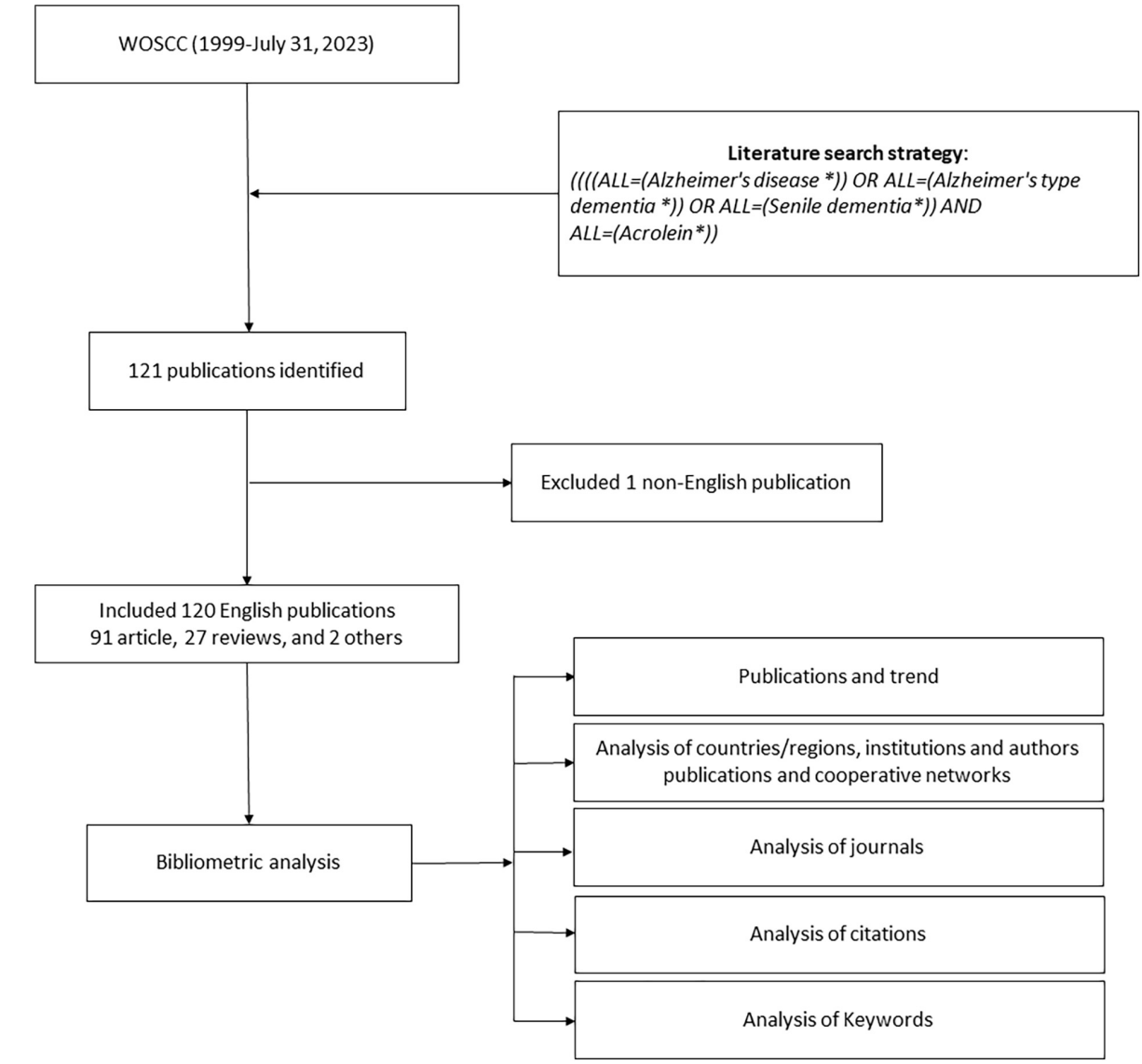

FIGURE 1
Flow chart of literature search and bibliometric analysis.

the most prominent keywords, we strictly adjust selection threshold a minimum of 5 occurrences. This process resulted in the retrieval of the most prominent keywords related to acrolein and AD.

CiteSpace software tool is another powerful tool for clustering research hot spots, identifying changes of the research direction by timeline, and predicting the research frontiers in the field. With the use of CiteSpace software tool, each cluster was ranked based on the elements and assigned a research category associated with its content. The names of the research categories for each cluster were determined according to log-likelihood ratio and mutual information. The clusters were arranged in ascending order of ID number, with smaller ID numbers indicating larger clusters and vice versa. Additionally, the software calculated the silhouette value to assess the homogeneity of each cluster. This metric evaluates how similar a keyword is to its own cluster compared to other clusters. A higher silhouette value indicates greater consistency and confidence in the keywords within the cluster.

Results

Publication output, document type, and language

The study covered research papers published between the years 1999 and July 2023. We found a total of 121 publications related to acrolein and AD in SCI-Expanded of Web of Science. These publications were indexed within six document types in the WoS. Among these document types, the category "Article" accounted for 91 publications, representing 76% of the total publications. Additionally, there were 27 publications categorized as "Review," constituting 23% of the 120 publications and 2 publications for "Others," representing 2% (**Figure 2A**). All the documents were originally written in English except one which is rewritten in Chinese.

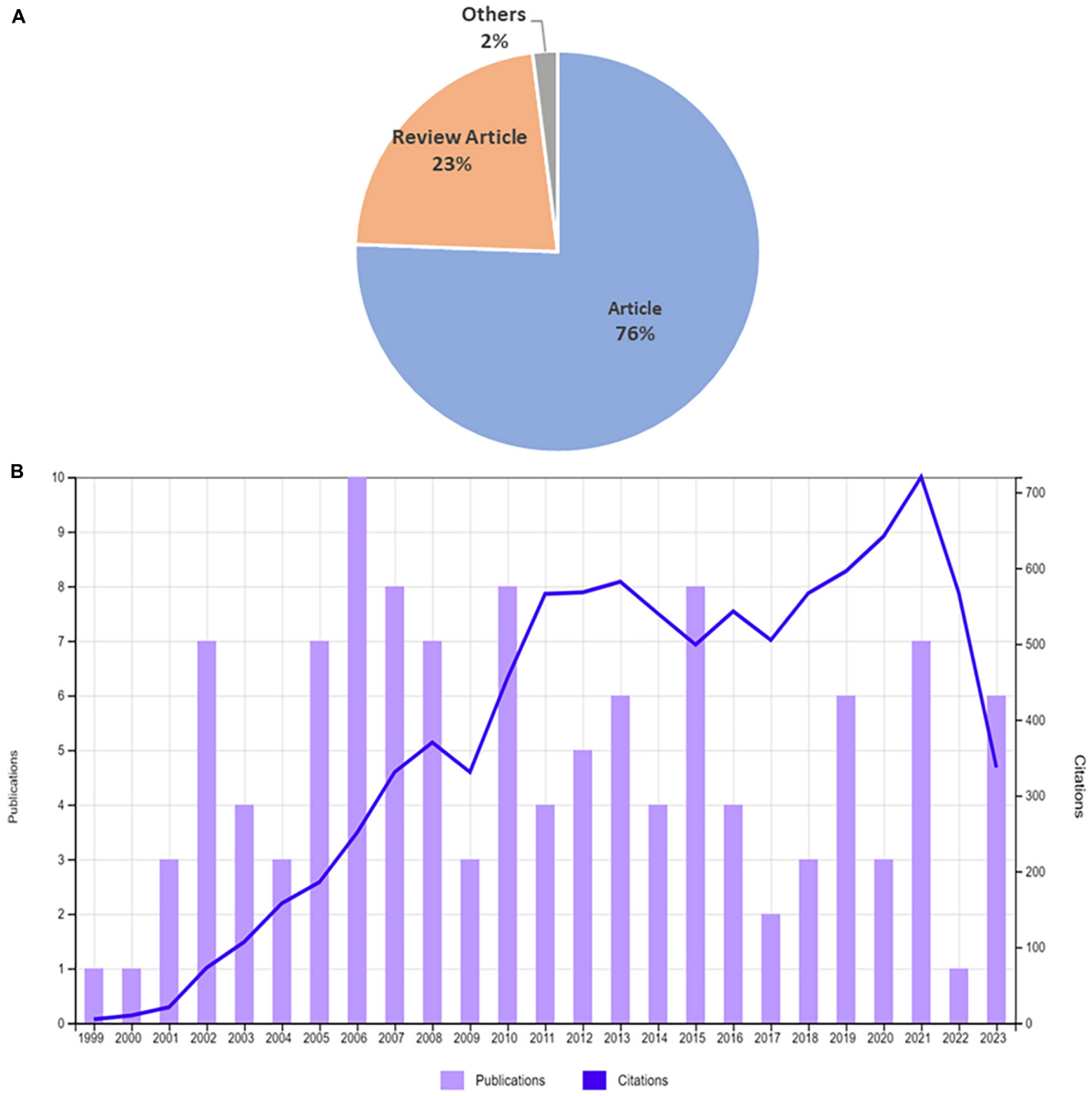

FIGURE 2
Publication distribution. Document type **(A)** and total articles per annum **(B)** in the field of acrolein and Alzheimer's disease research.

Figure 2B illustrates the annual count of research publications related to acrolein and AD. The data indicates a noticeable decline in the number of articles published in recent years compared to the preceding decade when these topics garnered significant attention.

Publication of countries/regions

There was a total of 22 countries that contributed to the publications on acrolein and AD. Among these countries, the majority of the articles were published by the USA, accounting for 52.5% (n = 63) of the total publications. In addition to the USA, other countries like China, Canada, and Japan also made noteworthy contributions, accounting for 15% (n = 18), 12.5% (n = 15), and 11.7% (n = 14) of the publications, respectively (Figure 3A). In Figure 3B, the annual publication trend of the four countries with the highest number of publications between 1999 and July 2023 is displayed. The data reveals that the USA experienced a substantial increase in publications during the last two decades but has since been declining in recent years, whereas China and Japan have consistently achieved significant publication outputs. Moreover, despite the recent decline in the USA's publications, they received the highest number of international collaborations in the field. Japan ranked second in terms of international collaborations, followed by China and Canada. Interestingly, countries like the UK, India, and Iran had no collaborations at all (Figure 4).

This indicates that research on acrolein and AD is a global effort, with a diverse range of countries contributing to the scientific

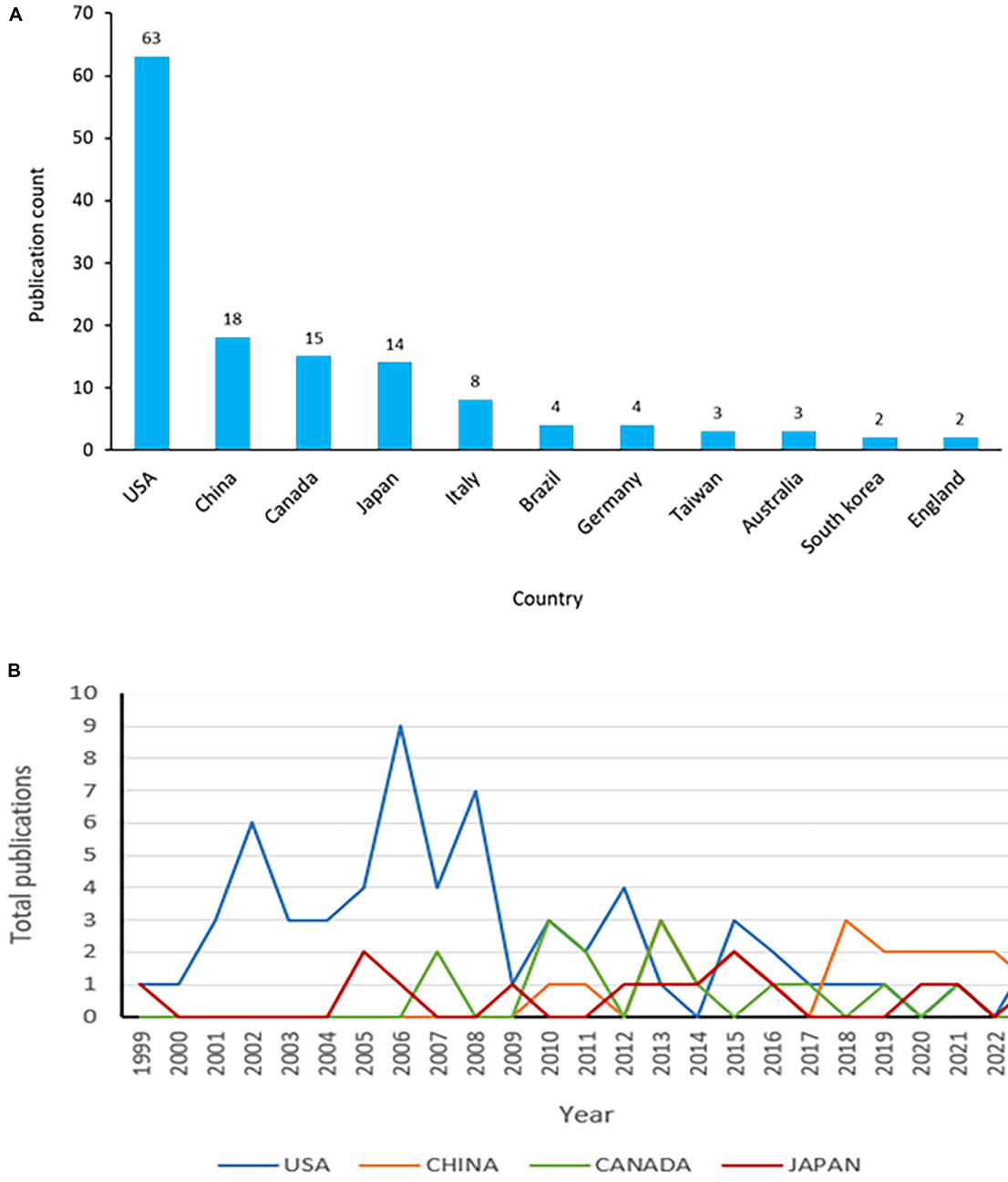

FIGURE 3
Top 10 countries with highest publications in acrolein and Alzheimer's disease research field. **(A)** Publication count of each country. **(B)** Annual publication trend of the top four countries.

literature. The USA stands out as the leading contributor, but other countries from different regions are also actively involved in studying the relationship between acrolein and AD. This collaborative approach fosters a broader understanding of the subject matter and helps in addressing the global challenge of dementia, including AD, as a public health concern.

Publication of institutions

The research on acrolein and its association with AD has been a collaborative effort involving a diverse range of institutions. A total of 162 institutions have published articles investigating the relationship between acrolein and AD. Among these institutions, the publication performance of the top 12 contributors is presented in Figure 5. Significantly, the University of Kentucky in the United States has played a prominent role in this research field, contributing 19.2% (n = 23) of all the articles on the subject. Following the University of Kentucky, Sun Yat-sen University has contributed 7.5% (n = 9) of the articles, and Lava University has contributed 5.8% (n = 7). Additionally, we visualized the institution collaborations network map in Figure 6. The institution with the highest collaboration was Sun Yat-sen University, having 16 links, a total link strength of 19.

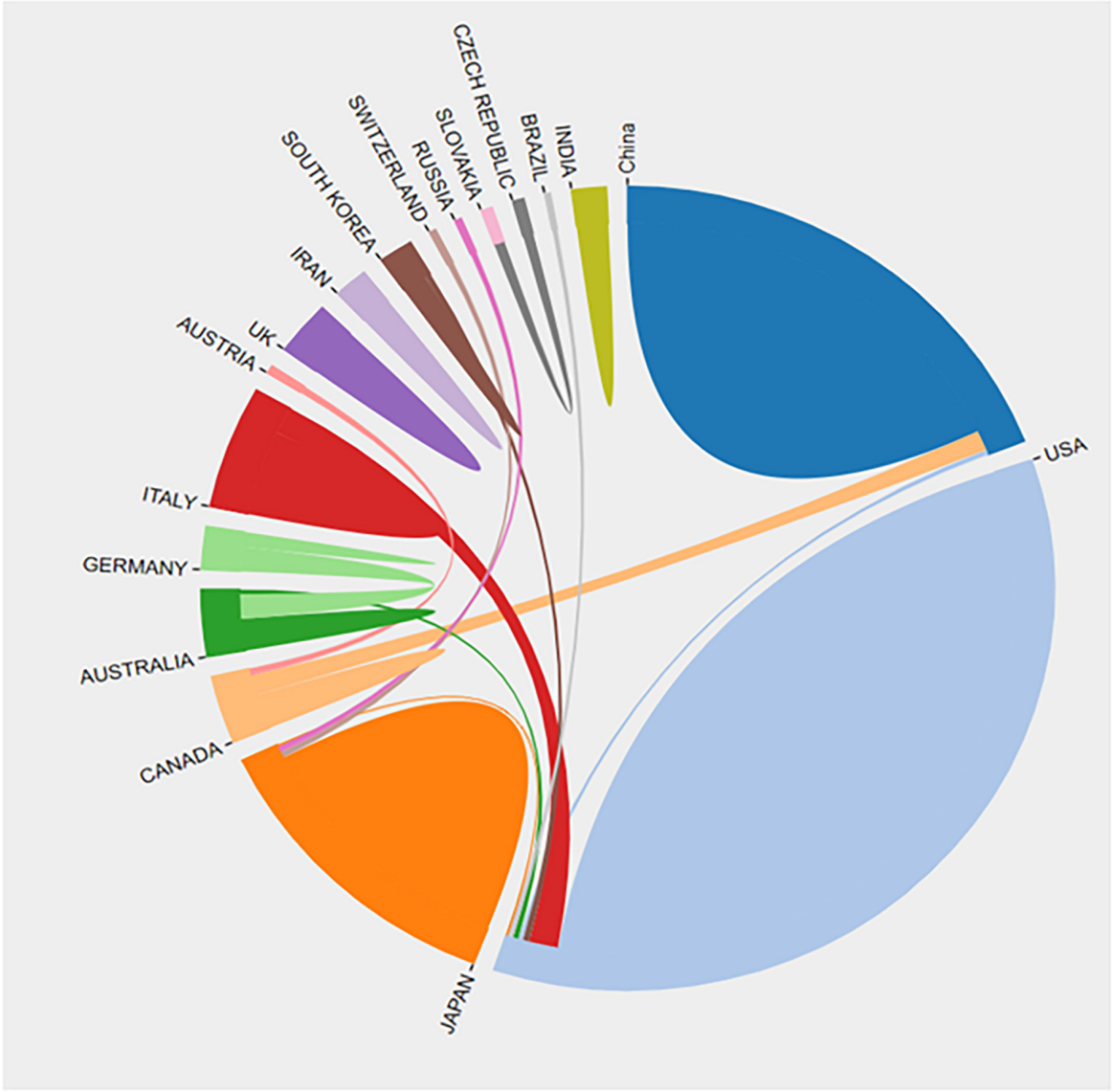

FIGURE 4
Inter-country/region publication in the acrolein and Alzheimer's disease research field. The links between countries are represented by colored lines. More linked lines indicate greater collaboration.

Publication of authors

A total of 451 authors made contributions to 120 papers related to acrolein and AD, which encompassed information about both the first and corresponding authors in the SCI-Expanded database. The 10 most productive authors in acrolein and AD research are listed in Table 1. Ramassamy C from the institution of Institut National De La Recherche Scientifique (INRS), Canada, ranks first with 11 publications, followed by Butterfield DA and Lovell MA, each with 7 publications. In terms of average citations, Butterfield DA had the most cited documents with 167.7 (Table 1). Figure 7 displays the co-authorship among authors, highlighting the collaboration patterns within the field. It reveals that Pi RB (Pi Rongbiao) from Sun Yat-sen University in China had the most extensive co-authorship collaborations, as indicated by 37 network lines connecting Pi RB to various other authors. This signifies a high level of collaborative activity involving Pi RB. The total link strength, which represents the overall intensity of collaborations, for Pi RB is 55. Following Pi RB, Ramassamy C (Ramassamy, Charles) ranks second in terms of co-authorship collaborations, with a total link strength of 53. This suggests that Ramassamy C is also actively engaged in collaborative research within the field, albeit slightly less extensively than Pi RB. Collaboration could play a crucial role in advancing research in the acrolein and AD domain. The extensive networks built by researchers like Pi RB and Ramassamy C demonstrate the value of collaborative efforts in generating knowledge, sharing expertise, and driving innovation within this research area. Such collaborative activities likely contribute to the development of more comprehensive and impactful solutions for understanding and addressing challenges related to acrolein and AD.

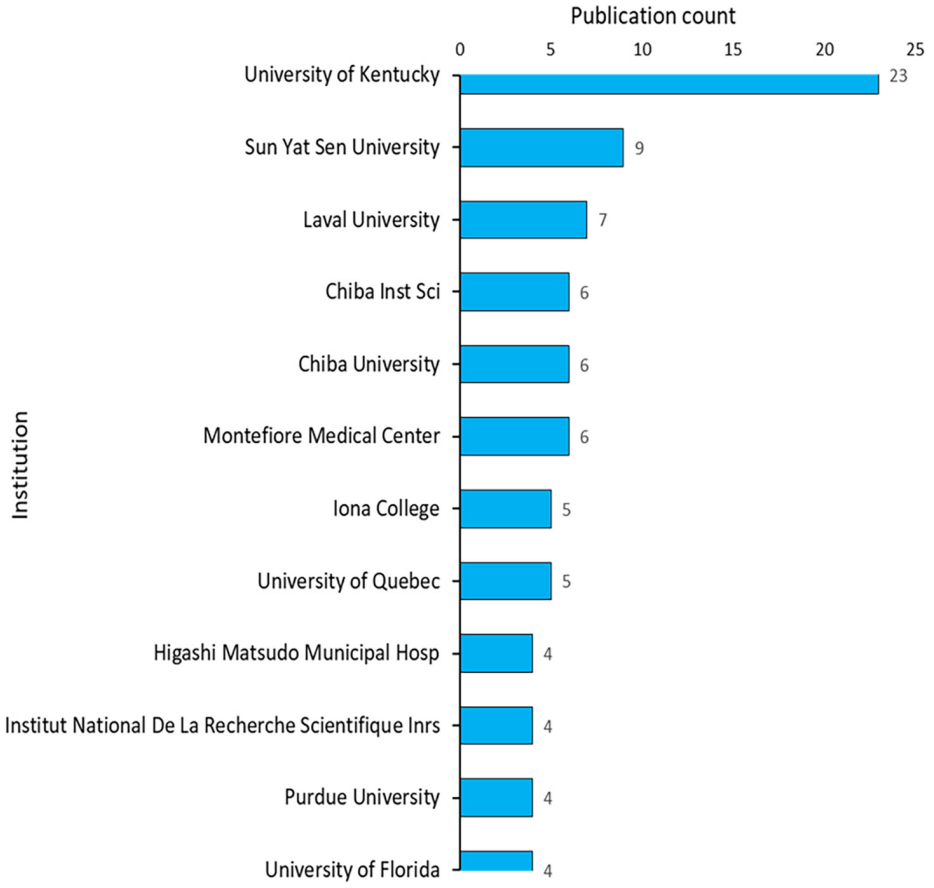

FIGURE 5
The top 12 institutions with the most publication in acrolein and Alzheimer's disease research field.

Journals and impact factor

The acrolein and AD papers were found within 19 journals. Table 2 presents the top 10 journals along with their respective impact factors. The leading journal in terms of the number of papers published on the subject is the "Journal of AD," accounting for 11.7% of the total publications. This journal holds a significant impact factor of 4.0, indicating its prominence in the scientific community. Following closely behind is "Neurobiology of Aging" with 5% of the articles and an impressive impact factor of 5.133. The journals "Free Radical Biology" and "Chemical Research in Toxicology" each contribute 3.3% of the articles and have impact factors of 8.101 and 3.973, respectively (Table 2).

Prolific cited papers

The top 15 most cited acrolein and AD related paper are listed in Table 3. These papers consist of both original articles and reviews documents. All the papers received >100 citations. The total number of citations for the top 15 cited papers was 4,967. The article entitled: "Metals, Oxidative Stress and Neurodegenerative Disorders," published in the journal of *Molecular and Cellular Biochemistry* with impact factor of 3.842, was the most cited paper with a total citation of 766. Four of the top 15 papers were published in *Neurobiology of Aging* with IF_{2023} of 5.133. Out of the 15 papers, three were published by the author "Butterfield, DA" and two by the author "Lovell, MA."

Keywords, clusters, and burst words

Analysis of keywords in article could serve as useful tool for identification of research hotspots and frontiers in a certain filed. In the present study, we identified an overall of 585 keywords from the 120 articles in Web of Science Core Collection (Figure 8A). Among these keywords, we subsequently identified the 31 most related keywords linking acrolein and AD (Figure 8B). The most significant keywords linking acrolein and AD were oxidative stress, lipid-peroxidation, acrolein amyloid-beta, alzheimer's-disease, mild cognitive impairment, mechanisms, activation, cerebrospinal-fluid, end-products, aldehydic product, *in vivo*, and *in vitro* (Table 4).

Using CiteSpace, we identified 15 major hotspot clusters from papers published between 2013 and 2023 (Figure 9A and Table 5). The largest cluster (#0) comprises 42 members and a silhouette value of 0.857. It is labeled as "*internalization pathway*" by log-likelihood ratio and "*assessing acrolein*" (0.87) by mutual information. The most three cited members in this cluster were *Alzheimer's disease*, *brain*, and *acrolein*. Cluster (#1) is the second

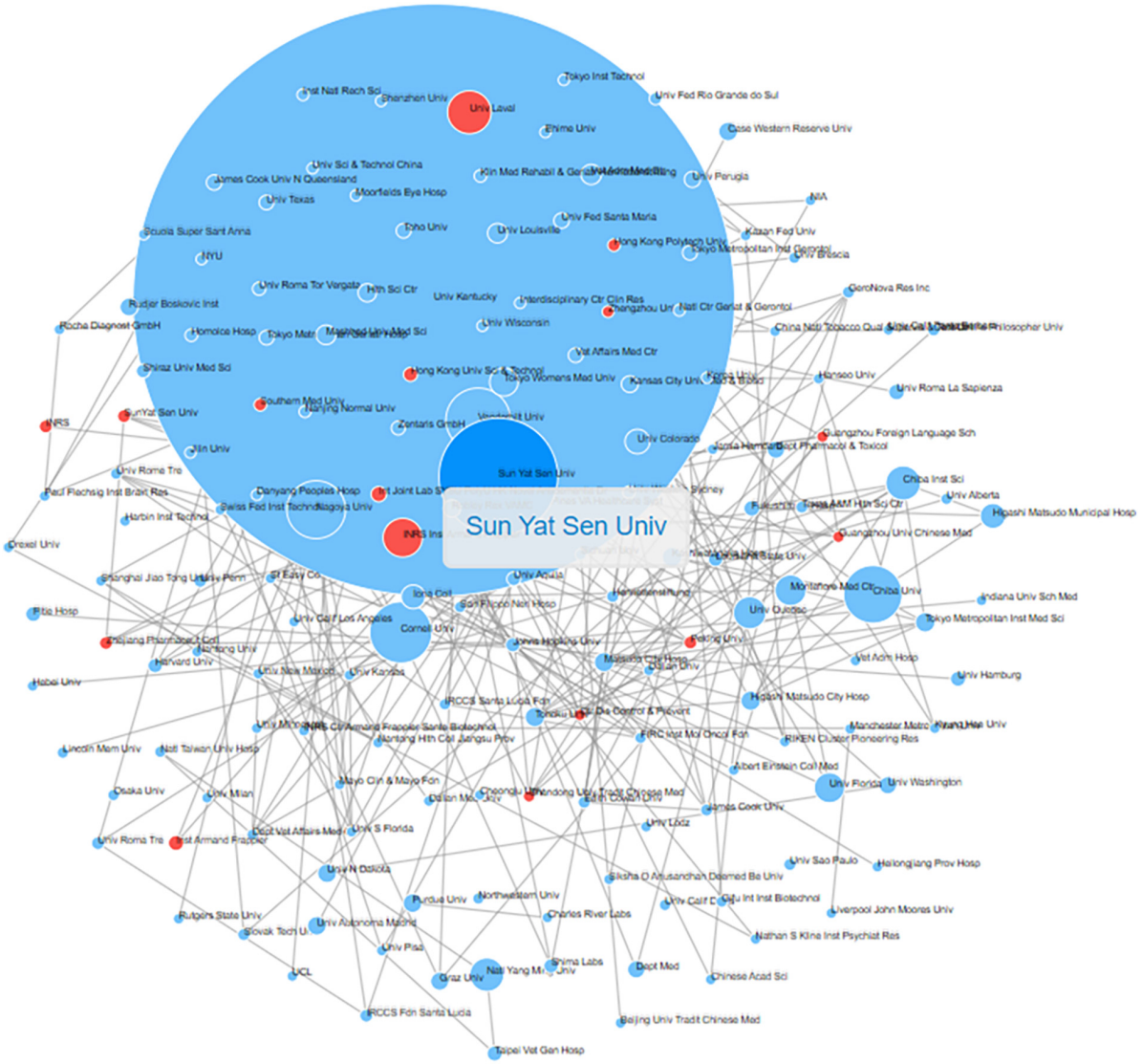

FIGURE 6
Institutions' collaboration network map in acrolein and Alzheimer's disease research field. The blue node represents institution and red node indicates institute collaboration.

TABLE 1 Top 10 authors with most publication.

Rank	Author	Publication	%	Citations	Average citations
1	Ramassamy C	11	9.2	443	40.3
2	Butterfield DA	7	5.8	1174	167.7
3	Lovell MA	7	5.8	977	139.6
4	Igarashi K	6	5.0	144	24.0
5	Kashiwagi K	6	5.0	144	24.0
6	Lopachin RM	6	5.0	543	90.5
7	Pi RB	6	5.0	132	22.0
8	Gavin T	5	4.2	452	90.4
9	Qin J	5	4.2	147	29.4
10	Yoshida M	5	4.2	130	26.0

TABLE 2 Top 10 journals with most publications.

Journal	Publication	%	Citations	Average citations	Impact factor (IF)
Journal of Alzheimer's Disease	14	11.7	59	4.2	4.00
Neurobiology of Aging	6	5.0	111	18.5	5.133
Free Radical Biology and Medicine	4	3.3	49	12.3	8.101
Chemical Research in Toxicology	4	3.3	21	5.3	3.973
Toxicological Sciences	3	2.5	26	8.7	4.109
Clinica Chimica Acta	3	2.5	20	6.7	6.314
Biochimica et Biophysica Acta-Molecular Basis of Disease	3	2.5	19	6.3	6.633
Toxicology Letters	3	2.5	18	6.0	4.271
Brain Research	3	2.5	11	3.7	3.61
Toxicology and Applied Pharmacology	3	2.5	8	2.7	4.46

TABLE 3 The top 15 most cited papers in the field.

Rank	Publication title	Total citation	References
1	Metals, oxidative stress and neurodegenerative disorders	766	Jomova et al., 2010
2	Evidence that amyloid beta-peptide-induced lipid peroxidation and its sequelae in Alzheimer's disease brain contribute to neuronal death	550	Butterfield et al., 2002
3	Acrolein is increased in Alzheimer's disease brain and is toxic to primary hippocampal cultures	369	Lovell et al., 2001
4	Lipid peroxidation in aging brain and Alzheimer's disease	368	Montine et al., 2002
5	Oxidative DNA damage in mild cognitive impairment and late-stage Alzheimer's disease	359	Lovell and Markesbery, 2007
6	Protein-bound acrolein: a novel marker of oxidative stress in Alzheimer's disease	340	Calingasan et al., 1999
7	Increased levels of 4-hydroxynonenal and acrolein, neurotoxic markers of lipid peroxidation, in the brain in mild cognitive impairment and early Alzheimer's disease	317	Williams et al., 2006
8	Molecular mechanisms of acrolein toxicity: relevance to human disease	308	Moghe et al., 2015
9	Cytochrome c oxidase and mitochondrial F1F0-ATPase (ATP synthase) activities in platelets and brain from patients with Alzheimer's disease	288	Bosetti et al., 2002
10	Lipoic acid as an anti-inflammatory and neuroprotective treatment for Alzheimer's disease	258	Maczurek et al., 2008
11	Involvements of the lipid peroxidation product, HNE, in the pathogenesis and progression of Alzheimer's disease	213	Butterfield et al., 2010
12	Lipoic acid as a novel treatment for Alzheimer's disease and related dementias	212	Holmquist et al., 2007
13	Molecular mechanisms of 4-hydroxy-2-nonenal and acrolein toxicity: nucleophilic targets and adduct formation	211	LoPachin et al., 2009
14	Copper and oxidative stress in the pathogenesis of Alzheimer's disease	209	Eskici and Axelsen, 2012
15	Elevated protein-bound levels of the lipid peroxidation product, 4-hydroxy-2-nonenal, in brain from persons with mild cognitive impairment	199	Butterfield et al., 2006

largest with 34 members and a silhouette value of 0.76. It is labeled as "*n-sh cell*" by log-likelihood ratio and "*assessing acrolein*" (0.28) by mutual information (Table 5).

CiteSpace software tool generated a timeline maps of the clusters and identify keyword bursts. In this study, the focus of acrolein and AD research has undergone a shift in the past decade. Key areas of interest have transitioned from topics such as "synthesis," "mouse model," "identification," "aldehyde dehydrogenase," "rat model," "guarana," "neurodegeneration," "protein-conjugation acrolein," "critical neurotoxic target," "carbonyl scavenger phenelzine," "molecular mechanism," "disease-like pathology," and "n-sh cells" to the current emphasis on the "internalization pathway" (Figure 9B).

The timeline map that visually represent the evolution of clusters, consisting groups of related keywords or topics, over time is represented in Figure 9B. The study noted a significant shift in the focus of acrolein and AD research over the past decade. Initially, researchers were interested in various topics such as synthesis methods, animal models (like mouse and rat models), identification techniques, specific enzymes (like aldehyde dehydrogenase), natural compounds (like guarana), neurodegeneration processes, protein-conjugation with acrolein, targets for neurotoxicity, treatments (like carbonyl scavenger phenelzine), molecular mechanisms, disease-like pathology studies, and specific cell types (like n-sh cells). However, the current emphasis in research has shifted toward the "internalization

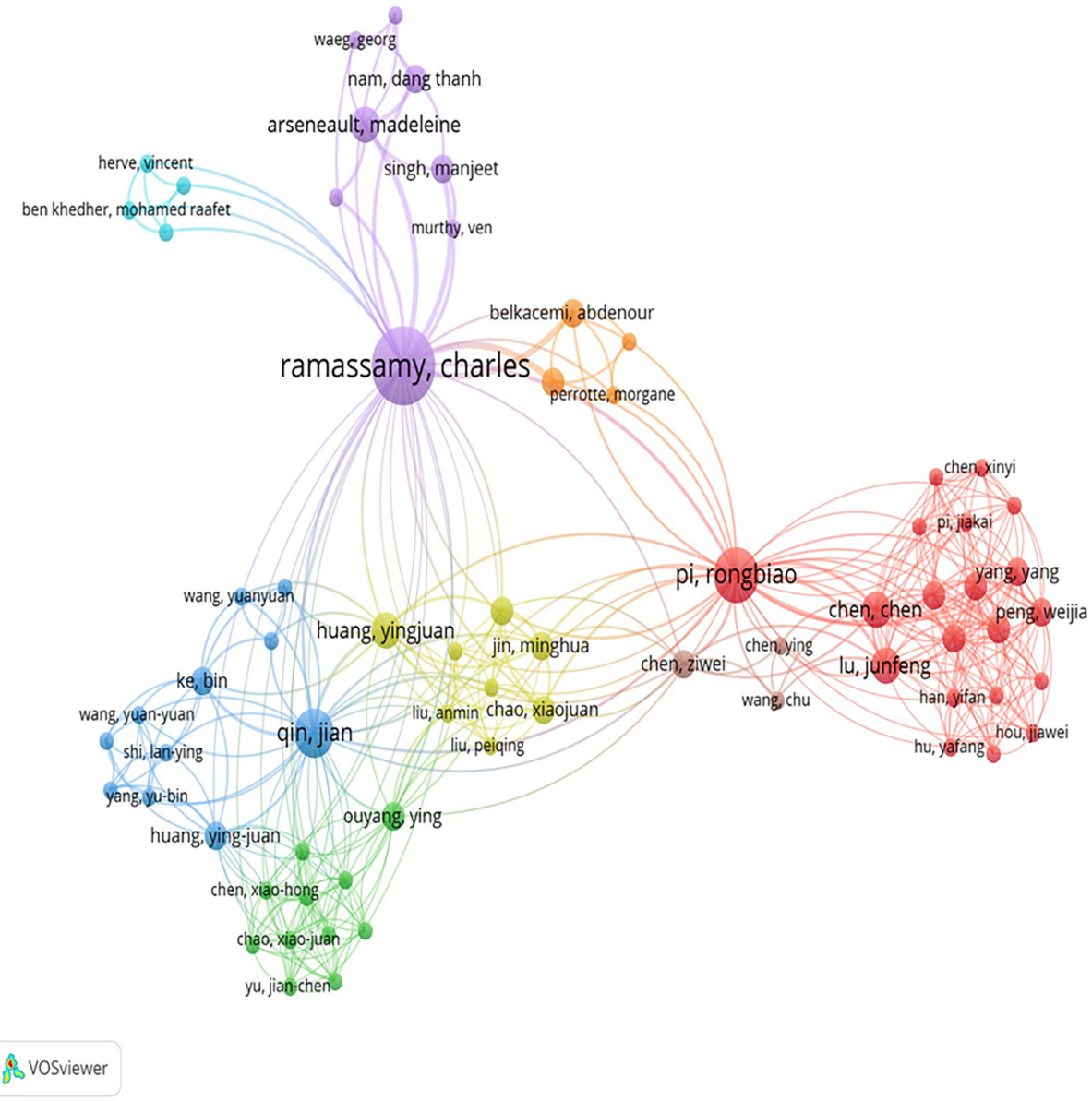

FIGURE 7
Authors' collaboration network map in acrolein and Alzheimer's disease research field. The map consists of 69 author and forms 8 collaboration clusters. Clustering is represented by colors, with authors in the same cluster sharing the same color. The size of circles reflects the frequency of collaboration, with larger circles indicating more collaboration.

pathway." This indicates a focus on understanding how acrolein enters cells and affects cellular processes, which is crucial in the context of AD.

CiteSpace also identified keyword bursts, marking periods of increased attention or activity around specific keywords, thereby indicating topics of sudden prominence in research. The top 22 keywords with the strongest citation bursts are represented in Figure 9C. In the period between 2021 and 2022, the keywords marker, synaptic dysfunction, mechanism, and hippocampus received notable attention in the field. As illustrated in the figure, the hotspots have evolved, moving from cognitive impairment, cell growth and death, and Aβ deposition to related markers. Subsequently, the focus shifted to synaptic dysfunction, mechanisms, hippocampus, metabolism, tau phosphorylation-related mechanisms, and further to dementia and identifying inhibitors. In addition, 16 keywords exhibited citation bursts from 2022 to 2023.

The analysis of acrolein and AD publications from 1999 to July 2023 reveals a dynamic and collaborative research landscape. The USA emerges as a major contributor, reflecting global efforts in understanding acrolein's role in AD. Institutions like the University of Kentucky and Sun Yat-sen University, along with prolific authors such as Ramassamy C and Butterfield DA, have significantly advanced knowledge in this area. Leading journals like the "Journal of AD" and "Neurobiology of Aging" have been instrumental in disseminating research findings. Keyword analysis underscores the importance of A-beta, oxidative stress,

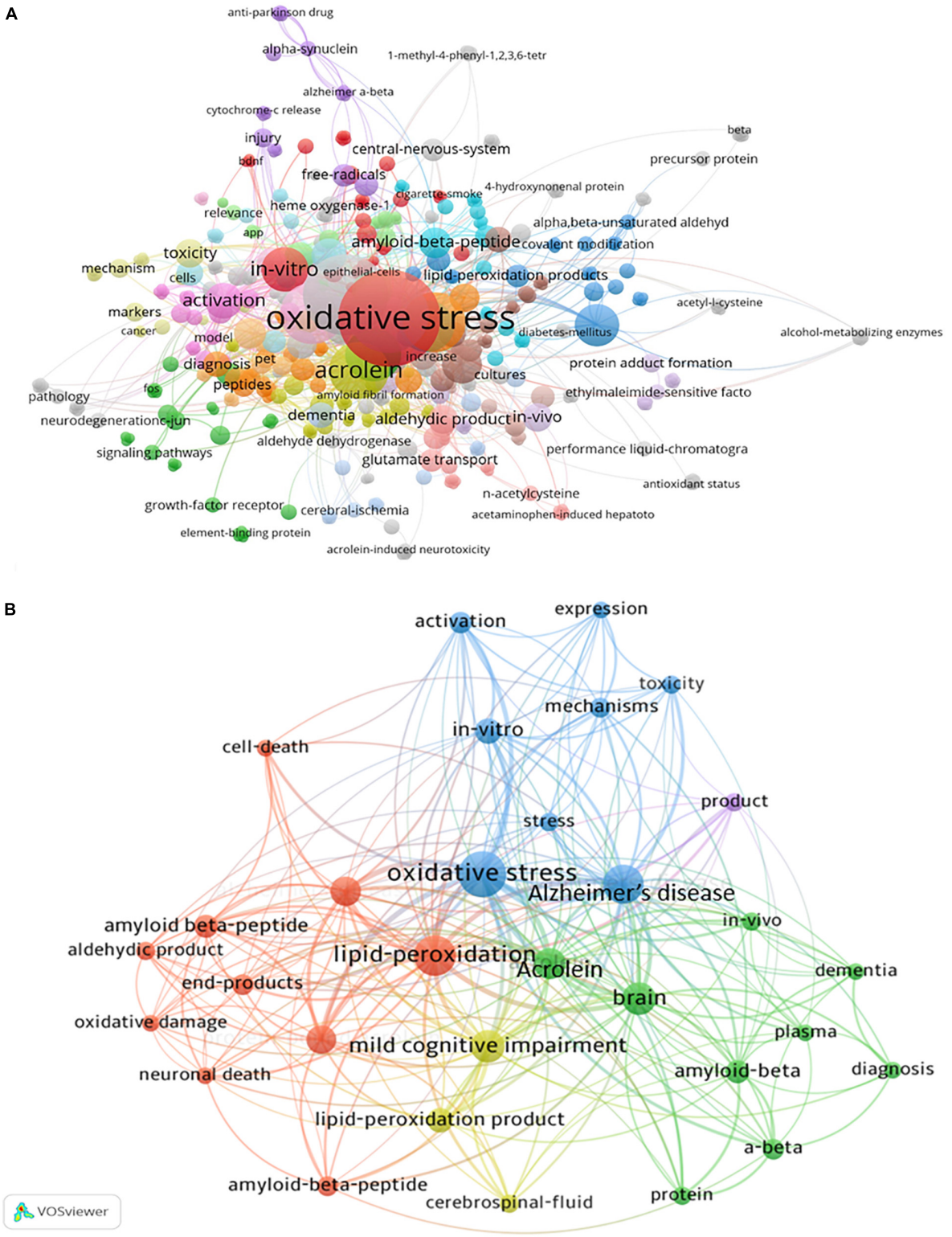

FIGURE 8
Analysis of keywords in acrolein and Alzheimer's disease research field. **(A)** Illustrates the complete network of 585 keyword co-occurrence map. **(B)** Shows the top 30 keyword co-occurrence network map. Clustering is represented by colors, with keywords in the same cluster sharing the same color. Circle size reflects keyword occurrence, with larger circles indicating more occurrences.

lipid oxidation, and the emerging focus on the "internalization pathway" in understanding AD pathology related to acrolein exposure. These findings highlight ongoing efforts to address the complex challenges posed by AD. Overall, the study showcases a collaborative and evolving research landscape, with an emphasis on key themes and advancements in acrolein-AD research. This

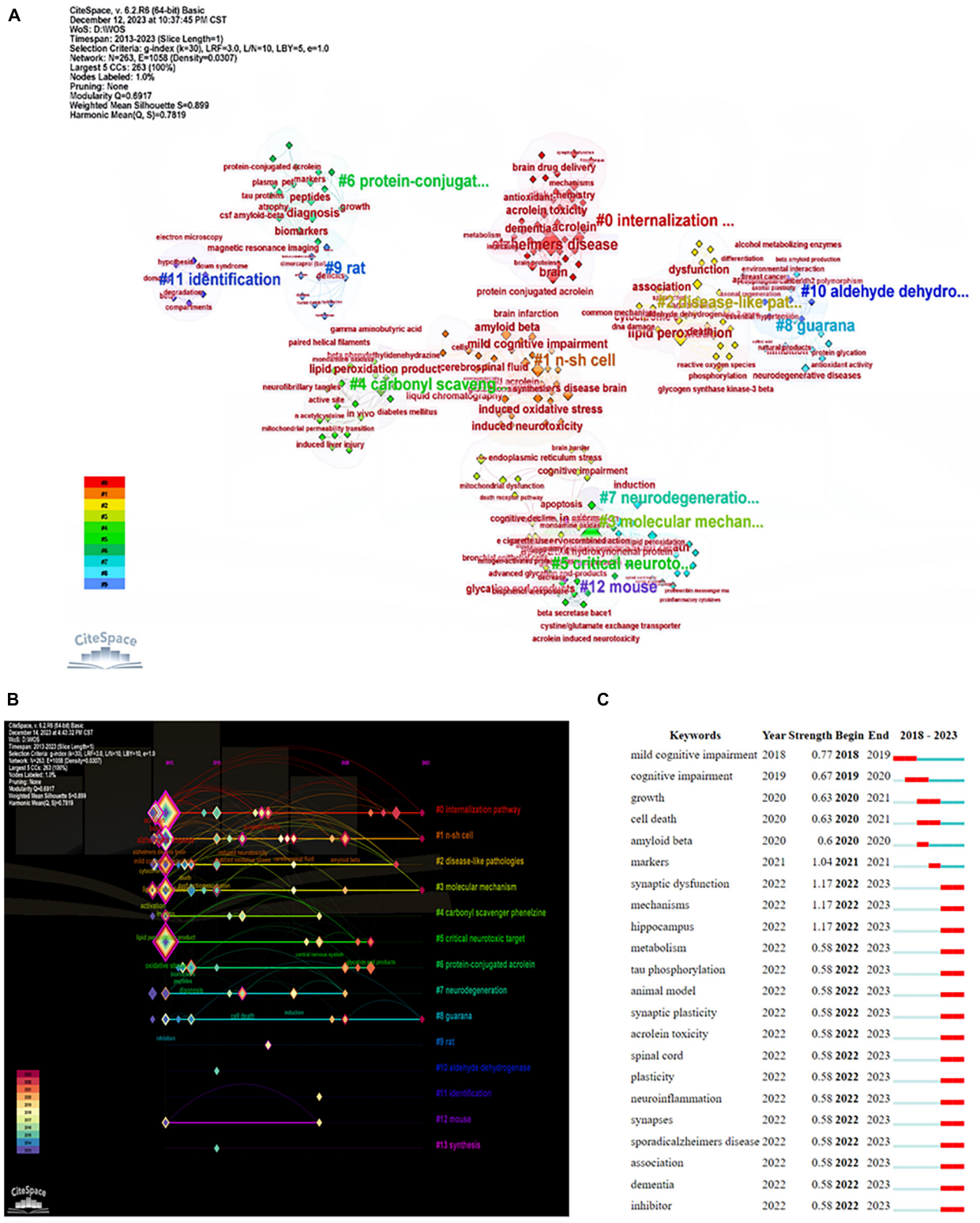

FIGURE 9
Research hotspots and frontiers in the field. **(A)** Represents the map of the top 15 hotspot clusters. These clusters are categorized into subjects, represented in different colors, with an identification number (ID) ranging from #0 to #15. The smaller the ID number, the greater the cluster, and vice versa. **(B)** Shows the timeline view of co-cited clusters including cluster subjects. This view effectively shows the variations in the emergence time and duration of clusters. The lines and labels transitioning from purple to red indicate more recent research areas. **(C)** Lists the top 22 keywords with the strongest citation burst. The strength value represents the frequency of citations. The red indicator represents the period during which a keyword gains attention.

TABLE 4 Top 20 keywords in acrolein and AD research.

Keyword	Occurrences	Total link strength
Oxidative stress	51	132
Lipid-peroxidation	37	120
Alzheimer's-disease	34	87
Brain	23	75
Mild cognitive impairment	22	73
Acrolein	20	73
Alzheimer's-disease brain	18	59
Protein-bound acrolein	17	49
In vitro	13	37
Lipid-peroxidation product	12	27
Amyloid beta-peptide	10	33
Amyloid-beta	10	32
Activation	9	26
A-beta	8	20
End-products	8	34
Amyloid-beta-peptide	7	16
Mechanisms	7	18
Aldehydic product	6	23
Cerebrospinal-fluid	6	19
In vivo	6	15

comprehensive analysis contributes valuable insights to the broader understanding of AD and informs future research directions in this critical domain.

Discussion

Acrolein and AD have been subjects of research due to their potential association and implications in neurodegenerative processes. While the link between acrolein and AD is intriguing, it is important to note that AD is a complex and multifactorial disorder with multiple contributing factors. Acrolein is just one of many potential factors that could play a role in the disease process.

Characteristics of publication outputs and citation impact

The findings from the analysis of 120 English documents related to acrolein and AD pathogenesis research in SCI-Expanded of Web of Science from 1999 to 2023 suggest significant changes in publication and citation trends in the field. During this period, acrolein and AD research garnered a considerable level of interest, leading to a substantial number of publications in various document types. The 120 English documents encompass a range of studies, including original research articles, reviews, and other specialized types of publications. This demonstrates the depth and breadth of research being conducted in this area.

However, the analysis also indicates a noticeable decline in the rate of new publications in recent years compared to previous years when interest in the topic was more prominent. This decline in publication rate may signal changes in the dynamics of research in the field. Several factors could contribute to this decline. One possible reason could be the saturation of research in the acrolein and AD pathogenesis field. As more studies are conducted and key findings are established, researchers may be focusing on other areas of investigation or moving toward exploring new frontiers in neuroscience and neurodegenerative disorders. Another potential factor influencing the decline in publication rate could be a shift in research focus. Scientific advancements and breakthroughs often redirect attention to different aspects of a research field (Larsen and von Ins, 2010).

As new findings emerge, researchers may choose to investigate different facets of acrolein and AD pathogenesis, leading to a shift in the overall research landscape (Engels et al., 2012; Wahid et al., 2022). Additionally, changes in funding priorities may also contribute to the observed trend. Shifting funding priorities can influence the allocation of resources to specific research areas, potentially leading to fluctuations in the number of new publications over time (Korytkowski and Kulczycki, 2019; Wahid et al., 2022). For researchers and stakeholders in the field, it is essential to take these trends into account when planning future studies and exploring new avenues of investigation. Understanding the current state of research and the factors impacting publication trends can help guide future research directions, inform resource allocation, and facilitate collaborative efforts to address critical gaps in knowledge.

Global participation: countries, institutions, and authors

This wide representation of countries, institutions and authors in the scientific literature on acrolein and AD highlights the global nature of research efforts in understanding this neurodegenerative condition. The USA notably stands out as the leading contributor, showcasing its strong involvement in advancing the understanding of AD and its potential link to acrolein, especially in the past two decades. However, there has been a decline in their contributions in recent years. The possible reason for this decline in the field could be the saturation of research, which occurs when fundamental questions in the field have been extensively answered, resulting in fewer novel findings and subsequently fewer publications. Additionally, shifts in research focus can occur due to technological advancements, changes in funding priorities, or emerging societal needs, causing researchers to divert their attention from certain topics. Furthermore, as knowledge in a field matures, researchers may focus more on refining existing theories or methodologies rather than making groundbreaking discoveries, leading to a slowdown in publication output. The USA's active participation and top rank in academic research have been consistently reported in previous studies (Jallow et al., 2020; Wang et al., 2023), reaffirming its significant role in scientific advancements. However, it is essential to acknowledge the active

TABLE 5 The largest 15 clusters in acrolein and AD research.

Cluster ID	Three must cited keywords	Size (SV)	Label (LLR)	Label (MI)	Average year
#0	Alzheimer's disease, brain, and acrolein	42 (0.857)	Internalization pathway (20.33, 1.0E-4)	Assessing acrolein (0.87)	2017
#1	Mild cognitive impairment, Alzheimer's disease brain, and amyloid beta	34 (0.76)	N-sh cell (18.75, 1.0E-4)	Assessing acrolein (0.28)	2017
#2	Lipid peroxidation, association, and dysfunction	33 (0.889)	Disease-like pathologies (18.29, 1.0E-4)	Oxidative modification (0.3)	2015
#3	*In vitro*, activation, and A-beta	26 (0.949)	Molecular mechanism (17.65, 1.0E-4)	Acrolein toxicity (0.33)	2018
#4	Lipid peroxidation product, *in vivo*, and beta phenylethylidenehydrazine	22 (0.985)	Carbonyl scavenger phenelzine (8.74, 0.005)	Carbonyl scavenger phenelzine (0.02)	2015
#5	Oxidative stress, cognitive impairment, and glycation end products	19 (0.908)	Critical neurotoxic target (9.5, 0.005)	Assessing acrolein (0.74)	2019
#6	Diagnosis, growth, and peptides	19 (0.908)	Protein-conjugated acrolein (15.18, 1.0E-4)	Polyamine biomarker (0.04)	2016
#7	Cell death, expression, and induction	17 (0.889)	Neurodegeneration (12.16, 0.001)	Joint action (0.11)	2016
#8	Inhibition, apolipoprotein, and neurodegenerative diseases	14 (0.884)	Guarana (12.16, 0.001)	Neurotoxicity (0.11)	2017
#9	Myelin damage, hydralazine, and disease	9 (1)	Rat (8.74, 0.005)	Rat (0.02)	2017
#10	Environmental interaction, aldh2 polymorphism, and alcohol metabolizing enzymes	7 (0.991)	Aldehyde dehydrogenase (8.34, 0.005)	Aldehyde dehydrogenase (0.03)	2015
#11	Hypothesis, beta, compartments	7 (1)	Identification (9.25, 0.005)	Identification (0.02)	2019
#12	Apoptosis, aggregation, and erk	6 (0.992)	Mouse (8.34, 0.005)	Mouse (0.03)	2018
#13	1st radiosynthesis, agents, and cinnamaldehydes	5 (1)	Synthesis (10.97, 0.001)	Synthesis (0.02)	2015
#14	Alpinetin, isomerase, and hesperetin	3 (1)	Acrolein-trapping capacity (8.34, 0.005)	Acrolein-trapping capacity (0.03)	2021

SV, silhouette value; LLR, log-likelihood ratio; MI, mutual information.

engagement of other countries from different regions, as this collaborative approach fosters a broader understanding of the subject matter and aids in addressing the global challenge of dementia, including AD, as a significant public health concern (Sexton et al., 2021; Alzheimer's Association, 2023). To foster international research collaboration, a comprehensive approach involves establishing collaborative networks and consortia among researchers, institutions, and funding agencies from different countries (Adams, 2012). These networks facilitate information sharing, joint funding opportunities, and cross-border projects. Promoting joint research initiatives through agreements, grants, and partnerships encourages diverse researchers to collaborate on common goals. Supporting exchange programs enhances collaboration by sharing knowledge and fostering cultural understanding. Improving communication with online tools and open-access platforms promotes global research transparency. Encouraging multidisciplinary projects leverages diverse expertise, while simplifying visas and providing mobility support aids seamless collaboration. Lastly, promoting cultural sensitivity ensures equitable participation and enriches collaborative research (Gewin, 2018; Nature., 2021).

The research on the association between acrolein and AD has indeed been a collaborative effort involving a diverse range of institutions. Notably, the University of Kentucky in the United States and Sun Yat-sen University in China have emerged as prominent contributors in this research field, making significant contributions in terms of publication output, collaboration, and citations. Both the University of Kentucky and Sun Yat-sen University have demonstrated substantial publication output, publishing a considerable number of articles on the subject. Their contributions have been instrumental in advancing the understanding of the relationship between acrolein and AD. Furthermore, these institutions have actively engaged in collaborations with other research entities, fostering a network of cooperative efforts in the field. Collaboration among institutions is crucial for tackling complex scientific questions and sharing expertise and resources. In addition to their publication and collaboration efforts, the research from these institutions has garnered a notable number of citations, indicating the impact and

influence of their work on the scientific community. Citations serve as a measure of the relevance and importance of research findings and indicate the recognition of contributions by other researchers in the field. The involvement of institutions from different countries, such as the University of Kentucky in the United States and Sun Yat-sen University in China, highlights the global nature of research on acrolein and AD. This international collaboration fosters a rich exchange of ideas, diverse perspectives, and a broader understanding of the subject matter.

Author participation in acrolein and AD research has been significant, with a total of 451 authors making contributions to 120 papers in the field. This indicates a diverse and collaborative effort involving numerous researchers from different institutions and regions. The top 10 most productive authors in this research area have played a crucial role in advancing the knowledge in acrolein and AD. These authors' active engagement reflects their dedication and expertise in the subject matter. Additionally, the impact of research output is measured by the number of citations received by the authors' works. These authors' documents, received >100 citations, making them highly influential in the field, indicating the significance and recognition of their research findings by other researchers. The collaborative nature of this research is evident from the co-authorship network among authors. Authors like Pi Rongbiao and Ramassamy C are the leaders in co-authorship network, fostering connections and collaborations with various authors around the globe. The active participation of authors from different institutions and countries underscores the global nature of this research effort. Such collaboration allows for the integration of diverse perspectives, expertise, and methodologies, ultimately enriching the overall understanding of the association between acrolein and AD. This collective effort by authors worldwide has contributed to advancements in diagnosis, treatment, and prevention strategies, making a significant impact on addressing AD as a critical public health concern.

Identifying research hotspots, frontiers, and emerging trend

The analysis of keyword co-occurrences proves highly valuable for pinpointing central themes, hotspots, and emerging areas of significance within a specific field. In this particular study, the VOSviewer analytical tool was employed to investigate both the keywords found within the titles. The objective was to unveil prevalent focal points and dominant domains within this realm of research. The findings show that acrolein continued to attract considerable interest in research on AD pathogenesis. Prominent primary keywords that emerged within this field belongs to acrolein and AD pathology. Notably, these keywords surfaced frequently across studies pertaining to acrolein and its role in the development of AD. The primary focus of these keywords lies in the intricate interplay between acrolein and AD, including its processing, protein interactions, and implications within the brain. It is noteworthy that this analysis highlights a strong connection between acrolein and research related to AD. The prevalence of these keywords indicates substantial interest and ongoing exploration into the possible relationship between oxidative stress, lipid peroxidation, and the role of acrolein in brain health and the progression of AD. The pivotal role of oxidative stress and Aβ in the onset and progression of AD is widely recognized. In recent years, the utilization of antioxidants and anti-amyloid therapy has gained popularity as a prominent strategy in the treatment of AD (Pritam et al., 2022; Zhang et al., 2023).

Through the analysis of keyword clusters, network maps, and keyword bursts, we have successfully identified significant topics and frontiers in the subject domain. In this study, the focus of acrolein and AD research has undergone a shift in the past decade. Indeed, the emergence of the "internalization pathway" as the largest cluster in the field has captured our attention. This suggests a significant focus and potentially pivotal insights within the context of acrolein and AD research. The prominence of this cluster underscores its importance and may indicate a critical aspect of the subject domain that warrants further investigation and exploration. Moreover, the "internalization pathway" cluster appears to encompass the most recent trending hotspots, including synaptic dysfunction, mechanisms, hippocampus, metabolism, tau phosphorylation, synaptic plasticity, acrolein toxicity, association, dementia, and inhibitors (**Figure 9C**). Indeed, elements such as brain drug delivery, antioxidants, brain chemistry, and infarction are also noteworthy and merit attention. These trends signify dynamic and evolving areas within the research landscape, indicating potential avenues for advancements and breakthroughs in our understanding of AD and acrolein-related mechanisms.

Internalization pathway

The internalization pathway is a crucial cellular process that involves the uptake of substances from the external environment into the cell. This broad term encompasses various types of endocytosis, each serving distinct purposes in cellular processes (Marsh and McMahon, 1999). The specific internalization pathway employed by a cell depends on the nature of the material being taken up and the mechanisms involved in the process (Schwab, 2001). Receptor-mediated endocytosis (clathrin-mediated endocytosis), caveolae, pinocytosis, and phagocytosis are among the mechanisms through which substances are internalized (Camblor-Perujo and Kononenko, 2022). This process is essential for diverse cellular functions, including nutrient uptake, signal transduction, and the removal of waste products. Understanding the dynamics of the internalization pathway is critical for unraveling cellular processes and has implications for various physiological and pathological conditions.

Amyloid-beta is a peptide that aggregates to form plaques in the brains of individuals with AD (Chen et al., 2017). Aβ aggregation has been shown to implicate multiple pathways in AD, including oxidative stress, inflammatory cascade, and caspase activation, which ultimately lead to neuronal damage (Sehar et al., 2022; Iliyasu et al., 2023). Mounting evidence indicates that the processing of APP is influenced by endocytosis and intracellular sorting (Rajendran et al., 2006; Chaufty et al., 2012). Given that the amyloidogenic processing involving β-secretase/γ-secretase occurs within endosomes, the generation of Aβ is reliant on the endocytosis of APP from the cell surface and its subsequent transit to the endosomes. Notably, cells expressing APP with impaired endocytosis capabilities demonstrate a marked reduction in Aβ production (Wu and Yao, 2009).

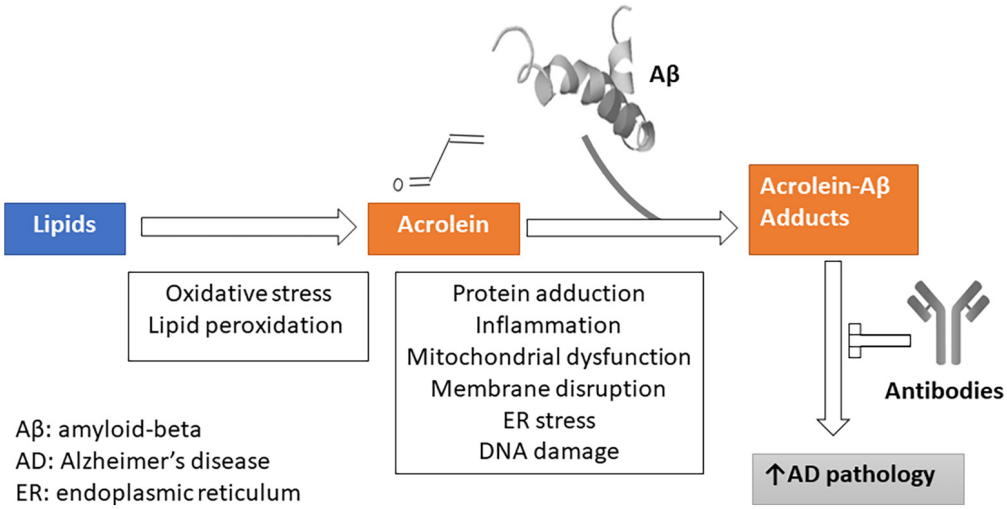

FIGURE 10
A hypothetical diagram on the complex relationships between acrolein, amyloid-beta, and cellular responses in Alzheimer's disease pathogenesis. Reactive oxygen species (ROS) from oxidative stress and lipid peroxidation alters lipid metabolic pathways, producing acrolein. Acrolein binds with amyloid beta, forming the harmful acrolein-Aβ adduct. This worsens AD pathology and hinders immune responses. These processes also trigger protein adduction, inflammation, mitochondrial issues, and DNA damage.

On the other hand, acrolein is a highly reactive aldehyde and a known byproduct of lipid peroxidation, a process associated with oxidative stress (Chen et al., 2017; Zhu et al., 2022). In AD, elevated levels of acrolein have been detected in the brains of affected individuals (Sanotra et al., 2023). While acrolein is known to induce cellular damage and exacerbate neuroinflammation, the specific mechanisms through which it enters neuronal cells, and whether its internalization is a significant contributor to AD pathology, are aspects that necessitate further exploration. The intricate interplay between acrolein and the internal cellular processes, particularly endocytosis, in the progression of AD is an area that demands deeper investigation.

Acrolein and Aβ interaction

Taking advantage of the findings from previous studies in our lab (Sanotra et al., 2023) and the current study, we made a hypothetical diagram to visually demonstrate the complex relationships between acrolein, Aβ, and cellular responses in AD pathogenesis (**Figure 10**). The alteration of lipid metabolic pathways, targeted by oxidants such as ROS following oxidative stress, leads to the formation of lipid peroxidation through polyunsaturated fatty acids. This process subsequently results in the production of acrolein, an end-product of lipid peroxidation. However, the increased production of acrolein initiates the recruitment of amyloid beta, ultimately resulting in the formation of the acrolein-Aβ adduct. The heightened presence of this adduct exacerbates the pathology of AD and hampers the natural immune response mediated by antibodies against AD onset. On the other hand, these modified metabolic processes trigger a cascade of responses, including protein adduction, inflammatory reactions, mitochondrial dysfunction, membrane disruption, endoplasmic reticulum stress, and DNA damage.

Strengths and limitations

To the best of our knowledge, our study marks the first bibliometric analysis conducted in the realm of acrolein and AD pathogenesis. This study has effectively unearthed the historical perspective of publications and citations within this field, identified major contributors including countries, institutions, and authors, and illuminated research hotspots and frontiers in AD research. The data employed for our study was meticulously extracted solely from the WoS, thereby ensuring the utilization of a comprehensive, reliable, and widely acknowledged dataset. It is pertinent to highlight that previous bibliometric analyses have similarly drawn from this database for their research (Jallow et al., 2021; Fei et al., 2022; Sun et al., 2022), further affirming its credibility and extensive adoption within the scientific community.

Nevertheless, this study does carry certain limitations. Firstly, due to the recurrence of the same author abbreviations in articles and the inability of bibliometric software to differentiate the contributions of authors with identical names, some degree of accuracy loss may remain unavoidable despite our efforts to rectify this issue. Secondly, while we have endeavored to organize the principal research contributions from the primary literature, the analysis remains a work in progress, and researchers are encouraged to delve deeper into the literature to uncover additional meaningful research trajectories. Thirdly, relying solely on WoS for article searches in bibliometric analysis may introduce biases by favoring high-impact and established journals, potentially overlooking valuable contributions from newer or niche journals. Additionally, WoS's incomplete data coverage can lead to gaps in the analysis, missing significant contributions. Furthermore, the time lag in indexing within WoS may affect the accuracy and timeliness of bibliometric analyses, particularly in rapidly evolving research areas.

Conclusion

Overall, research on acrolein and its potential role in AD involves collaboration between countries, institutions, and authors, reflecting the global effort to tackle the challenges posed by dementia and neurodegenerative conditions. The Journal of Alzheimer's Disease has garnered the highest number of publications in this field, solidifying its preeminent status. The United States emerges as the most prolific country concerning publications, citations, and international partnerships within this domain. The University of Kentucky in the United States takes the lead as the most productive institution, while Sun Yat-sen University boasts the highest count of international collaborations. Author "Ramassamy C" has notably published a majority of the papers within this field. The co-occurrence of keywords, keyword clusters, and burst detection has illuminated the cross-talk between acrolein and AD. The major focus in the field includes oxidative stress, lipid peroxidation, Aβ, and cognitive impairment. An emerging trend in the research category appears to be the involvement of the internalization pathway, extending to areas such as synaptic dysfunction, mechanisms, hippocampus, metabolism, tau phosphorylation, synaptic plasticity, acrolein toxicity, neuroinflammation, association, dementia, and inhibitors. It is important to underscore that research into acrolein and AD remains ongoing, necessitating further studies to comprehensively unravel the depth of their correlation and potential implications in the onset and progression of AD. As our knowledge advances, this area of research may open new avenues for therapeutic interventions or preventive strategies for AD.

Data availability statement

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

Author contributions

AJ: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Visualization, Writing – original draft. DN: Data curation, Investigation, Writing – original draft. MS: Data curation, Investigation, Writing – review & editing. C-HH: Funding acquisition, Resources, Writing – review & editing. Yi-FL: Project administration, Resources, Writing – review & editing. Yu-FL: Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Validation, Writing – review & editing.

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Conflict of interest

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

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Entertainment activities and the risk of Alzheimer's disease: a Mendelian randomization analysis

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Background: Effective prevention is key to addressing the increasing prevalence and mortality of Alzheimer's disease. Assessing the causal relationship between modifiable entertainment activity factors and the risk of Alzheimer's disease is important for developing public health measures, but establishing causal relationships in epidemiological data may be challenging.

Methods: This study using the two-sample Mendelian randomization analysis aimed to investigate the causal effect of entertainment activity factors on the risk of Alzheimer's disease. Summary statistics from publicly available genome-wide association studies were used to analyze 14 modifiable entertainment activity. The inverse variance weighted random effects method as the primary analytical method to estimate causal effects was used. Additionally performed MR-Egger, weighted median and weighted model methods to assess the robustness of the results. The reliability of our findings was validated through systematic sensitivity analyses and tests for heterogeneity.

Results: We found significant correlation between time spent using computer (odds ratio 0.998; 95% confidence interval 0.996–0.999; $p = 0.013$) and Alzheimer's disease, compared to other studied entertainment activities that had no significant causal relationship with Alzheimer's disease.

Conclusion: Our findings support the hypothesis that increased computer use may reduce the risk of Alzheimer's disease, providing potential strategic directions for the prevention of neurodegenerative diseases.

KEYWORDS

Alzheimer's disease, entertainment activities, Mendelian randomization, time spent using computer, causal relationship

1 Introduction

Alzheimer's disease (AD) stands as the predominant form of dementia, representing a neurodegenerative condition marked by gradual cognitive decline and behavioral disturbances. Recent data underscore a persistent rise in both the prevalence and mortality rates of AD (Alzheimer's Association, 2016). In light of the lack of pharmacological interventions capable of arresting disease progression, the emphasis is squarely on preventative strategies as pivotal in addressing AD. Further elucidation of the etiology of AD and the proposition of actionable prevention measures hold significant importance for AD prevention (Lane et al., 2018).

The cause of AD remains uncertain and is mainly related to genetics, age, environmental factors and lifestyle (Lane et al., 2018; Scheltens et al., 2021). There are challenges to formulating prevention strategies based on these risk factors, such as the fact that genetic factors are difficult to change and age is not reversible. Modifiable risk factors for diseases are those that can lower the risk of developing a specific disease through lifestyle changes or preventive measures. These factors typically stem from individual lifestyle habits, environmental influences, or health management practices, and can be easily adopted by individuals in their daily lives (Kivipelto et al., 2018). Multiple aspects have been identified as potential modifiable risk factors for AD, including diet, exercise, cognitive reserve, sleep patterns, air quality, and entertainment activities. However, the causal relationship is not yet fully understood (Livingston et al., 2017).

Investigating the causal relationship between entertainment activities as part of an individual's adaptive behavior and the risk of AD is crucial for developing effective public health interventions. However, establishing causal relationships in epidemiological data can be challenging. Adaptive behavior encompasses a range of social, conceptual, and practical skills exhibited in daily behavior, reflecting individuals' ability to adapt to environmental demands. It serves as a fundamental basis for assessing intellectual function (Tassé et al., 2012). In modern lifestyles, entertainment activities occupy a significant portion of adaptive behavior. Therefore, focusing on entertainment activities within daily adaptive behaviors may be a meaningful strategy for AD prevention. Entertainment activities typically encompass a range of pursuits that individuals engage in for relaxation, pleasure, or excitement, often characterized by their practical applicability. Previous research has demonstrated that serious games can enhance the quality of life for older adults with cognitive impairment by improving learning function and promoting physical activity (Abd-Alrazaq et al., 2023). Additionally, exercise games or training observed in patients with AD have been shown to support healthy aging and exert neuroprotective effects on the brain (Stanmore et al., 2017; Huuha et al., 2022). However, the number of epidemiological studies exploring the causal association between entertainment activities and AD remains relatively limited (Kuźma et al., 2018). Furthermore, these studies often focus on specific types of activities or populations and have not yet established a comprehensive and systematic research framework. Research on the effects of entertainment activities on AD is still in its early stages, and many findings require further validation and in-depth exploration (Ströhle et al., 2015; Stanmore et al., 2017; Abd-Alrazaq et al., 2023).

The application of traditional epidemiological studies to evaluate the causal relationship between adaptive behavior factors and the risk of AD is limited by confounding factors and potential bias from reverse causation (Davies et al., 2018). Mendelian randomization (MR) offers a methodological approach within epidemiology that uses genetic variants as instrumental variables (IV) to infer causality between risk factors and the outcome of interest. MR provides unbiased estimates of causality because genetic variants are inherited randomly from parents to offspring, independent of potential confounders. Therefore, this analytical method yields more definitive evidence regarding causality (Bowden and Holmes, 2019; Richmond and Davey, 2022).

The objective of this study is to investigate the influence of entertainment activities on AD within individual lifestyles. Here, we conducted a two-sample MR analysis to evaluate the causal impact of 14 entertainment activity factors on the risk of AD. The findings from this study could offer significant insights for preventing AD and contribute to the development of relevant prevention strategies.

2 Materials and methods

2.1 Study design and data sources

This two-sample MR analysis was performed following the instructions of the STROBE-MR checklist. Sensitivity analyses and single nucleotide polymorphism (SNP) filtering were performed according to the guidelines (Sanderson et al., 2022). Using summary statistics from the publicly available genome-wide association studies (GWAS) on the following 14 entertainment activities: Leisure/social activities: Adult education class (Adult education), Leisure/social activities: Pub or social club (Pub/club), Leisure/social activities: Religious group (Religious group), Leisure/social activities: Sports club or gym (Sports/gym), Leisure/social activities: Other group activity (Leisure(Other group)), Leisure/social activities: None of the above (Leisure(None)), Number of days/week walked 10+ minutes (Physical(light)), Number of days/week of moderate physical activity 10+ minutes (Physical(moderate)), Number of days/week of vigorous physical activity 10+ minutes (Physical(vigorous)), Time spent driving (Driving), Time spent outdoors in summer (Outdoors(summer)), Time spent outdoors in winter (Outdoors(winter)), Time spent using computer (Computer), Time spent watching television (TV)(TV); outcome: Alzheimer's disease (AD). Included study sample sizes ranged from 310,555 to 488,285 individuals, all of European ancestry. Details of traits and corresponding studies are provided in Table 1.

2.2 Instrumental variable selection

For each exposure included in this analysis, we selected genetic instruments that were statistically significant at a threshold of $p < 5 \times 10^{-8}$ based on the published GWAS for the respective trait, utilizing publicly available summary statistics. Subsequently, we conducted linkage disequilibrium (LD) clumping to ensure independence among the instruments used for each trait. This was achieved by selecting only the SNP with the lowest p-value from all SNPs exhibiting an LD $r^2 \geq 0.001$. To minimize the impact of weak instrument bias on causal inference, the F-statistic values were all above 10. And applied the Steiger filter to remove SNPs with a larger R-Squared in AD than entertainment activities (Supplementary Table S1).

The GWAS data for Leisure/social activities was obtained from the UK Biobank, which conducted a survey on Leisure/social

TABLE 1 Summary of the genome-wide association studies (GWAS) included in this two-sample MR study.

Category	Exposures/outcomes	Dataset	Sample size	Number of SNPs	Population	First author/ Year
Alzheimer's disease	Alzheimer's diseases	ieu-b-5067	488,285	12,321,875	European	Woolf B/2022
Adaptive behavior	Leisure/social activities: Adult education class	ukb-b-1553	461,369	9,851,867	European	Elsworth B/2018
Adaptive behavior	Leisure/social activities: Pub or social club	ukb-b-4171	461,369	9,851,867	European	Elsworth B/2018
Adaptive behavior	Leisure/social activities: Religious group	ukb-b-4667	461,369	9,851,867	European	Elsworth B/2018
Adaptive behavior	Leisure/social activities: Sports club or gym	ukb-b-4000	461,369	9,851,867	European	Elsworth B/2018
Adaptive behavior	Leisure/social activities: Other group activity	ukb-b-5076	461,369	9,851,867	European	Elsworth B/2018
Adaptive behavior	Leisure/social activities: None of the above	ukb-b-4077	461,369	9,851,867	European	Elsworth B/2018
Adaptive behavior	Time spent doing light physical activity	ukb-b-4886	454,783	9,851,867	European	Elsworth B/2018
Adaptive behavior	Time spent doing moderate physical activity	ukb-b-4710	440,266	9,851,867	European	Elsworth B/2018
Adaptive behavior	Time spent doing vigorous physical activity	ukb-b-151	440,512	9,851,867	European	Elsworth B/2018
Adaptive behavior	Time spent driving	ukb-b-3793	310,555	9,851,867	European	Elsworth B/2018
Adaptive behavior	Time spent outdoors in summer	ukb-b-969	419,314	9,851,867	European	Elsworth B/2018
Adaptive behavior	Time spent outdoors in winter	ukb-b-6811	364,465	9,851,867	European	Elsworth B/2018
Adaptive behavior	Time spent using computer	ukb-b-4522	360,895	9,851,867	European	Elsworth B/2018
Adaptive behavior	Time spent watching television (TV)	ukb-b-5192	437,887	9,851,867	European	Elsworth B/2018

activities among 461,369 individuals. Classify the response to the question "Which of the following do you attend once a week or more often? (You can select more than one)" into six distinct categories: "Adult education class" (ukb-b-1553), "Pub or social club" (ukb-b-4171), "Religious group" (ukb-b-4667), "Sports club or gym" (ukb-b-4000), "Other group activity" (ukb-b-5076) and "None of the above" (ukb-b-4077). The instrumental variables employed in this study encompassed the following categories: Adult education (4 SNPs), Pub/club (18 SNPs), Religion group (23 SNPs), Sports/Gym (7 SNPs), Leisure (other group) (4 SNPs), and Leisure (None) (10 SNPs).

The GWAS data for Physical (light) was obtained from the UK Biobank (ukb-b-4886), which conducted a survey on Physical(light) among 454,783 individuals. Classify the response to the question "In a typical WEEK, on how many days did you walk for at least 10 min at a time? (Include walking that you do at work, traveling to and from work, and for sport or leisure)." A total of 14 SNPs as instruments from Physical(light).

The GWAS data for Physical(moderate) was obtained from the UK Biobank (ukb-b-4710), which conducted a survey on Physical(moderate) among 440,266 individuals. Classify the response to the question "In a typical WEEK, on how many days did you do 10 min or more of moderate physical activities like carrying light loads, cycling at a normal pace? (Do not include walking)." A total of 15 SNPs as instruments from Physical(moderate).

The GWAS data for Physical(vigorous) was obtained from the UK Biobank (ukb-b-151), which conducted a survey on Physical(vigorous) among 440,512 individuals. Classify the response to the question "In a typical WEEK, how many days did you do 10 min or more of vigorous physical activity? (These are activities that make you sweat or breathe hard such as fast cycling, aerobics, heavy lifting)." A total of 9 SNPs as instruments from Physical(vigorous).

The GWAS data for Driving was obtained from the UK Biobank (ukb-b-3793), which conducted a survey on Driving among 310,555 individuals. Classify the response to the question "In a typical DAY, how many hours do you spend driving?" A total of 6 SNPs as instruments from Driving.

The GWAS data for Outdoors(summer) was obtained from the UK Biobank (ukb-b-969), which conducted a survey on Outdoors(summer) among 419,314 individuals. Classify the response to the question "In a typical DAY in summer, how many hours do you spend outdoors?" A total of 39 SNPs as instruments from Outdoors(summer).

The GWAS data for Outdoors(winter) was obtained from the UK Biobank (ukb-b-6811), which conducted a survey on Outdoors(winter) among 364,465 individuals. Classify the response to the question "In a typical DAY in winter, how many hours do you spend outdoors? "A total of 4 SNPs as instruments from Outdoors(winter).

The GWAS data for Computer was obtained from the UK Biobank (ukb-b-4522), which conducted a survey on Computer among 360,895 individuals. Classify the response to the question "In a typical DAY, how many hours do you spend using the computer? (Do not include using a computer at work; put 0 if you do not spend any time doing it)" A total of 78 SNPs as instruments from Computer.

The GWAS data for TV was obtained from the UK Biobank (ukb-b-5192), which conducted a survey on TV among 437,887 individuals. Classify the response to the question "In a typical DAY, how many hours do you spend watching TV? (Put 0 if you do not spend any time doing it)" A total of 103 SNPs as instruments from TV.

The GWAS data for AD was obtained from the IEU OpenGWAS project (ieu-b-5067), which conducted among 488,285 individuals, adjusted for age, sex, genotyping chip, and the first 10 genetic principal components. The details have been previously elucidated (Larsson et al., 2022).

2.3 Statistical analyses

In these serial two-sample MR analyses, we employed the inverse variance weighted (IVW) random effects method as a meta-analysis of variant-specific Wald ratios for each SNP to estimate the combined

causal effect in both directions. The IVW method assumes independence and validity of IV (Smith and Ebrahim, 2003). However, it may overlook mediated effects or potential pleiotropy from other risk factors, leading to bias and violation of IV assumptions when horizontal pleiotropy exists among instrument SNPs (Bowden et al., 2015). Therefore, we additionally applied MR-Egger, weighted median, and weighted mode methods to assess robustness (Sanderson et al., 2022). The MR-Egger method assumes no association between the magnitude of pleiotropic effects and the strength of genetic-phenotype associations across all instruments (Bowden et al., 2015). Weighted mode requires a valid subset with consistent causal effects while weighted median assigns 50% weight to variables from valid instruments (Bowden et al., 2016). These supplementary analyses evaluate how alternative specifications affect MR results by considering possible pleiotropic effects. To detect heterogeneity, we used Cochran's Q statistic with significance set at $p < 0.05$. Furthermore, we assessed horizontal pleiotropy using the MR-PRSSO analysis where $p < 0.05$ indicates its presence. All statistical analyses were performed using R 3.6.0 with the TwoSampleMR package (RRID: SCR_019010) (Figure 1).

3 Results

The F-statistic for all instrumental variables exceeds 10, indicating the absence of weak instrument bias in our analysis (Supplementary Table S1). We analyzed 14 entertainment activities for their associations with AD by the IVW random effects method. The forest plot of the association between the risk of suffering from AD and each of the entertainment activity is shown in Figure 2. Figure 3 shows scatterplots of the associations of each genetic variant plotted against their association with the corresponding outcomes for each genetic variant. We found a statistically significant causal effect of time spent using computer on AD (OR 0.998; 95% CI 0.996–0.999; $p = 0.013$). Sensitivity analyses found no evidence of heterogeneity in Cochran's Q statistic ($p = 0.691$) and there was no horizontal pleiotropy effect in the MR-PRESSO analysis ($p = 0.699$). There were no significant correlations between leisure/social activities, weekly exercise, time spent driving, time spent outdoors in summer, time spent outdoors in winter, or time spent watching television with AD. Full results are provided in Supplementary Table S2. The leave–one–out sensitivity further corroborated the aforementioned conclusion (Supplementary Table S3).

4 Discussion

In summary, our two-sample MR study revealed a significant association between genetically predicted time spent using computers and the risk of AD. Our findings suggest that increased computer use is associated with a reduced risk of developing AD. However, we did not find evidence supporting the hypothesis that leisure or social activities, weekly exercise, time spent driving, time outdoors in summer, time outdoors in winter, or time spent watching television are causally related to the risk of AD.

The association between computer usage and AD is discernible, with prior studies offering insights into this relationship. Evidence suggests that computer training for individuals with AD can positively impact AD progression and enhance quality of life (Klimova et al., 2018). Additionally, meaningful computer engagement may contribute to preventing or delaying dementia (Liapis and Harding, 2017). Using computers often involves a range of cognitive activities such as information searching and problem-solving, which require active thought and brain operation, promoting neuronal connections and cognitive function stimulation. Long-term engagement in these activities may help maintain brain activity and potentially reduce the risk of AD. Computers also serve as a platform for social interaction through email, social media, etc., which can combat loneliness and improve mental health, potentially aiding in AD prevention (Chen and Schulz, 2016). Furthermore, computers offer flexible interventions that can be used by patients with limited physical capabilities.

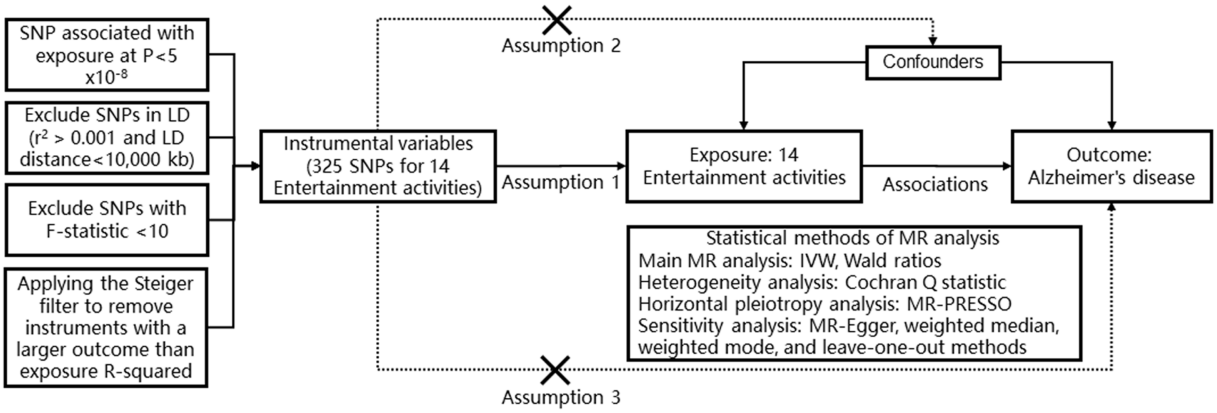

FIGURE 1
The design and flowchart of MR analysis in our study. This schematic representation highlights the research inquiry, analysis workflow, and utilized data in our study. Leveraging large-scale publicly available genome-wide association study (GWAS) summary statistics data, we conducted Mendelian randomization (MR) analysis to investigate the causal relationship between 14 entertainment activities and Alzheimer's disease. Assumption 1: Sensitivity analysis was employed to validate the robustness of our MR findings. Assumption 2: The variant is significantly associated with the exposure. The variant is not associated with any confounder of the exposure-outcome association. Assumption 3: The variant does not affect the outcome, except possibly other biological pathways (i.e., horizontal pleiotropic effect) with the exposure SNP, single nucleotide polymorphism; MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier; MR, Mendelian randomization; IVW, inverse variance weighted.

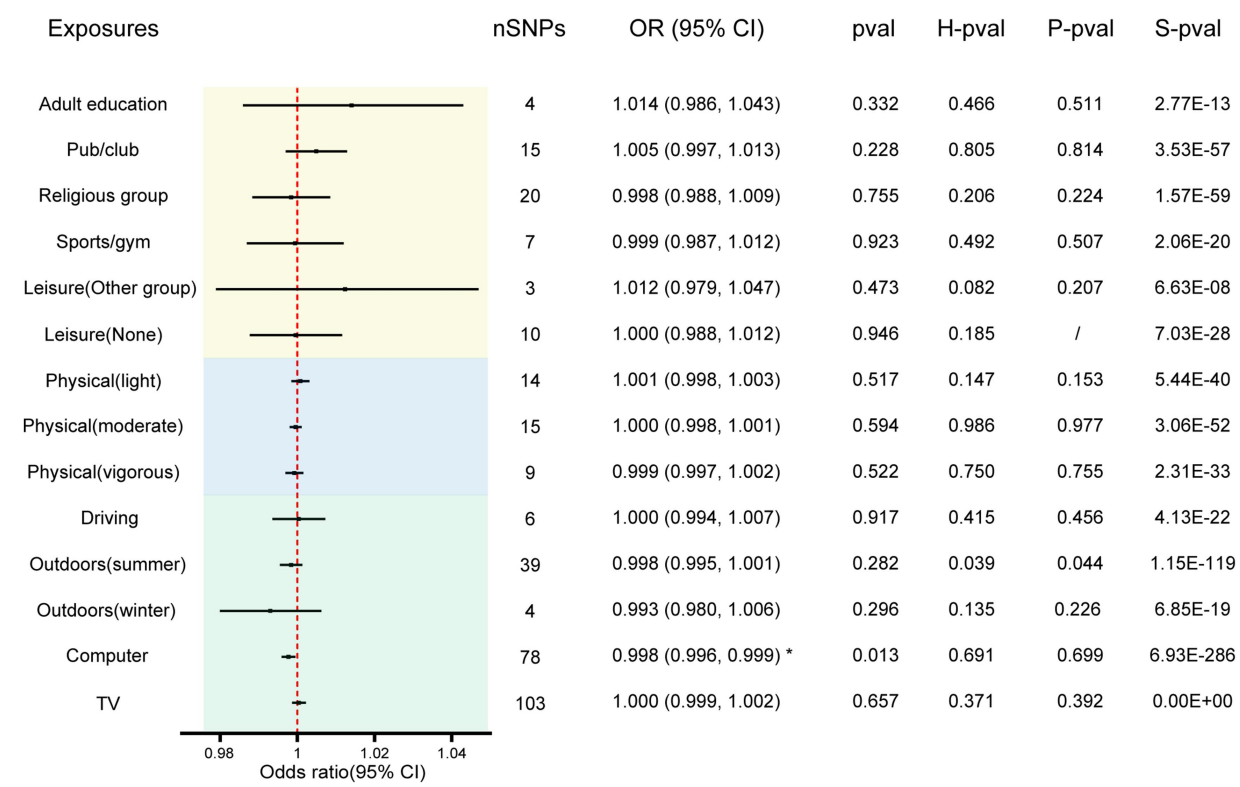

FIGURE 2
The effect of entertainment activities on AD. Results are from the IVW method of the two-sample MR analysis. * Indicates significant association with causal effect. The size of the box represents the weight of the study. SNP, single nucleotide polymorphism; OR, Odds ratios; CI, Confidence interval; H-pval, heterogeneity *p*-value; P-pval, horizontal pleiotropy *p*-value; S-pval, Steiger test *p*-value.

Additionally, computer use may be associated with factors such as education level, economic status, and type of occupation, which themselves could influence AD risk (Nguyen et al., 2016; Korologou-Linden et al., 2022). Further confirmation of computer use as a modifiable risk factor for AD will assist individuals and primary healthcare units in developing actionable strategies for AD prevention and control, offering unique advantages. However, a study indicated that overstimulation from prolonged screen time during brain development can increase the risk of neurodegenerative diseases in adulthood (Manwell et al., 2022). Therefore, it is crucial to balance the duration and manner of computer use, avoiding excessive dependence and sedentary habits. Combined with proper rest and exercise, computers can be valuable tools in our daily lives.

Our research findings also present some discrepancies with previous conclusions. While many studies have demonstrated positive effects of physical exercise, social engagement, and outdoor activities on AD, our study did not find significant correlations (Karssemeijer et al., 2017; Ciofi et al., 2022; Huuha et al., 2022; Joshi et al., 2024). For instance, higher levels of physical activity have been linked to a reduced risk of AD and may enhance cerebral blood flow, modulate amyloid beta turnover, and exert neuroprotective effects on the brain (De la Rosa et al., 2020; Huuha et al., 2022). There is also evidence suggesting that leisure and social activities can enhance cognitive health in individuals with or at risk of AD (De la Rosa et al., 2020; Joshi et al., 2024). Additionally, participating in outdoor activities can promote feelings of well-being, provide enjoyable sensory experiences, and strengthen community connections for people with AD (Ciofi et al., 2022). The inconsistency in study results may stem from the complex nature of AD as a neurological disorder, influenced by various factors that may not have been adequately considered or controlled in our study, thus impacting the accurate assessment of their impact on AD.

The study exhibits both strengths and limitations. On the positive side, it covers a broad spectrum of entertainment activity factors and boasts a large sample size. However, potential drawbacks include the long preclinical phases of AD or changes caused by AD that may have occurred before diagnosis (Dubois et al., 2016). We were limited to summary-level data rather than individual-specific data, precluding the assessment of specific genetic variants at the individual level. Furthermore, our study population consisted solely of individuals of European ancestry, and genetic structure and disease prevalence differ across ethnicities, potentially limiting the generalizability of our findings to other ethnic groups (Lake et al., 2023). Additionally, some traits in our study had a relatively small number of genetic tools (< 10 SNPs each), posing a risk of weak instrument bias that could affect study precision and reliability. Looking ahead, with a deeper understanding of AD and rapid advancements in neuroscience, epidemiology, and related fields, future studies are likely to delve further into the correlation between entertainment activities and AD. Given that MR primarily assesses associated impacts, additional high-quality studies are imperative to investigate the potential benefits of entertainment activities on AD. This research promises to deepen our understanding of AD pathogenesis and provide robust scientific evidence to inform prevention and treatment strategies for the disease.

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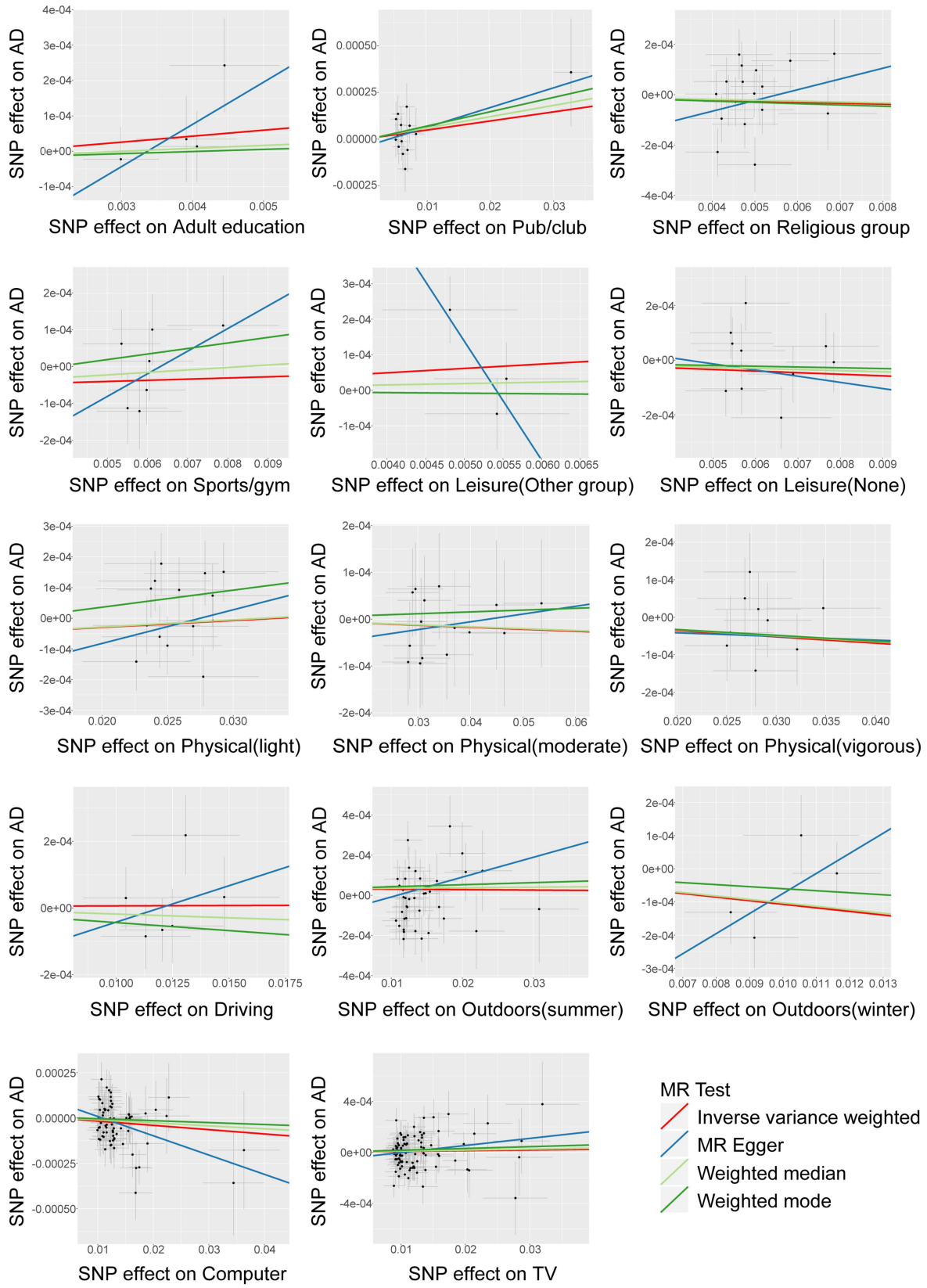

FIGURE 3
Assessment of significant causality in genetic associations between entertainment activities factors and AD. Each point indicates the associated change in trait level and the increased risk for each variant. The horizontal coordinate represents how much genetic variation is associated with exposure factors, and the vertical coordinate represents how much genetic variation is associated with disease risk. Horizontal and vertical lines through each point indicate the corresponding 95% CI for genetic association. The colored lines show the trait slope of the results obtained by applying various different MR methods.

5 Conclusion

In conclusion, the results demonstrate a potential causal relationship between time spent using a computer and AD. This finding provides important insights for AD prevention and may facilitate the development of relevant prevention strategies. Nevertheless, further interventional trials are needed to elucidate the underlying mechanisms.

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

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

Author contributions

TL: Data curation, Funding acquisition, Writing – original draft, Writing – review & editing. LW: Data curation, Writing – original draft, Formal analysis. YZ: Data curation, Writing – original draft. HL: Methodology, Supervision, Writing – review & editing. JL: Data curation, Funding acquisition, Methodology, Writing – original draft, Writing – review & editing.

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Conflict of interest

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

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2024.1419317/full#supplementary-material

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A nomogram for individualized prediction of mild cognitive impairment in patients with subjective cognitive decline during physical examinations: a cross-sectional study

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Background and objectives: To develop a nomogram for mild cognitive impairment (MCI) in patients with subjective cognitive decline (SCD) undergoing physical examinations in China.

Methods: We enrolled 370 patients undergoing physical examinations at the Medical Center of the First Hospital of Jilin University, Jilin Province, China, from October 2022 to March 2023. Of the participants, 256 were placed in the SCD group, and 74 were placed in the MCI group. The population was randomly divided into a training set and a validation set at a 7:3 ratio. A least absolute shrinkage and selection operator (LASSO) regression model was applied to optimize feature selection for the model. Multivariable logistic regression analysis was applied to construct a predictive model. The performance and clinical utility of the nomogram were determined using Harrell's concordance index, calibration curves, and decision curve analysis (DCA).

Results: Cognitive reserve (CR), age, and a family history of hypertension were associated with the occurrence of MCI. The predictive nomogram showed satisfactory performance, with a concordance index of 0.755 (95% CI: 0.681–0.830) in internal verification. The Hosmer–Lemeshow test results suggested that the model exhibited good fit ($p = 0.824$). In addition, DCA demonstrated that the predictive nomogram had a good clinical net benefit.

Discussion: We developed a simple nomogram that could help secondary preventive health care workers to identify elderly individuals with SCD at high risk of MCI during physical examinations to enable early intervention.

KEYWORDS

mild cognitive impairment, subjective cognitive decline, predictive nomogram, cognitive reserve, early detection

1 Background

With population aging, China's elderly population will exceed 300 million, accounting for more than 20% of the total population. This represents a stage of moderate population aging; China is expected to enter a stage of severe population aging by approximately 2035 (Mao et al., 2020). Alzheimer's disease (AD) is the most common type of dementia in the elderly population and is characterized by progressive, irreversible cognitive decline. In China, 15.07 million individuals aged 60 years and over have dementia; it has become the country with the most AD patients in the world, and the number of AD patients is only increasing (Ren et al., 2022). AD is a major threat to the health of China's elderly population and the sustainable development of China; thus, identification, early diagnosis and treatment of AD are urgently needed. However, drug trials for the prevention and treatment of specific pathophysiological processes of AD have struggled to escape a cycle of failure (Huang et al., 2020). Although the specific causes of failure are extremely complex, a key factor is missing the optimal time for treatment; indeed, irreversible damage to brain tissue has already occurred in patients with mild to moderate AD dementia (Breijyeh and Karaman, 2020). This merits a change in perspective, as prevention may be more important than treatment. Specifically, the focus of dementia research should shift from tertiary prevention ("treat those who are sick") to secondary prevention ("preventing one case is better than developing ten cures"). Given the current limited understanding of AD, real advances in managing AD may lie in early recognition and intervention (Barnett et al., 2014; Fan and Wang, 2020).

Mild cognitive impairment (MCI) is a prodromal stage of AD, mainly manifesting as varying degrees of mild decline in cognitive functions such as memory, attention, language and visuospatial skills. The annual conversion rate of MCI to AD has reached 10–15%; thus, MCI represents a key stage for the early detection and diagnosis of dementia. More attention to MCI patients may greatly facilitate the secondary prevention of AD. Approximately 12.2% of the elderly population aged 55 years and over in China suffers from MCI, resulting in a high disability rate that is seriously threatening the health of elderly individuals and imposing heavy burdens on family and society. Subjective cognitive decline (SCD), which precedes mild cognitive impairment, is an initial stage in the development of Alzheimer's disease and is considered the preclinical stage of AD. It is characterized by self-reported decreased memory despite normal cognitive performance. This phenomenon is very common in elderly people. Studies on related markers have also found that the SCD population exhibits similar physiological changes to the AD population, further suggesting that the SCD population is at high risk of AD; SCD has become an international research hotspot for AD, setting off a wave of secondary prevention trials for AD (Fan and Wang, 2020; Pichet Binette et al., 2021). According to a longitudinal follow-up study (Lista et al., 2015), approximately 6.6% of patients with SCD progress to MCI each year, while approximately 2.3% of patients with SCD progress even further to AD. Therefore, in clinical practice, early identification of SCD and MCI populations and effective differentiation of the two during physical examinations are important for secondary prevention of AD. SCD patients misdiagnosed with MCI may receive redundant antidementia therapy, which has small benefits and risks of adverse drug reactions and higher costs. There are also potentially harmful consequences of misdiagnosis with MCI for patients and their families, such as discrimination, stigma and overmedication, leading to increased anxiety or stress and, moreover, cognitive deterioration. In contrast, patients with MCI who are misdiagnosed with SCD are at risk of not receiving appropriate dementia care due to underdiagnosis, delaying treatment of the condition. Therefore, it is highly important to distinguish SCD and MCI in health examinations, determine simple factors for identifying SCD and MCI, and accurately diagnose and administer interventions to MCI patients in a timely manner to reduce the risk of future disease progression.

Millions of people worldwide suffer from MCI, and the diagnosis still relies mainly on highly skilled neurologists, with diagnostic criteria including patients' medical history, objective cognitive performance, performance on neuropsychological tests such as the Mini-Mental State Examination (MMSE), use of structural MRI to diagnose MCI, or invasive sampling of cerebrospinal fluid. Clinicopathological studies have shown that clinicians have a diagnostic sensitivity ranging from 70.9 to 87.3% and specificity ranging from 44.3 to 70.8%. While MRI data have revealed that MCI produces characteristic brain changes, such as hippocampal and parietal lobe atrophy, these features are thought to lack specificity for MCI. Given this relatively imprecise diagnostic prospect, the invasiveness of CSF sampling and PET scans for diagnosis, and the lack of clinicians specializing in the diagnosis of MCI among secondary prevention personnel in developing countries, simple and convenient diagnostic models are needed that can derive high-precision predictions from practice-wide data. This study provides a new method for determining diagnostic models of SCD and MCI and reports a series of features that can distinguish SCD and MCI based on easily obtained data. These findings are expected to help to screen SCD patients to identify those at high risk of MCI in secondary care settings with few medical personnel and to provide a useful tool for the early diagnosis and treatment of MCI. Finally, the nomogram is used to transform the complex regression equation into a simple and visual graph, so that the results of the prediction model are more readable and have higher use value. A nomogram is a graphical tool that integrates multiple prognostic factors into a single model to predict the probability of a clinical event, such as the development of a disease. It provides an individualized risk assessment based on patient-specific variables, making it a valuable resource for personalized medicine.

2 Methods

2.1 Study design and participants

This was a cross-sectional study conducted in Northeast China. The China Alzheimer's Disease Report (2021) identified Jilin Province as the province with the highest incidence of dementia in this region. The study subjects were recruited from the Physical Examination Center of the First Hospital of Jilin University in Northeast China from October 2022 to March 2023. Middle-aged and elderly individuals (aged between 50 and 75 years old) arriving for physical examinations were scheduled to undergo brain computed tomography

Abbreviations: SCD, Subjective cognitive decline; MCI, Mild cognitive impairment; AD, Alzheimer's disease; CR, Cognitive reserve; LASSO, Least absolute shrinkage and selection operator.

(CT) or magnetic resonance imaging (MRI) scans. Included individuals had no previous diagnosis of dementia, normal or corrected-to-normal vision and hearing, and were able to communicate normally and participate in the complete neuropsychological tests and imaging examination needed to diagnose SCD and MCI. All subjects provided written informed consent upon entry into the study, and the study was approved by local institutional review boards at all participating sites and registered in the Chinese Clinical Registry (ChiCTR2200055112).

In this study, 370 physical examination subjects were screened, and all subjects were evaluated in terms of neuropsychological criteria. A unified scale was adopted according to the requirements, standardized language was used in the evaluation, and patients with visual, hearing or writing disabilities who could not complete the scale evaluation were excluded (Figure 1). Two neurologists diagnosed those who met the clinical diagnostic criteria with SCD or MCI (Supplementary Table S1).

2.2 Data collection

Patients or their close relatives completed a semistructured questionnaire that assessed clinical and cognitive functioning. The interview was conducted by a trained neuropsychological

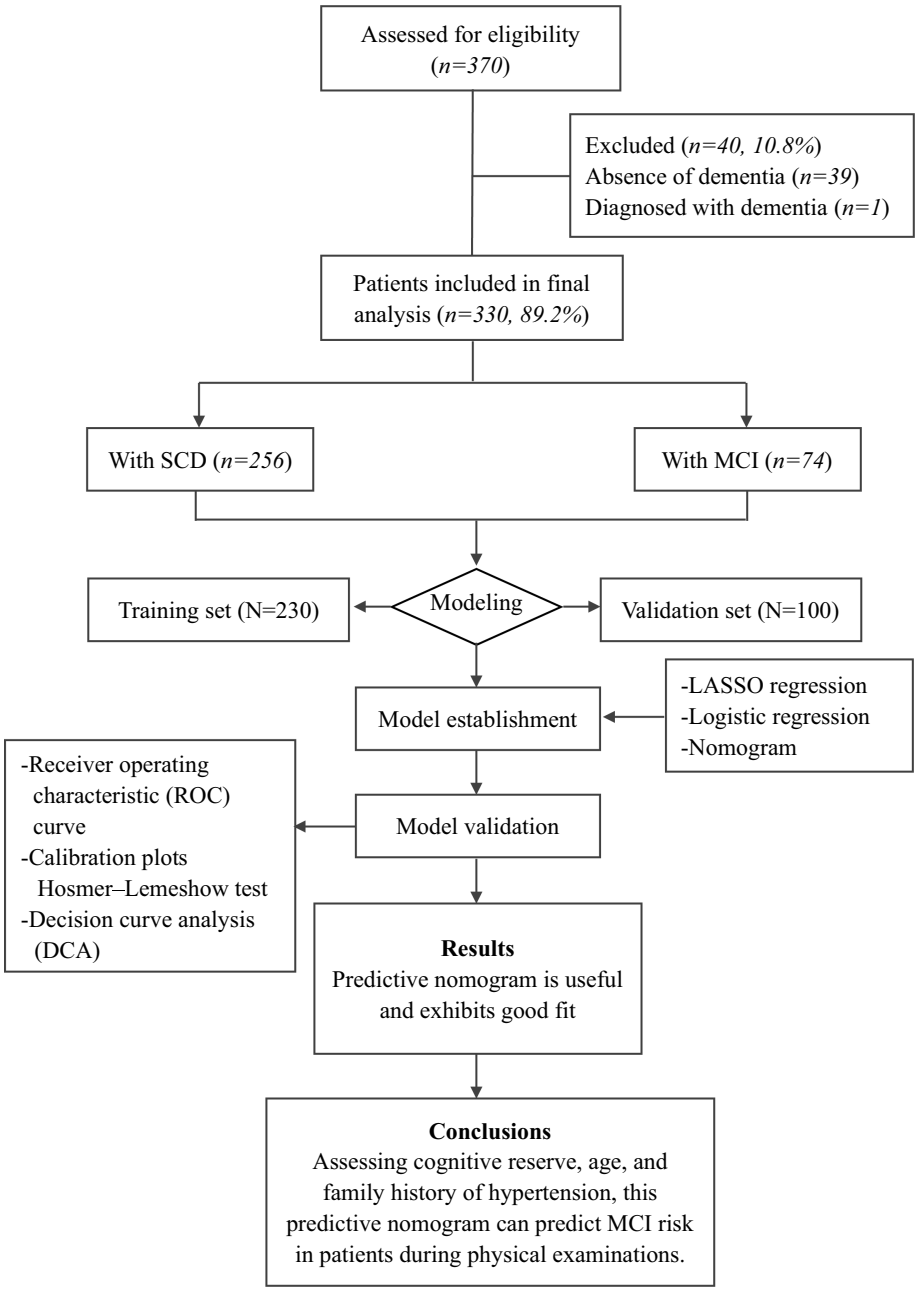

FIGURE 1
Flowchart of patient enrollment and procedures.

evaluator and lasted approximately 120 min. The sociodemographic information collected included age, sex, ethnicity, education level, occupation, family history, and lifestyle factors.

Variables assessed in the physical examination included muscle strength, thigh circumference, blood pressure, heart rate, grip strength, pace, gait, balance, etc. Patients' medical history and family history were examined for stroke, diabetes, coronary heart disease, hypertension, hyperlipidemia, cancer, psychiatric disorders, etc.

Neuropsychological tests were used to assess participants' overall cognitive performance, performance in specific cognitive domains, psychobehavioral symptoms and mental health. These tests included the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Activities of Daily Living (ADL) scale, Functional Activities Questionnaire (FAQ), Auditory Verbal Learning Test (AVLT), Shape Alignment Test–Parts A and B (STT-A&B), Memory and Executive Screening (MES), Animal Naming Test (ANT), Clinical Dementia Rating (CDR) scale, Hamilton Depression Scale (HAMD), Hamilton Anxiety Scale (HAMA), and Neuropsychiatric Inventory (NPI). Finally, the results were synthesized to categorize cognitive function according to results on the Clinical Dementia Rating (CDR) scale.

Cognitive reserve (CR): The Cognitive Reserve Scale (CRS) is a new CR assessment that evaluates a person's participation in cognitively stimulating activities throughout their lifetime (León et al., 2014). The Chinese version of the CRS is a 24-item self-report questionnaire. It is divided into four categories: daily activities, training information, hobbies, and social life. Items are rated on a 5-point Likert scale from 0 (never) to 4 (three or more times per week). It contains three life stages: youth (18–35 years), middle age (36–64 years) and old age (≥65 years). Participants respond to items on the appropriate life-stage subscale for their age. The total score ranges from 0 to 96, with higher scores indicating more frequent participation in activities and higher CR in each life stage. Cognitive reserve scores were calculated at the different life stages (youth, middle age, and old age), and the total CRS score was equal to the score on the stage completed.

2.3 Statistical analysis

R 4.0.4 software was used for statistical analysis. The qualitative data are presented as n (%), and the χ^2 test was used for group comparisons. The quantitative data are presented as $\bar{\chi} \pm s$, and the independent-sample *t* test was used for group comparisons. Quantitative data that did not exhibit a normal distribution are described as the median (IQR), and the Mann–Whitney U test was used for group comparisons. The "glmnet" software package was used to establish a LASSO logistic regression model to explore the distinguishing factors of SCD and MCI, and the cross-validation method was used to harmonize the selection of parameter λ. The Bayesian information criterion (BIC) was used to evaluate the goodness-of-fit of the model, and the area under the curve (AUC), Brier score and calibration curve were used to evaluate the discrimination and accuracy of the predictive model. GraphPad Prism software was used to generate a forest plot of the LASSO logistic regression prediction model. The rms package was used to plot the nomogram of the LASSO logistic regression prediction model and the calibration curve of the model. In a two-tailed test, the alpha level was set at 0.05.

3 Results

3.1 Basic information and single factor analysis

Among the 330 subjects, the mean age was 61.73 ± 7.88 years, 196 were female (59.39%), 319 were married (96.7%), 256 had SCD (77.6%), and 74 had MCI (22.4%). The demographic and clinical characteristics according to group are shown in Tables 1, 2.

3.2 Multifactor analysis and variable selection

The data were randomly split into a training set and a validation set in a 7:3 ratio. Factors identified as significant ($p < 0.10$) in the univariate analysis were included as independent variables, and progression to MCI was included as the dependent variable. The LASSO regression and logistic regression models were established using the testing set. The screening of variables according to lambda values from the LASSO logistic regression model is shown in Figure 2. Figure 2A shows the corresponding curve between log(λ) and the number of independent variables; the ordinate shows the mean-square error (MSE) of the model, the lower abscissa shows log(λ), and the upper abscissa shows the number of independent variables in the model with nonzero coefficients corresponding to different log(λ) values. In Figure 2B, the left dashed line represents the MSE minimum optimal harmonic coefficient (λ.min), and the right dashed line represents the MSE within one standard error of the optimal λ (λ.1se). Figure 2B shows the relationship between log(λ) and the LASSO regression coefficient. As λ increased, the degree of compression of the estimated coefficients of each independent variable of the model increased, the coefficient of the independent variable with little impact on the dependent variable was compressed to 0, and the number of independent variables decreased. In this study, λ.1se was selected as the optimal model, and the independent variables included in the logistic regression model were cognitive reserve, age, sex, lalopathy, gait change, thigh circumference, diabetes, alcohol consumption, family history of hypertension, and family history of cancer.

3.3 Model construction

To develop the diagnostic model of MCI, the above 10 variables identified by univariate analysis and LASSO regression were included in the multivariate logistic regression analysis, and the results of the logistic regression model showed that cognitive reserve, age, and family history of hypertension were the factors that distinguished MCI from SCD. The LASSO logistic regression forest plot (Figure 3) visually displays the effects of relevant factors (ORs and 95% CIs). The predictive model had an AUC of 0.755 (95% CI: 0.681–0.830); the internal validation in the validation set yielded a value of 0.711 (95% CI: 0.563–0.859) (Figure 4). A nomogram was constructed to provide a convenient personalized tool for predicting the probability of MCI and visually display the prediction score for MCI (Figure 5). The variables included in the nomogram—age, cognitive reserve (CR) score, and family history of hypertension—were initially identified by univariate analysis and then filtered by LASSO regression and logistic regression analysis, which are considered superior to selecting predictors from univariate analysis. The variables

TABLE 1 Demographic characteristics of study participants.

Characteristic		All	SCD	MCI	*p* value
		(*n* = 330)	No (*n* = 256)	Yes (*n* = 74)	
Age (years), mean ± SD		61.73 ± 7.88	60.30 ± 7.53	66.68 ± 7.05	<0.001
	<65 years old (%)	218 (66.1)	190 (74.2)	28 (37.8)	<0.001
	≥65 years old (%)	112 (33.9)	66 (25.8)	46 (62.2)	
Ethnicity					0.393
	Han Chinese	311 (94.2)	243 (94.9)	68 (91.9)	
	Other	19 (5.8)	13 (5.1)	6 (8.1)	
Male sex, %		134 (40.6)	97 (37.9)	37 (50.0)	0.080
Education level, %					0.023
	Lower education	85 (25.5)	58 (22.7)	27 (36.5)	
	Higher education	245 (74.2)	198 (77.3)	47 (63.5)	
Occupation, %					0.052
	Physical	70 (21.2)	48 (18.8)	22 (29.7)	
	Intellectual	260 (78.8)	208 (81.3)	52 (70.3)	
Marital status, %					0.019
	Married	319 (96.7)	251 (98.0)	68 (91.9)	
	Other	11 (3.3)	5 (2.0)	6 (8.1)	
History of solitude, %					0.263
	No	298 (90.3)	234 (91.4)	64 (86.5)	
	Yes	32 (9.7)	22 (8.6)	10 (13.5)	
Lifestyle factors					
	Smoking	58 (17.6)	41 (16.0)	17 (23.0)	0.224
	Drinking alcohol	93 (28.2)	66 (25.8)	27 (36.5)	0.079
	Drinking tea/coffee	169 (51.2)	131 (51.2)	38 (51.4)	1.000
Exercise habit, %					0.372
	No	54 (16.4)	39 (15.2)	15 (20.3)	
	Yes	276 (83.6)	217 (84.8)	59 (79.7)	
Social activities, %					
	Low	115 (34.8)	82 (32.0)	33 (44.6)	0.139
	Medium	152 (46.1)	123 (48.0)	29 (39.2)	
	High	63 (19.1)	51 (19.9)	12 (16.2)	

selected for the nomogram were chosen based on their significant associations with mild cognitive impairment (MCI) as identified through univariate and multivariate analyses. Age is a well-known risk factor for cognitive decline. The CR score reflects an individual's cognitive reserve, which is crucial for buffering against cognitive deterioration. A family history of hypertension has been linked to an risk of cognitive impairment due to its impact on vascular health.

3.4 Model evaluation

The proposed model was well calibrated (Figure 6). The Hosmer–Lemeshow test yielded a nonsignificant *p* value of 0.824 ($p > 0.05$, suggesting that the model exhibited good fit to the data), thereby suggesting that there was no statistical departure from a perfect fit between the predicted and observed values.

To assess its clinical usefulness, decision curve analysis (DCA) was also performed. The decision curve based on the nomogram in this study showed that the threshold probability of MCI in SCD patients was 5–50% (Figure 7), and use of this nomogram to predict MCI provided significantly more benefit than either the treat-all scheme or the treat-none scheme. We further used the clinical impact curves to predict the risk stratification of 1,000 people (Figure 8). By comparing the costs and benefits of different treatment options, secondary care doctors select a personalized treatment plan according to the patient's specific condition.

4 Discussion

In the present study, a nomogram was constructed to predict the risk of MCI among SCD patients. This nomogram incorporated 3

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TABLE 2 Clinical characteristics and performance of the participants.

Characteristic		All	SCD	MCI	*p* value
		(*n* = 330)	No (*n* = 256)	Yes (*n* = 74)	
Cognitive reserve (score), mean ± SD		42.39 ± 11.86	43.47 ± 11.26	38.65 ± 13.14	0.002
Step test, %					0.020
	Normal	212 (64.2)	173 (67.6)	39 (52.7)	
	Abnormal	118 (35.8)	83 (32.4)	35 (47.3)	
Five standing tests, %					0.010
	Normal	245 (74.2)	199 (77.7)	46 (62.2)	
	Abnormal	85 (25.8)	57 (22.3)	28 (37.8)	
Grip strength					0.010
	Strong	302 (91.5)	240 (93.8)	62 (83.8)	
	Weak	28 (8.5)	16 (6.3)	12 (16.2)	
Anthropometric measurements, mean ± SD					
	Head circumference (cm)	55.17 ± 2.44	55.23 ± 2.39	54.95 ± 2.61	0.373
	Height (cm)	164.27 ± 7.56	164.03 ± 7.42	165.09 ± 8.01	0.291
	Weight (kg)	66.42 ± 11.48	66.27 ± 11.40	66.93 ± 11.81	0.662
	Waistline (cm)	84.41 ± 11.17	83.81 ± 11.26	86.47 ± 10.66	0.072
	Hipline (cm)	99.67 ± 7.41	99.34 ± 7.44	100.80 ± 7.22	0.136
	Arm circumference (cm)	29.05 ± 3.84	28.95 ± 3.85	29.41 ± 3.82	0.364
	Thigh circumference (cm)	50.00 ± 6.87	49.67 ± 6.44	51.19 ± 8.14	0.094
	Calf circumference (cm)	35.64 ± 3.78	35.67 ± 3.58	35.53 ± 4.42	0.777
Memory loss					0.001
	No	36 (10.9)	28 (10.9)	8 (10.8)	
	Yes	294 (89.1)	228 (89.1)	66 (89.2)	
Decreased concentration					0.125
	No	218 (66.1)	175 (68.4)	43 (58.1)	
	Yes	112 (33.9)	81 (31.6)	31 (41.9)	
Executive dysfunction					0.115
	No	308 (93.3)	242 (94.5)	66 (89.2)	
	Yes	22 (6.7)	14 (5.5)	8 (10.8)	
Lalopathy					0.007
	No	315 (95.5)	249 (97.3)	66 (89.2)	
	Yes	15 (4.5)	7 (2.7)	8 (10.8)	
Disorientation					0.019
	No	316 (95.8)	249 (97.3)	67 (90.5)	
	Yes	14 (4.2)	7 (2.7)	7 (9.5)	
Visual impairment					1.000
	No	253 (76.7)	196 (76.6)	57 (77.0)	
	Yes	77 (23.3)	60 (23.4)	17 (23.0)	
Hearing impairment					0.625
	No	262 (79.4)	205 (80.1)	57 (77.0)	
	Yes	68 (20.6)	51 (19.9)	17 (23.0)	
Dysphagia					1.000
	No	320 (97.0)	248 (96.9)	72 (97.3)	

(Continued)

TABLE 2 (Continued)

Characteristic		All	SCD	MCI	*p* value
		(*n* = 330)	No (*n* = 256)	Yes (*n* = 74)	
	Yes	10 (3.0)	8 (3.1)	2 (2.7)	
Gait change					0.001
	No	295 (89.4)	237 (92.6)	58 (78.4)	
	Yes	35 (10.6)	19 (7.4)	16 (21.6)	
Sleep disturbances					0.757
	No	241 (73.0)	188 (73.4)	53 (71.6)	
	Yes	89 (27.0)	68 (26.6)	21 (28.4)	
Present illness					
	Stroke	21 (6.4)	14 (5.5)	7 (9.5)	0.276
	Hypertension	101 (30.6)	74 (28.9)	27 (36.5)	0.252
	Diabetes	52 (15.8)	32 (12.5)	20 (27.0)	0.004
	Dyslipidemia	118 (35.8)	91 (35.5)	27 (36.5)	0.891
	CHD	58 (17.6)	38 (14.8)	20 (27.0)	0.023
Number of comorbidities, %					0.630
	0	132 (40.0)	100 (39.1)	32 (43.2)	
	1	92 (27.9)	74 (28.9)	18 (24.3)	
	2	54 (16.4)	44 (17.2)	10 (13.5)	
	≥3	52 (15.8)	38 (14.8)	14 (18.9)	
Family history, %					
	Dementia	49 (14.8)	38 (14.8)	11 (14.9)	1.000
	Stroke	77 (23.3)	59 (23.0)	18 (24.3)	0.876
	Hypertension	143 (43.3)	122 (47.7)	21 (28.4)	0.003
	Diabetes	88 (26.7)	69 (27.0)	19 (25.7)	0.882
	Dyslipidemia	55 (16.7)	47 (18.4)	8 (10.8)	0.157
	CHD	89 (27.0)	77 (30.1)	12 (16.2)	0.025
	Cancer	64 (19.4)	59 (23.0)	5 (6.8)	0.002

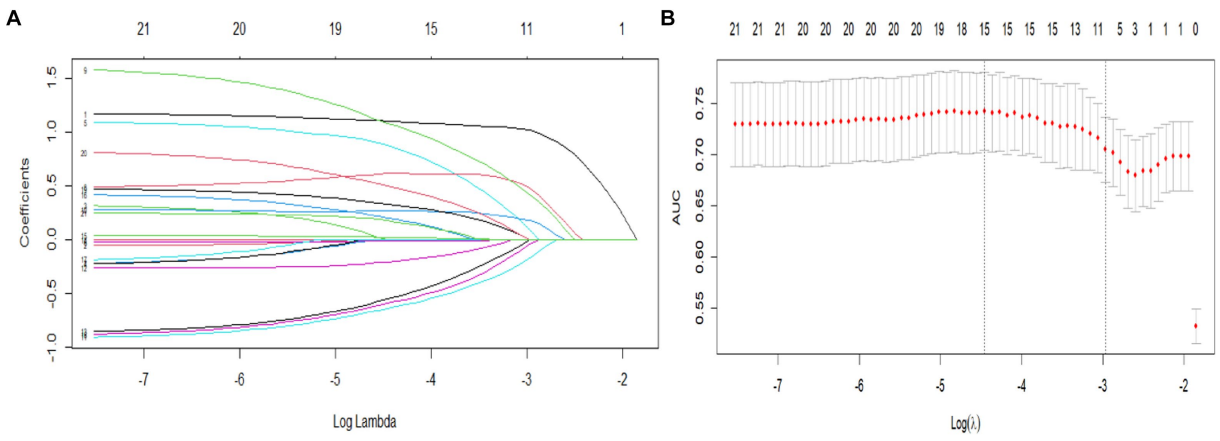

FIGURE 2
Predictor selection using LASSO regression analysis with 10-fold cross-validation. **(A)** LASSO coefficients from the regression analysis. The tuning parameter (lambda) was used to select the AUC. **(B)** Coefficient profile plot created against the log (lambda) sequence. In the present study, predictor selection was performed according to the 1-SE criteria (right dotted line), and 10 nonzero coefficients were selected.

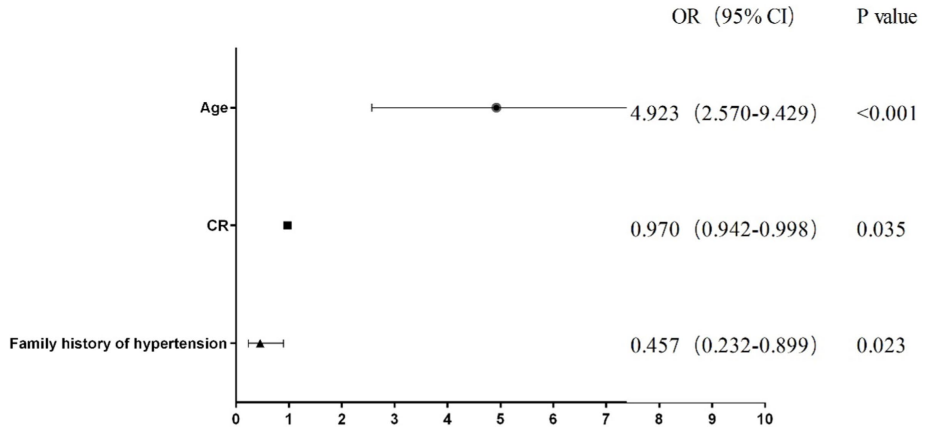

FIGURE 3
Forest plot of the LASSO logistic regression model.

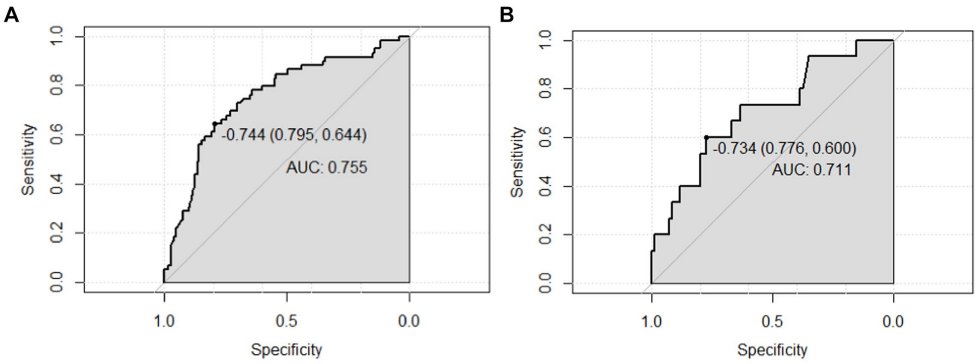

FIGURE 4
AUC values (representing the discriminatory ability) of the model. **(A)** AUC of the training set, and **(B)** AUC of the validation set. AUC, area under the curve.

variables, namely, age, CR score, and family history of hypertension. The nomogram showed good discriminatory ability, calibration, and clinical usefulness.

Mild cognitive impairment (MCI) is an intermediate state between the cognitive decline associated with healthy aging and dementia, and approximately 12 to 18% of people aged 60 or older are living with MCI (Davis et al., 2018; Xue et al., 2018; Radler et al., 2020). This stage is crucial as approximately one-third of people living with MCI due to Alzheimer's disease progress to dementia within 5 years. Understanding the prevalence and progression of MCI is essential for developing effective preventive strategies and interventions. Conversely, there is a 53% chance of reversal of MCI to normal cognition after implementing a reasonable intervention (Wood, 2016). Thus, MCI is a high-risk, unstable stage and is the best "intervention window" for AD prevention and treatment. Regardless of country or region, during the physical examination of elderly patients, the possibility of MCI should be routinely considered; when patients complain of memory impairment and other cognitive decline, early identification of MCI and risk prediction is particularly important. However, elderly individuals in China lack health awareness of dementia prevention, and there is a lack of professional health care hospitals and routine primary care examinations in communities. However, the diagnosis of MCI at large medical institutions is very rigorous and requires neuropsychological and imaging data as well as genetic testing. Most of the available prediction models are based on cognitive scale scores and/or neuroimaging data, which are often not feasible to apply in the community or other health care settings and, to some extent, rely on professional use. It is still necessary to develop an effective tool to screen for mild cognitive impairment that also considers individual differences. A potential correlation between cognitive reserve and cognitive performance was found in the early stage of this study, and the various cognitive scores of patients were combined into a quantitative index of cognitive reserve, which addressed such individual differences to a certain extent.

With regard to the risks of MCI, a variety of cognitive habits (Sha et al., 2022), such as personal affairs management (Jiang and Xu, 2014; de Souto Barreto et al., 2018), learning and training (Tarumi et al., 2019; De Wit et al., 2021), and hobbies and social activities (Su et al., 2017; Wang et al., 2020; Zhaoyang et al., 2021), have been explored, but current models for predicting the risk of MCI do not integrate these variables. In addition, several community-based

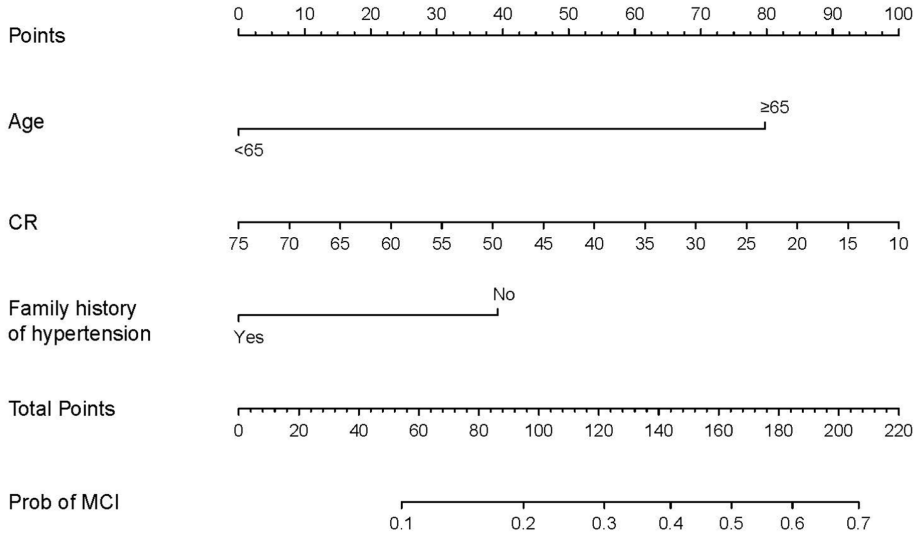

FIGURE 5
Predictive nomogram for MCI and its algorithm. First, a point was determined for each variable of an SCD patient on the uppermost rule; then, all scores were summed, and the total number of points was calculated. Finally, the corresponding predicted risk of MCI was determined on the lowest rule.

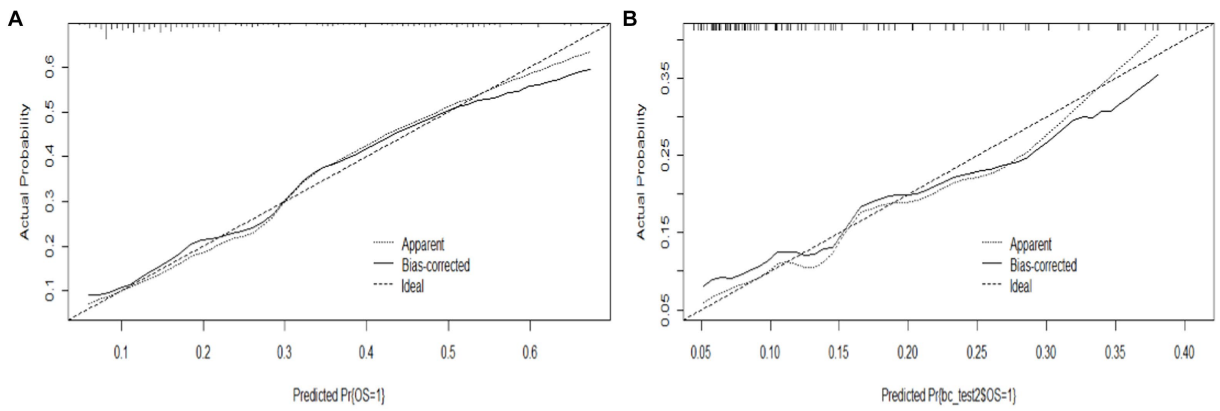

FIGURE 6
Calibration curve of the model. **(A)** Calibration curve of the training set, and **(B)** calibration curve of the validation set.

population-based models for predicting MCI have been developed that can improve the diagnosis of MCI (Arevalo-Rodriguez et al., 2021; Lu et al., 2021; McCleery et al., 2021). However, the identification of MCI in these populations is mostly based on the overall cognitive scale score (i.e., classification, not a clinical diagnosis), because most of these classifications only use the overall cognitive scale score, and few use the new standard combined with a separate score on a specific cognitive domain, which – from the perspective of clinical diagnosis – lacks a certain degree of credibility. According to the recent diagnostic criteria for SCD and MCI, it is necessary to conduct separate investigations of various cognitive domains (such as memory, executive function, and language) to assist with clinical diagnosis. In addition, we found few studies that developed models to distinguish between SCD and MCI risks. In the current study, a nomogram for the diagnosis of MCI in SCD patients was constructed based on 3 variables. The variables included in the nomogram were initially identified by univariate analysis and then filtered by LASSO regression and logistics regression analysis, which are considered superior to selecting predictors from univariate analysis (Balachandran et al., 2015). In addition, we assessed the clinical importance of these predictors. With regard to cognitive reserve, a review suggested that the cognitive reserve scale used in the present study is an appropriate tool for assessing the cognitive reserve of the population (Kartschmit et al., 2019), based on a longitudinal assessment considering the frequency of engaging in brain stimulation activities over a lifetime. In terms of sociodemographic characteristics, the cognitive reserve score is not affected by sex, and the possible effect of age is corrected by the computation of the average cognitive reserve score. Therefore, age was controlled for and did not affect cognitive reserve scores, so the results were not biased. In terms of supporting evidence, cognitive reserve refers to the ability of individuals to adaptively use neural networks to compensate for brain damage, which can buffer the

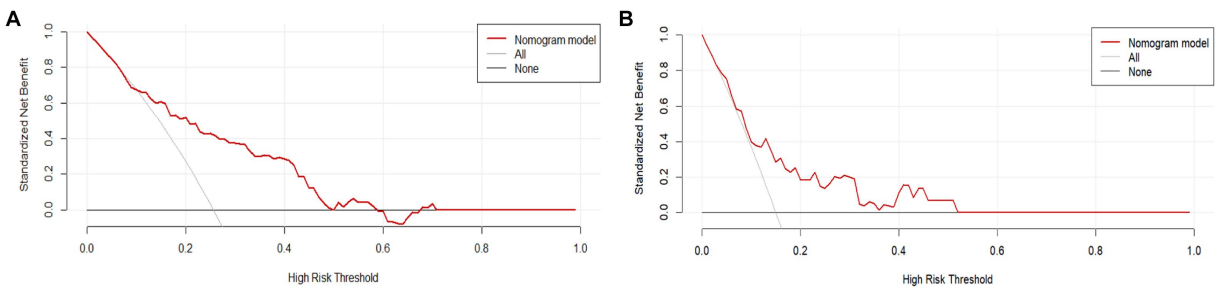

FIGURE 7
DCA of the nomogram. The solid red line represents the nomogram performance. **(A)** DCA of the training set, and **(B)** DCA of the validation set. DCA, Decision curve analysis.

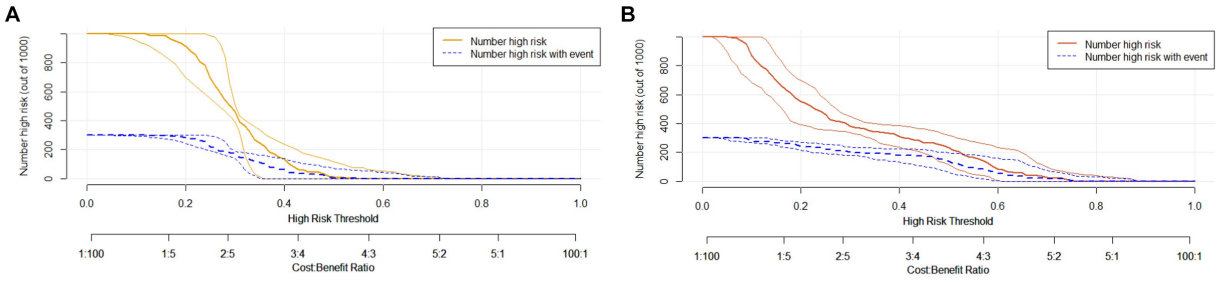

FIGURE 8
Clinical impact curve of the complex model. Curve interpretation: the yellow **(A)** and red curves **(B)** indicate the number of people classified as positive (high risk) by the simple model **(A)** and the complex model **(B)** at each threshold probability; the blue curve [(number high) risk with outcome] is the number of true positives for each probability threshold.

negative effect of brain pathology in terms of clinical manifestations, promote the successful response to brain pathology, and ensure the optimization of clinical manifestations or behavioral achievements. The results of this study indicate that the level of cognitive reserve is a protective factor against mild cognitive impairment, and the higher the level of cognitive reserve was, the lower the incidence of mild cognitive impairment.

Regarding age, it has been reported that the incidence of MCI increases with age (Overton et al., 2019; Gaugler et al., 2022). Patients with a family history of hypertension have a low risk of cognitive impairment. Cognitive impairment is often associated with hypertension, but the impact of a family history of hypertension on patients' cognitive function is modifiable (Qin et al., 2021). This phenomenon may be related to rumination in elderly individuals. Among individuals with a family member with hypertension, the development of a positive perspective is an important determinant of the impact of active rumination on hypertension risk, preventing individuals from suffering from hypertension and cognitive impairment in the future. Family history may be the factor that promotes individuals to actively reflect and re-examine their cognitive function. Such participants may pay more attention to lifestyle factors to reduce the influence of genetic factors on cognitive function, but the cognitive mechanisms underlying the heritability of cognitive dysfunction have yet to be elucidated.

These 3 predictors are easy to obtain clinically, the nomogram had good discriminative ability and calibration, and the DCA results indicate its clinical usefulness. Since cognitive reserve is not yet fully included in public screenings and health awareness, cognitive reserve education is useful for structuring and quantifying patients' cognitive habits. Therefore, this free nomogram may help community health care institutions and large medical institutions to screen for mild cognitive impairment in patients.

There are some limitations of this study. First, the participants all voluntarily scheduled physical examinations at regional centers in China, and there were regional differences in the prevalence of mild cognitive impairment. Future studies could include external datasets and/or data from multiple centers to verify the results of this study. Second, the selection of predictors was not comprehensive because some indicators are used to diagnose diseases. To avoid diagnostic evaluation bias, this study did not consider biochemical indicators (levels of amyloid, tau protein, etc.), neuroimaging indicators related to MCI, or common MCI screening scales (such as the Montreal Cognitive Assessment). In future studies, more comprehensive factors need to be included to improve prediction accuracy. Second, a classification standard was not identified for the cognitive reserve variable, which would affect the convenience of using the nomogram. Therefore, future research should combine cognitive function and cognitive reserve assessments, which may be more ideal for the identification of MCI, and seek the optimal combination of factors in models to predict MCI risk. Despite these limitations, the study is the first to develop a nomogram based on cognitive reserve to predict the risk of MCI in SCD patients.

5 Conclusion

In summary, this study developed a simple nomogram that could help secondary preventive health care workers to identify elderly individuals with SCD at high risk of MCI during physical examinations to enable early intervention. By using this effective tool to screen for MCI in older patients during physical examinations or in the community to promote the early detection of MCI, interventions can be used to prevent MCI and dementia in patients who may have SCD, reducing patient stigma, and optimize medical resource allocation and clinical decision-making. Health management interventions and preventive care for young SCD patients with high cognitive reserves should be improved to inform them of expected future quality of life and reduce the risk of future progression to MCI.

Data availability statement

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

Ethics statement

The studies involving humans were approved by the Ethics Committee of School of Nursing, Jilin 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

TZ: Conceptualization, Data curation, Formal analysis, Investigation, Software, Writing – original draft, Writing – review & editing. LD: Investigation, Writing – original draft, Writing – review & editing. PL: Writing – original draft, Writing – review & editing, Investigation. KH: Writing – original draft, Writing – review & editing, Investigation. YW: Data curation, Writing – original draft, Writing – review & editing, Resources. LC: Conceptualization, Resources, Supervision, Writing – original draft, Writing – review & editing.

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Conflict of interest

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

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2024.1443309/full#supplementary-material

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Time trends in Alzheimer's disease mortality attributable to metabolic risks and smoking in China from 1990 to 2019: an age-period-cohort analysis

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Background: With the increase in the aging population worldwide, Alzheimer's disease has become a rapidly increasing public health concern. In the Global Burden of Disease Study 2019, there are three risk factors judged to have evidence for a causal link to Alzheimer's disease and other dementias: smoking, high body-mass index (HBMI), and high fasting plasma glucose (HFPG).

Objective: This study aimed to analyze trends in AD mortality and the relevant burden across China from 1990 to 2019, as well as their correlation with age, period, and birth cohort.

Methods: The data were extracted from the GBD 2019. Trends in AD mortality attributable to metabolic risks (HFPG and HBMI) and smoking were analyzed using Joinpoint regression. The age-period-cohort (APC) model was used to evaluate cohort and period effects.

Results: From 1990 to 2019, the overall age-standardized mortality rate of AD increased, especially in women. There was an increase in AD mortality due to smoking in the net drift, and it was more significant in women (0.46, 95%CI = [0.09, 0.82]) than men (−0.03, 95%CI = [−0.11, 0.05]). For the cause of HFPG, the net drift values for men and women were 0.82% and 0.43%. For HBMI, the values were 3.14% and 2.76%, respectively, reflecting substantial increases in AD mortality.

Conclusion: Time trends in AD mortality caused by metabolic risks and smoking in China from 1990 to 2019 have consistently increased. Therefore, it is necessary to prevent excessive weight gain and obesity during the later stages of life, especially for females.

KEYWORDS

Alzheimer's disease, risk factors, metabolic risks, high body mass index, high fasting plasma glucose, smoking, time trends

1 Introduction

As a result of the increasing number of old individuals globally, Alzheimer's disease (AD) has emerged as a growing public health problem (Yan et al., 2019). In 2019, AD was one of the most burdensome neurological conditions in China, with disability-adjusted life years (DALYs) of 189.47 (75.72–453.76). There were 10 million AD patients in China in 2020, and with the rapid growth of an aging population, it is expected to exceed 20 million by 2050 (Yin et al., 2024). According to our recent study, AD's overall age-standardized mortality rate (ASMR) increased. Between 2000 and 2019, recorded deaths from AD climbed by about 145% (Frick et al., 2023). The COVID-19 pandemic in 2020 and 2021 may have exacerbated AD mortality trends (Alzheimer's and Dementia, 2023).

The factors contributing to injury and disease, including environmental, behavioral, and metabolic risks, are the key areas where the most effective way to prevent a decline in health is through public health initiatives (Li et al., 2022). Therefore, to improve population health, it is necessary to understand both the injuries and diseases that contribute to the health burden, and the risks that contribute to them (GBD 2017 Risk Factor Collaborators, 2018). Analyzing the extent of risk factors for AD mortality and providing interventions from behavioral and metabolic perspectives is an essential public health measure to reduce health loss effectively. In the Global Burden of Diseases, Injuries, and Risk Factors Study 2019 (The Global Burden of Disease [GBD], 2019), three risk factors were determined to possess substantial evidence supporting a causal connection to AD: smoking, high body mass index (HBMI), and high fasting plasma glucose (HFPG) (Institute for Health Metrics and Evaluation [IHME], 2020). Smoking is commonly acknowledged as a significant contributor to premature morbidity and mortality. However, effectively tracking smoking rates and trends worldwide has proven difficult (GBD 2015 Tobacco Collaborators, 2017). Smoking might indirectly impact the risk factors for several diseases, including diabetes mellitus, coronary heart disease, and other metabolic diseases because smoking causes vasoconstriction, atherogenesis, thrombogenesis, and endothelial dysfunction (Zhou and Wang, 2021). Metabolic factors can affect the course of AD. The progress in metabolomics has revealed the intricate nature of the dynamic changes linked to the evolution of AD, highlighting the challenges in creating effective therapeutic strategies Wilkins (Cheng et al., 2018; Wilkins and Trushina, 2018). Previous epidemiological research suggests that there is a connection between insulin resistance, diabetes, and an increased risk of AD. A longitudinal study noted that HFPG, measured up to four decades before death from AD, is associated with greater concentrations of glucose in brain tissue throughout the brain (Leibson et al., 1997; Ott et al., 1999; Luchsinger et al., 2001; An et al., 2018). Animal experiments have demonstrated that elevated blood glucose levels are associated with increased blood-brain barrier permeability (Rom et al., 2020) and neuronal apoptosis (Russell et al., 1999). High blood glucose can stimulate the production of reactive oxygen species by plasma albumin (Mohanty et al., 2000), induce endothelial dysfunction (Sena et al., 2013), promote systemic inflammation, increase the number of activated microglial cells, and initiate neuroinflammation, consequently impacting cognitive and memory functions (Drake et al., 2011; Wanrooy et al., 2018). Epidemiological studies have shown that patients with diabetes have a 1.3-fold to 5.5-fold increase in risk of developing AD in comparison with healthy individuals. Even among participants without diabetes, the risk of AD and other dementias increased with increasing glucose levels. As accumulating evidence suggests an association between HFPG with AD and other dementias, it is necessary to evaluate the global burden of AD and other dementias attributable to HFPG to identify the vulnerable population and formulate comprehensive prevention strategies to respond to the rapidly growing burden of AD and other dementias. Efforts have been undertaken to explore the variations in AD mortality over time and mortality rates unique to different age groups. Nevertheless, the impact of metabolic risks and smoking on AD mortality to temporal and cohort effects remains unclear (Vancheri et al., 2022). This Article aims to examine time trends in AD mortality caused by metabolic risks and smoking in China. We analyzed pertinent data obtained from GBD 2019 to aid in formulating focused policies and strategies for dementia control, improving public health, and guiding the efficient distribution of medical resources.

2 Materials and methods

2.1 Data source and study design

The risk factors of AD deaths in China were from the GBD 2019 Study at the national level (GBD 2019 Diseases and Injuries Collaborators, 2020), freely available from the Global Health Data Exchange.[1] The methodology, statistical techniques, and metrics used in the GBD 2019 project have been documented elsewhere, such as sex- and age-specific annual deaths and ASMR of AD caused by HBMI, HFPG, and smoking. The GBD 2019 encompasses 369 diseases and injuries, 21 regions, and 204 countries and territories (GBD 2019 Demographics Collaborators, 2020; GBD 2019 Risk Factors Collaborators, 2020; Roth et al., 2020). HFPG was defined as fasting plasma glucose above the theoretical minimum-risk exposure level, 4.8–5.4 mmol/L, and HBMI as BMI $\geq$ 25 kg/m^2 (The Global Burden of Disease [GBD], 2019; Li et al., 2023).

2.2 Alzheimer's disease identification

According to the cause list mapped to the 10th International Statistical Classification of Diseases and Related Health Problems (ICD-10), the GBD 2019, and the ICD-10 codes (The Lancet Infectious Diseases, 2018; WHO, 2021; Dhana et al., 2022), According to the ICD-10, AD is recognized as G30.0 Early-onset AD (<65 years old) and G30.1 Late-onset AD (>65 years old).

2.3 Statistical analyses

To evaluate the extent of changes in mortality due to AD over time, we employed the joinpoint regression model (version 4.9.1).

1 https://vizhub.healthdata.org/gbd-results/

The joinpoint regression model is a collection of linear statistical models used to evaluate the trends in AD mortality attributable to metabolic risks and smoking. This model is a calculating approach to estimate the changing rule of illness rates using the least square method, avoiding the non-objectivity of typical trend analyses based on linear trends. Calculating the square sum of the residual error between the estimated and actual values yields the turning point of the shifting trend. The fundamental concept of joinpoint is to partition a continuous trend line into distinct parts, every characterized by continuous linearity, to assess the disease-changing characteristics unique to distinct time intervals (Kim et al., 2000). Joinpoint (version 4.9.1.0; National Cancer Institute, Rockville, MD, USA) was used to create this model. The joinpoint model allowed us to assess the average annual percent changes (AAPCs) and the related 95% confidence intervals (CIs) (Fu et al., 2023). AAPC was determined by assigning weights to the regression coefficients of annual percent changes (APCs) to measure the trend across the period. The APC uses a log-linear model to compute each segment, with APC = $[e(\beta)-1] \times 100\%$, and the symbol β represents the gradient of the trend segment (Muggeo, 2010). We use a permutation test to determine the related segment significance of APCs; the Joinpoint Regression Programme revealed the best-proposed model. The APC model, grounded on the Poisson distribution, can capture the accumulated effect of health risks. The APC model can be expressed in a general logarithmic linear form:

$$\rho = \alpha_a + \beta_p + \gamma_c$$

where ρ indicates the expected rate, α_a, β_p, and γ_c indicate the effects of age, period, and cohort of the APC model (Clayton and Schifflers, 1987). In this study, the age effect pertains to variations in AD mortality resulting from physiological and pathological changes occurring naturally with advancing age. The period effects refer to variations in AD mortality resulting from different events that transpire as time goes on. The cohort effects pertain to variations in AD mortality rates resulting from modifications to one's way of life or exposure to risk factors that differ inter-generationally.

To examine differences in age, time, and cohort concerning the AD mortality trends caused by smoking and metabolic risks, we utilized the APC model provided by the National Cancer Institute[2] (Rosenberg et al., 2014). This study focused on adults aged 50+. The age groups were separated into eight categories, each spanning 5 years, ranging from 50–54 to 85 years and older. The period was divided into six consecutive phases of 5 years each, starting from 1990 to 1994 and ending in 2015 to 2019. As a result, ten consecutive birth cohorts were created by grouping individuals based on their age and the period they were born in, ranging from the 1905 to 1910 cohort to the 1965–1969 cohort. The logarithmic linear trend, known as the drift, was employed to construct the AAPC for outcome measurements across time, considering both period and birth cohort. The longitudinal age curves were constructed to illustrate the impact of age by computing the estimated rates specific to each age group for the reference cohort (Zhou et al., 2024). The impact of the period and cohort was indicated by the rate ratios (RRs) compared to the reference period and cohort while considering chronological age and the non-linear aspect of the period and cohort (McNally et al., 1997). Local drift values reflected the temporal trend of AD mortality caused by risk factors in each specific age group. A mortality shift was judged substantial if the absolute drift value exceeded 1% (Guo et al., 2023). The Wald chi-squared test was employed to ascertain the statistical significance of the functions; the two-sided $p < 0.05$ means statistical significance (Nikooienejad and Johnson, 2021).

2 https://analysistools.cancer.gov/apc/

3 Results

3.1 Trends in AD mortality attributable to metabolic risks and smoking

Table 1 and Supplementary Figures 1, 2 display the trends in AD mortality related to smoking, HFPG, and HBMI. The number of deaths from AD in China increased from 23998 to 93441 over the past three decades, and the mortality rate increased from 2.03 to 6.57%. We conducted a more in-depth analysis of the ASMR of AD caused by smoking, HFPG, and HBMI. The number of deaths from AD attributable to smoking increased by 2.5-fold between 1990 and 2019 (from 15782 to 55531), and ASMR increased in both men (AAPC = 0.37%, 95%CI = [0.25, 0.48]) and women (AAPC = 0.70%, 95%CI = [0.60, 0.80]), especially in women. ASMR of AD attributable to HFPG indicated an increasing trend among the entire population (AAPC = 0.09%, 95%CI = [−0.07, 0.25]). ASMR of AD caused by HBMI significantly increased in the cohort (AAPC = 2.35%, 95%CI = [2.21, 2.48]), which was higher in men (AAPC = 2.70%, 95%CI = [2.56, 2.84]) than that in women (AAPC = 2.29%, 95%CI = [2.19, 2.39]).

3.2 ASMR for AD attributable to metabolic risks and smoking

Table 1 and Supplementary Figures 1–3 listed the AD mortality attributable to smoking, HFPG, and HBMI by year, age, period, and cohort from 1990 to 2019. AD mortality rises with age; a similar trend is also observed in AD mortality attributable to smoking and HFPG in all periods (Figures 1A–C). From 1990 to 2019, AD mortality attributable to HBMI increased in 50+ age groups (Figure 1C). Mortality caused by smoking in individuals aged 50+ increased from 1990 to 2014, then declined from 2015 to 2019 (Figure 1B). The AD mortality caused by smoking, HFPG, and HBMI showed an increasing trend with age in people over 60 years old, and both reached the highest in the age group of 80–84 (Figures 1D, E).

3.3 Net drift and local drift in age groups

During the study period, there was an increase in AD mortality attributable to smoking, as indicated by the overall net drift (%/year) (0.13, 95%CI = [0.05, 0.20]), which was more significant in the net drift for women (0.46, 95%CI = [0.09, 0.82]) than

TABLE 1 Age-standardized mortality rate per 100,000 of AD attributable to smoking, HFPG, and HBMI in 1990 and 2019, and its temporal trends from 1990 to 2019.

Sex	Smoking			High fasting plasma glucose			High body-mass index		
	ASMR (1990) (95%UI)	ASMR (2019) (95%UI)	AAPC% (95%CI)	ASMR (1990) (95%UI)	ASMR (2019) (95%UI)	AAPC% (95%CI)	ASMR (1990) (95%UI)	ASMR (2019) (95%UI)	AAPC% (95%CI)
Both	3.07 (0.64~8.99)	3.50 (0.78~9.63)	0.47[a] (0.39~0.55)	1.63 (0.16~6.57)	1.71 (0.18~6.63)	0.09 (−0.07~0.25)	0.86 (0.07~3.26)	1.67 (0.22~5.65)	2.35[a] (2.21~2.48)
Male	6.25 (1.36~18.20)	6.92 (1.51~19.79)	0.37[a] (0.25~0.48)	1.31 (0.11~5.02)	1.79 (0.16~7.15)	0.56[a] (0.38~-.73)	0.63 (0.04~2.50)	1.36 (0.11~4.71)	2.70[a] (2.56~2.84)
Female	1.28 (0.25~3.92)	1.56 (0.34~4.55)	0.70[a] (0.60~0.80)	1.79 (0.15~7.70)	1.58 (0.14~6.02)	−0.07 (−0.85~0.10)	0.97 (0.07~3.90)	1.85 (0.21~6.35)	2.29[a] (2.19~2.39)

UI, uncertainty interval; ASMR, age-standardized mortality rate; CI, confidential interval; AAPC, average annual percentage change; a statistically significant ($p < 0.05$). Population estimates: the GBD was queried for the mortality per 5-year age group from 1990 to 2019, as well as population estimates for each year (https://ghdx.healthdata.org/record/ihme-data/global-population-forecasts-2017--2100).

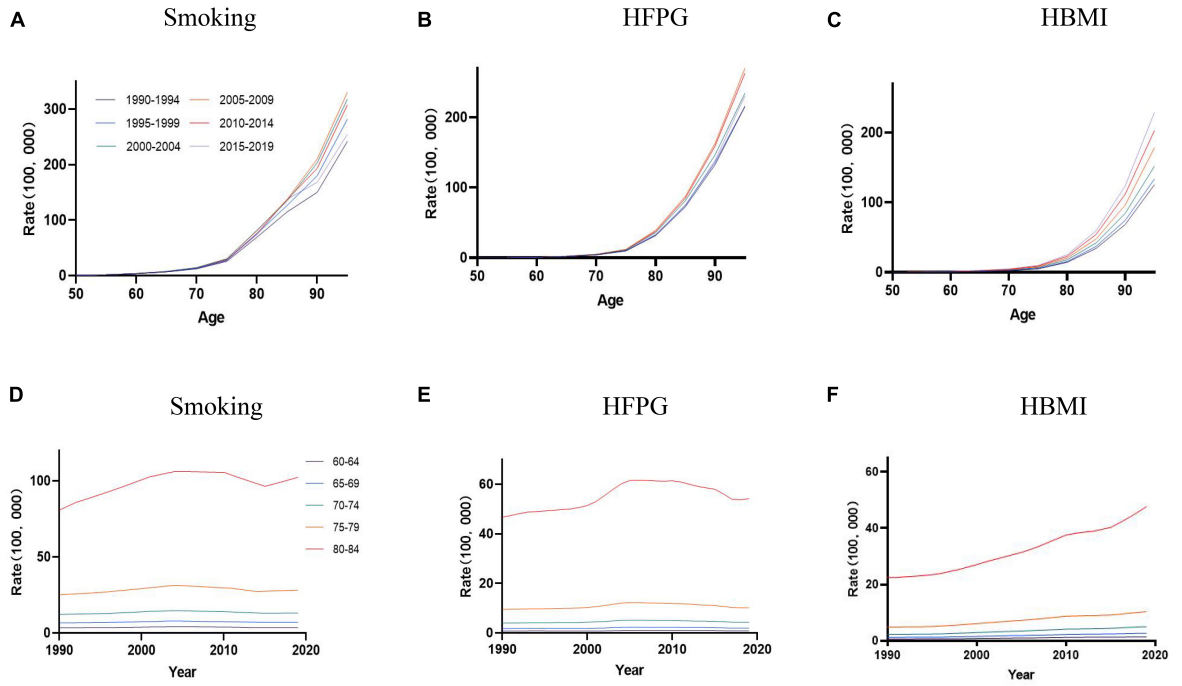

FIGURE 1
The age-specific mortality rates of AD were attributable to smoking, HFPG, and HBMI in the period between 1990 and 2019, and the cohort-specific mortality rate of AD was attributable to metabolic risks by age group between 1990 and 2019. **(A–C)** Values of the mortality for AD attributable to smoking, HFPG, and HBMI in China from 1990 to 2019. **(D–F)** Survey years were arranged into consecutive 5-year periods from 1990 to 1994 (median, 1992), 1995 to 1999 (median, 1997), 2000 to 2004 (median, 2002), 2005 to 2009 (median, 2007), 2010 to 2014 (median, 2012), and 2015 to 2019 (median, 2017).

men (−0.03, 95%CI = [−0.11, 0.05]). The net drift values of AD mortality caused by HFPG for men and women were 0.82% (95% CI = [0.60, 1.05]) and 0.43% (95% CI = [0.22, 0.64]), respectively, while those for HBMI were 3.14% (95% CI = [2.89, 3.39]) and 2.76% (95% CI = [2.55, 2.96]), reflecting a substantial increase in AD mortality.

Local drift values of AD mortality caused by HFPG and HBMI were above 0 in 50+ groups; the trend for HFPG showed a stable trend in AD mortality in both men and women, while the trend for HBMI initially enhanced and then reduced in men and women. The most significant decrease was observed in males between the ages of 75–80 (−21.39%%; 95%CI: −24.72~−18.07) and women aged 75–80 (−20.37%%; 95%CI: −22.84~−17.9). In contrast, local drift values of AD mortality caused by smoking were partly less than 0 for men, showing an initial increase, followed by a decrease, and then another increase across all ages in men; for women, the trend showed a decrease followed by an increase (Figures 2A–C).

3.4 APC effects on AD mortality attributable to metabolic risks and smoking

Age effects on AD mortality caused by smoking, HFPG, and HBMI follow the exponential increase trends, with a significantly

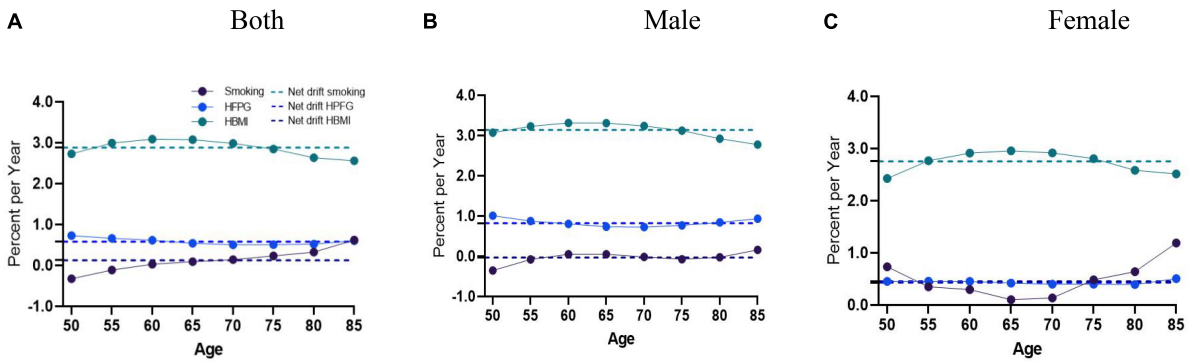

FIGURE 2
Local drift with net drift values of the mortality for AD attributable to metabolic risks (HFPG and HBMI) in China from 1990 to 2019. **(A)** Corresponding to both sexes; **(B)** corresponding to males; **(C)** corresponding to females. The dots and shaded areas denote percentage and their corresponding 95%CI.

accelerated rate observed in individuals aged 80 and above. AD mortality attributable to HBMI in men of all age groups and women aged 50∼70 remained consistently low. Attributable to HBMI, AD mortality in women was more significant than in men aged 70+ (Figures 3A–C).

Age effects: The overall population-wide changes (Net Drift) and 95% confidence intervals for AD mortality attributable to smoking, HFPG, and HBMI in China between 1990 and 2019 were 0.13 (95% CI = [0.05, 0.20]), −0.58 (95% CI = [0.43, 0.73]), and 2.88 (95% CI = [2.72, 3.04]), AD mortality enhanced with age after age 60 years. In the overall and male populations, AD mortality attributable to smoking was significantly higher than the mortality attributable to HFPG and HBMI. In the female population, AD mortality attributable to HFPG slightly outpaced mortality trends attributable to smoking and HBMI (Figures 3A–C).

Period effects: The period effects of AD mortality attributable to HBMI for the overall, men and women all trended upward from 1990 to 2019 in China. Using 2000–2004 as the reference value, the period effect of AD mortality attributable to smoking increased until 2000–2004 and then decreased. The period effects of AD mortality caused by HFPG rose between 1990 and 2019 and have all trended downward since then (Figures 3D–F).

Cohort effects: Birth cohort effects attributable to smoking and HFPG mortality rates remained relatively flat from 1905 to 1950, with a relative increase in mortality rates attributable to HFPG and a decrease in mortality rates attributable to smoking after 1950, and a steady upward trend in the period effects of AD mortality rates attributable to HBMI for the overall, male, and female populations, with a more pronounced trend of growth over time (Figures 3G–I).

4 Discussion

This study thoroughly evaluated the temporal trends in AD mortality attributable to smoking and metabolic risks (HFPG and HBMI). The number of AD deaths rose by 289.37% in 2019 compared with 1990, with the mortality rate rising by 233.65% and the standardized mortality rate rising by 20.62%. The study indicated that the AD mortality and standardized mortality rates attributable to smoking, HFPG, and HBMI in China demonstrated a consistent upward trajectory between 1990 and 2019, which may be attributed to the increasing population of older individuals in China. As of the conclusion of 2023, the total number of individuals who were 60 years old or older amounted to 296.97 million, representing 21.1% of the country's entire population. In China, the AD deaths number caused by smoking in 2019 increased by 251.86% from 1990, the mortality rate increased by 193.23%, and the standardized mortality rate increased by 14.01%. The AD deaths number caused by HFPG in 2019 increased by 267.86% from 1990, the mortality increased by 207.27%, and the standardized mortality increased by 4.27%. The AD deaths number attributable to HBMI in China in 2019 increased by 573.66% from 1990, mortality increased by 456.67%, and standardized mortality increased by 94.19%. Age is an essential factor in AD mortality, and the results showed that the AD mortality rate attributable to smoking, HFPG, and HBMI in China increased with age, and it was most pronounced, especially in the population aged 60+ years.

Nevertheless, the increased mortality linked with AD is not just attributed to life expectancy but is also influenced by an increase in premorbid diagnosis or identification (Zhao et al., 2021). In recent years, AD's diagnostic efficiency and classification accuracy have been improved due to advancements in artificial intelligence and neuroimaging, and the detection rate has been increasing (Scheltens et al., 2021). Unfortunately, due to the many clinical characteristics and intricate pathology classifications of AD contributing to its variability, there is no effective treatment, and the available treatments only slow down the progression of AD (Lee et al., 2019). The large base of AD patients, high diagnosis rate, and difficulty of cure lead to a cohort effect presenting an elevated trend in AD mortality. Early identification of AD can potentially improve clinical outcomes and enhance the quality of life for both patients and caregivers, although it may not affect the course of the disease or the rate at which it progresses (Sano, 2004; Kokkinou et al., 2021). Due to neuropathologic changes in AD patients occurring insidiously before diagnosis, early and accurate prediction of high-risk factor populations is needed (Kivimäki et al., 2023). Cardiovascular health is directly related to brain health or cerebrovascular health. Since the brain relies heavily on arteries to transport blood, oxygen, and nutrients and to remove waste and toxins, it is vital to have healthy arteries in the brain.

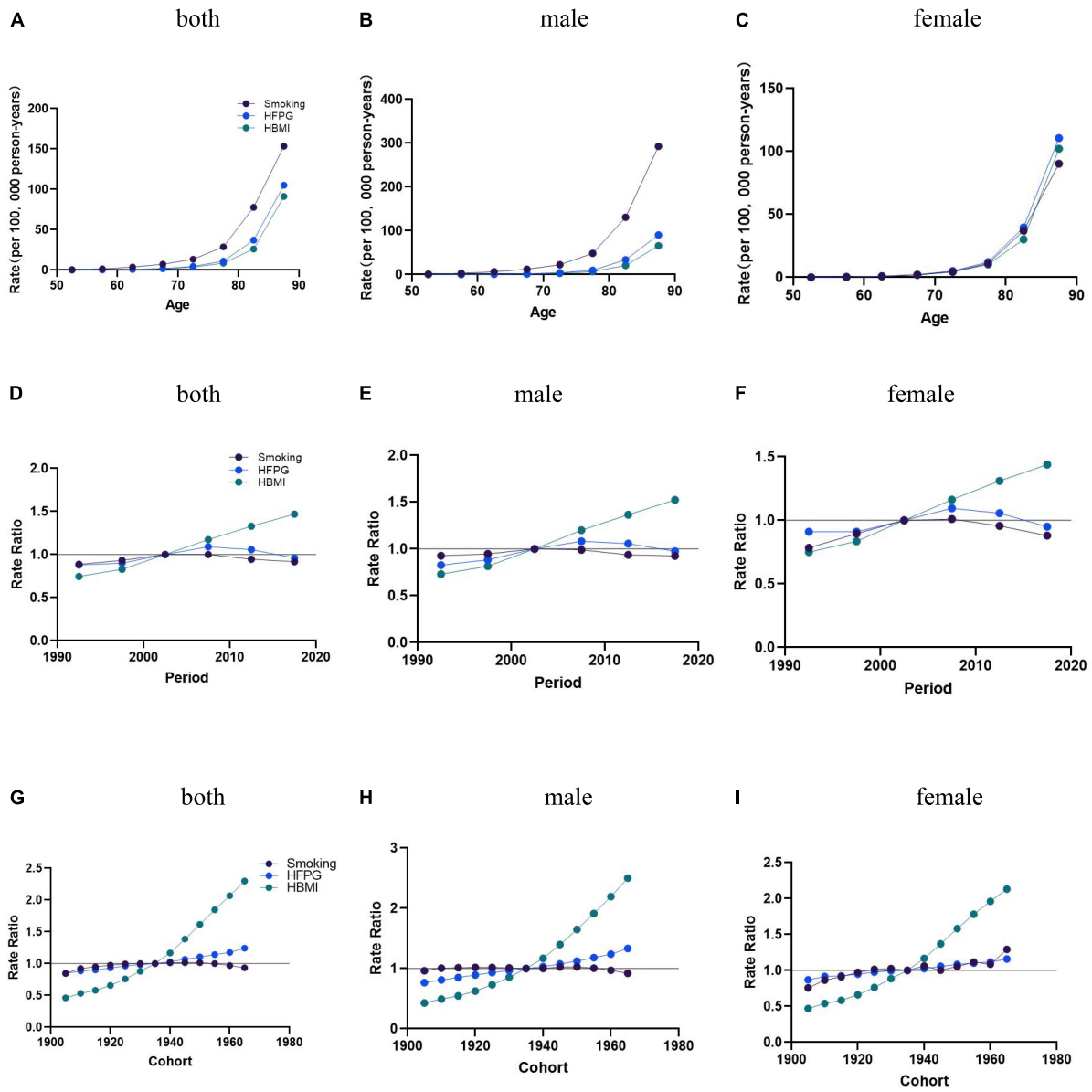

FIGURE 3
The age-period-cohort (APC) results of AD attributable to smoking, HFPG, and HBMI in China from 1990 to 2019. **(A–C)** Fitted longitudinal age curves of AD mortality (per 100,000) attributable to smoking, HFPG, and HBMI, with **(A)** corresponding to both sexes, **(B)** corresponding to males, **(C)** and corresponding to females. **(D–F)** The rate ratio of each period compared with the reference (2000–2005) adjusted for age and nonlinear cohort effects, with **(D)** corresponding to both sexes, **(E)** corresponding to males, **(F)** and corresponding to females. **(G–I)** The rate ratio of each cohort compared with the reference (cohort 1900–1980) adjusted forage and nonlinear period effects, with **(G)** corresponding to both sexes, corresponding to males, and **(I)** corresponding to females. The dots and shaded areas denote mortality rates or rate ratios.

When these arteries are damaged, narrowed by blockages of fat and cholesterol, or even completely blocked, the brain is unable to get the vital substances it needs to function, which damages the brain and weakens its ability to fight off infection and disease processes, and can even lead to dementia if specific areas of the brain are sufficiently damaged. With age, the production of cerebrospinal fluid decreases, a decline exacerbated by AD, and people are increasingly exposed to risk factors for HFPG and HBMI. The latest recommendations suggest that a brain-healthy diet that reduces smoking behavior reduces the risk of heart disease and diabetes and is low in saturated fat and cholesterol, which can help protect the brain from disease. Lifestyle factors such as smoking and diabetes may exacerbate AD, and changing lifestyle is one of the comprehensive ways to treat AD. In addition, doctors can accurately classify patients according to their disease risk. High-risk patients will begin treatment with risk reduction, such as medication, weight loss, exercise, and lifestyle changes. Early detection, early intervention, use of appropriate medication, and comprehensive lifestyle adjustments can all dramatically reduce morbidity and mortality in individuals who follow treatment regimens (Sahyouni et al., 2021). This combination of treatments for the disease is an ideal way to avoid the harmful consequences of cardiovascular disease and is a similar treatment that could treat AD.

The mortality of risk factors for AD has significantly increased, including smoking, HFPG, and HBMI; the risk factors can potentially interact with the birth cohort and lead to an increased death rate in individuals with AD. On average, older adults born later in the cohort had higher education levels. The rising levels of education among older individuals during the previous 15 years may have influenced the outcomes of dementia and mortality (Langa et al., 2008). Increased levels of education are thought to be linked to a higher "cognitive reserve", meaning that the brains of individuals with more education may endure more damage (such as AD pathology or reduced blood flow) before reaching the point of clinically noticeable impairment (Scarmeas et al., 2006; Stern, 2006). Therefore, those with higher levels of education exhibit more advanced brain pathology, leading to a faster deterioration in cognitive function and a higher likelihood of AD death (Cagney and Lauderdale, 2002).

AD mortality caused by HBMI has significantly increased in both, especially in women. HBMI had a more significant effect on the female population in both the period effect and the age effect, suggesting that the combination of smoking and HBMI may have contributed to the birth cohort effect (Jones et al., 2023). Although age is the primary factor in the probability of fatalities caused by AD, lifestyle choices and health circumstances specific to various genders can also influence AD mortality (Health and Retirement Study, 2023; Dhana et al., 2024). The disparities could be attributed to the physiological distinctions inherent in men and women (Ballard et al., 2011). Decision makers could prioritize gender disparities in AD attributable to HBMI and develop appropriate measures to decrease AD mortality. Due to the influence of social culture and living habits, men are more likely than women to be exposed to drinking, high-calorie diet, smoking, and other risk factors leading to HBMI, resulting in a higher BMI growth rate than women, significantly increasing the risk of death from AD. Among the aging population in China, elderly care institutions can strictly control the diet of AD patients, publicize and increase the supply of unsaturated fatty acid food, reduce saturated fatty acid intake, and guide the elderly population to develop better eating habits (Critselis and Panagiotakos, 2020). Women had a higher likelihood of mortality due to AD, while there is no notable connection in men. Therefore, women become a critical intervention group for senile dementia, and health education for male obesity groups should be paid attention to in order to reduce the risk of senile dementia and disease damage. China should strengthen the publicity and education of HBMI on the risk of senile dementia, attach importance to and support the whole population, all-around and life-cycle weight health management, and provide personalized weight loss and cognitive function training services for high-risk groups.

The cohort effect showed that the standardized AD mortality rate attributed to smoking and HFPG increased more slowly compared to the overall AD mortality rate, suggesting that there is still a need to enhance the regulation of smoking habits and diabetes mellitus. The standardized AD mortality rate attributed to HBMI increased more greatly, with a more significant effect on the female population, suggesting that obesity and the level of health have a more remarkable influence on AD mortality and that corresponding health management measures should be developed in a targeted manner.

Time effects showed that AD mortality caused by smoking in China increased from 1990 to 2005 and then decreased from 2005 to 2020, caused by the World Health Organization Framework Convention on Tobacco Control (GBD 2015 Tobacco Collaborators, 2017) officially approved in China on 11 October 2005. China will enter the deep aging society around 2035, facing the challenge of rapid aging and the overlapping risk of death from smoking-induced diseases. Han and Zhou (2015) noted that the severity of the anti-smoking policy positively correlates with the severity of the aging population. AD mortality attributable to smoking has been slightly decreasing in the last several years, which may be attributed to the fact that China has gradually emphasized tobacco control actions and introduced tobacco control measures at the local level. From the perspective of tobacco control, the price elasticity of tobacco products can be used to judge the impact on tobacco consumption. As the price of tobacco products increases, consumers may begin to reassess the impact of smoking on their health and finances, resulting in a reduction in nicotine intake or cessation of smoking. The introduction of excise taxes could therefore provide an economic incentive for tobacco consumers to reduce or stop smoking. It is generally accepted that better management of smoking is already a public health goal for reducing AD mortality, however, many studies overlooked the adverse effects of smoking on women. AD mortality attributable to smoking has decreased slightly in the overall and male populations, which may be due to effective interventions of tobacco control measures in China. Conversely, our study concludes that smoking has had an impact on AD mortality in older women in recent years, it has shown a slight upward trend in the female population. The older female population is a high-risk group for the burden of attribution to smoking, which causes platelet clumping in the brain and thus predisposes to vascular dementia. Older women are more susceptible to AD deaths attributable to smoking behaviors as they age (Doll and Peto, 1981). Older women are affected by the cross-influence of HBMI and smoking risk factors, leading to the aggravation of AD. Shivpuri et al. (2012) and Ishii et al. (2012) noted that women participants exhibited a higher vulnerability to inflammation, potentially rendering them more prone to developing diabetes and metabolic syndrome. Typically, those who smoke tend to have a lower BMI than individuals who do not smoke when matched for age. However, when smokers quit smoking, they often experience a weight increase (Pan et al., 2015; Turnquist et al., 2024). Compared to the population of non-smoking women, the population of women who had ever regularly smoked had a notably elevated risk of mortality from a severe illness, and smokers had a lower BMI than age-matched nonsmokers (Chou et al., 2004, Ellulu, 2018). Moreover, AD develops progressively, as indicated by a multitude of research (Vermunt et al., 2019). Globally, women outlive men by an average of 4.5 years (GBD 2021 Demographics Collaborators, 2024). Due to men having a shorter life expectancy, the manifestations of AD may not have been fully evident at the time of the premature demise. However, women experienced a more significant number of AD-related deaths compared to men, leading to a greater burden for them (Zhao et al., 2021). Therefore, tobacco control policies for women should not be ignored. Although the female smoking population is significantly less than the male population, the female smoking population is more negatively affected, which means that with the progress of the times and the development of culture, female smokers have gradually become a group that needs attention and research. Public health policies should pay attention to the influence of smoking

factors on the mortality rate of AD in the female population, avoid the phenomenon of weakening the role of female smokers, fill the gaps in the previous tobacco control policies for the whole population and even tend to men, and control smoking behavior, to achieve the purpose of reducing the mortality rate of AD and more beneficial to the health of the whole population.

In addition, subsequent investigations have revealed a notable rise in the likelihood of developing AD due to smoking, particularly in noncarriers of the APOEε4 allele (Ott et al., 1998; Merchant et al., 1999; Aggarwal et al., 2006). The heritability of late-onset AD is significantly high, with estimates ranging from 60 to 80% (Gatz et al., 2006; Sullivan et al., 2019). Risk factors of older adults for AD are worth studying. This study focused on risk variables that can be changed or modified, such as smoking and metabolic risks.

For the first time, we analyzed GBD 2019 data to reveal the temporal trend of death from AD in China that can be attributed to smoking, HFPG, and HBMI. Using the APC model, we calculated the individual impacts of age, period, and cohort on death due to AD. Additionally, the local drift values accurately represented the temporal trend of AD mortality caused by smoking, HFPG, and HBMI in each age group. Differentiating between the drivers of changes in AD mortality in various periods and birth cohorts was made possible by analyzing period and cohort effects. Our work can help track the aims of sustainable development and identify the target populations for prevention and treatment based on adverse trends in AD mortality attributed to smoking, HFPG, and HBMI in certain age groups.

5 Limitations

This study used the GBD 2019 data, which could not explore the changes in AD mortality trends attributed to smoking, HFPG, and HBMI in different regions of China. While we considered period and cohort effects, our APC analysis relied on the estimated cross-sectional data from the GBD. Thus, extensive cohort investigations are necessary for validating the hypotheses of this study.

6 Conclusion

In this study, we showed that time trends in AD mortality caused by metabolic risks and smoking in China from 1990 to 2019 have consistently risen. Thus, it is essential to prevent being overweight or obese throughout old age; it is crucial to acknowledge the significance of enhancing the elderly population as well, especially females, and the necessity of promoting smoking prevention and control knowledge and promoting healthy lifestyles to reduce the mortality of AD attributed to smoking in China. The results of this study will also help develop and assess the efficacy of AD and treatment and rehabilitation techniques in China.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: https://ghdx.healthdata.org/gbd-2019.

Author contributions

SS: Data curation, Formal analysis, Visualization, Writing – original draft, Writing – review and editing. TZ: Data curation, Methodology, Writing – review and editing. HY: Writing – review and editing. TX: Writing – review and editing. YY: Software, Writing – review and editing. MS: Validation, Writing – review and editing. HL: Project administration, Writing – review and editing. QH: Formal analysis, Writing – review and editing. WW: Data curation, Resources, Writing – original draft. HFY: Project administration, Writing – review and editing. XH: Data curation, Investigation, Writing – review and editing.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2024.1425577/full#supplementary-material

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Occlusion dysfunction and Alzheimer's disease: Mendelian randomization study

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Aim: Occlusion dysfunction (OD) is increasingly linked to Alzheimer's disease (AD). This study aimed to elucidate the causal relationship between OD and AD using Mendelian randomization (MR) analysis.

Materials and methods: Genome-wide association study (GWAS) meta-analysis data obtained from FinnGen, IEU Open GWAS, and UK Biobank (UKBB) was represented as instrumental variables. We validated the causal relationship between periodontal disease (PD), loose teeth (PD & occlusion dysfunction), dentures restoration (occlusion recovery), and AD.

Results: According to the MR analysis, PD and AD have no direct causal relationship (P = 0.395, IVW). However, loose teeth significantly increased the risk of AD progression (P = 0.017, IVW, OR = 187.3567, 95%CI = 2.54E+00–1.38E+04). These findings were further supported by the negative causal relationship between dentures restoration and AD (P = 0.015, IVW, OR = 0.0234, 95%CI = 1.13E-03–0.485).

Conclusion: The occlusion dysfunction can ultimately induce Alzheimer's disease. Occlusion function was a potentially protective factor for maintaining neurological health.

KEYWORDS

occlusion dysfunction, Alzheimer's disease, periodontal disease, Mendelian randomization, epidemiology

Introduction

Occlusion dysfunction (OD) commonly arises from missing teeth and severe periodontal disease (PD) (Ramseier et al., 2017). As a chronic inflammatory disease, PD is widespread among the elderly and has become a crucial global health issue (Eke et al., 2015). Mechanistically, PD and related complications were closely associated with neurodegenerative diseases, such as Alzheimer's disease (AD) (Hajishengallis, 2022). In which, OD serve as the risk factor for the maintenance of neurological health (Teixeira et al., 2014). Based on the importance of neurological health, the potential causal relationships among OD, PD, and AD deserve in-depth exploration.

As a chronic neurodegenerative disorder with complex etiology, AD is characterized by the accumulation of a protein called amyloid-β (Aβ) in brains. During autopsies, PD related *Porphyromonas gingivalis* (Pg) have been found in the brains of AD patients (Jungbauer et al., 2022). These bacteria can invade the central nervous system and cause inflammation by producing certain molecules (Singhrao et al., 2015). Furthermore, the elevated levels of inflammatory factors resulting from PD can contribute to an inflammatory in the brain (Kamer et al., 2008a,b). Meanwhile, AD patients often experience severe PD due to a combination of factors, including the diminished ability and lack of motivation to maintain oral hygiene (Gao et al., 2020). Currently, there is a lack of direct clinical evidence demonstrating the clear association between AD and PD.

Previous research has demonstrated that OD can contribute to brain impairments and cognitive decline, such as reduced synapses, degeneration of nerve cells, and inhibition of neurotransmitter release (Terasawa et al., 2002; Okihara et al., 2014). Additionally, AD is often accompanied by atrophy in both the cortical and subcortical areas of the brain, particularly in the internal olfactory cortex and hippocampus (Teipel et al., 2006; Wang et al., 2020). Thus, occlusal function has emerged as a novel factor in understanding the causes of AD.

Mendelian randomization (MR) is a novel methodology to assess causal relationships between target exposures and diseases or traits. While randomized controlled trials (RCTs) are considered the gold standard approach for testing causality, they are often constrained by financial and ethical considerations, and confounding factors may introduce biases (Sekula et al., 2016). MR helps overcome these issues by using genetic variants, known as single nucleotide polymorphisms (SNPs), which are strongly associated with the traits being studied. This approach helps reduce biases that can occur in traditional RCTs (Ebrahim and Davey Smith, 2008). MR research has yielded significant findings regarding the potential causal associations between environmental risk factors and diseases, with numerous high-impact publications in esteemed journals (Ference et al., 2019; Jones et al., 2021).

In this study, we aimed to systematically evaluate the causal association between PD, OD (loose teeth), occlusion recovery (dentures restoration), and AD using MR analysis. Significantly, our findings demonstrate a strong causal relationship between OD and AD ($p = 0.0171$, IVW), providing a novel perspective on the impact of PD on AD and highlighting the crucial role of OD in the development of AD. This article contributes to the development of new therapeutic strategies for the prevention and treatment of AD.

Material and methods

The datasets for exposure, including PD, loose teeth, and dentures restoration, as well as the outcome data for AD, were systematically searched from multiple genome-wide association study (GWAS) meta-analysis data sources, including IEU Open GWAS, FinnGen, and UK Biobank. Initially, all combinations of conditions were screened using MR analysis. The datasets with the most significant outcomes were selected for further investigation (Figure 1). It is important to note that all the data used in this study are publicly available (Table 1), and the download link is provided in the Data Availability Statement section.

Instrumental variables

According to the previous study (Emdin et al., 2017), instrumental variables must satisfy three key assumptions: relevance, independence, and exclusion restriction. To address the requirements of MR, we have outlined the steps for screening instrumental variables. The screening criteria are as follows: (1) Initially, we selected SNPs that exhibited a strong association with the exposure ($p < 5.0 \times 10^{-8}$, PD; $p < 5.0 \times 10^{-6}$, loose teeth; $p < 5.0 \times 10^{-7}$, dentures restoration). (2) The linkage disequilibrium (LD) of these SNPs was calculated, and only those SNPs meeting the following conditions were retained: $r^2 < 0.001$, kb = 10000 (3) To minimize bias, we eliminated all palindromic SNPs among the retained ones. (4) Using the R package "MR-PRESSO", we identified and removed a pleiotropic among all reserved SNPs. (5) Additionally, we employed the PhenoScanner database[1] to exclude confounding factors and risk variables (Table 2). The remaining SNPs were subsequently utilized for MR analysis (Table 3).

Mendelian randomization

To investigate the causal relationship between exposure and outcome, we employed four methodologies: MR Egger, Weighted median, Inverse variance weighted (IVW), and Weighted mode. Previous research has demonstrated that IVW analysis is the most reliable and accurate approach (Bowden et al., 2016). Therefore, we primarily relied on the IVW analysis, considering the additional methods as supplementary. When the p-value of IVW analysis was less than 0.05 and the odds ratio (OR) values exceeded 1 for all four methods, we inferred that exposure was a significant risk factor for AD.

Sensitivity analyses

To ensure the reliability of our findings from the MR analysis, a sensitivity analysis was performed. Heterogeneity was assessed using the Cochrane Q test for both MR Egger and IVW methodologies. A Q_pval value greater than 0.1 indicates the absence of heterogeneity among the studies. Furthermore, we employed MR Egger to examine pleiotropy. An Egger_intercept close to 0 or a p-value (between the intercept and 0) greater than 0.05 suggests the absence of pleiotropy in the results. Additionally, we conducted a leave-one-out permutation analysis to evaluate the impact of individual SNPs on the overall results.

Results

Periodontal diseases

Based on our screening criteria, we identified 5 SNPs after excluding 1 palindromic SNP. Among these 5 SNPs, no

1 http://www.phenoscanner.medschl.cam.ac.uk/

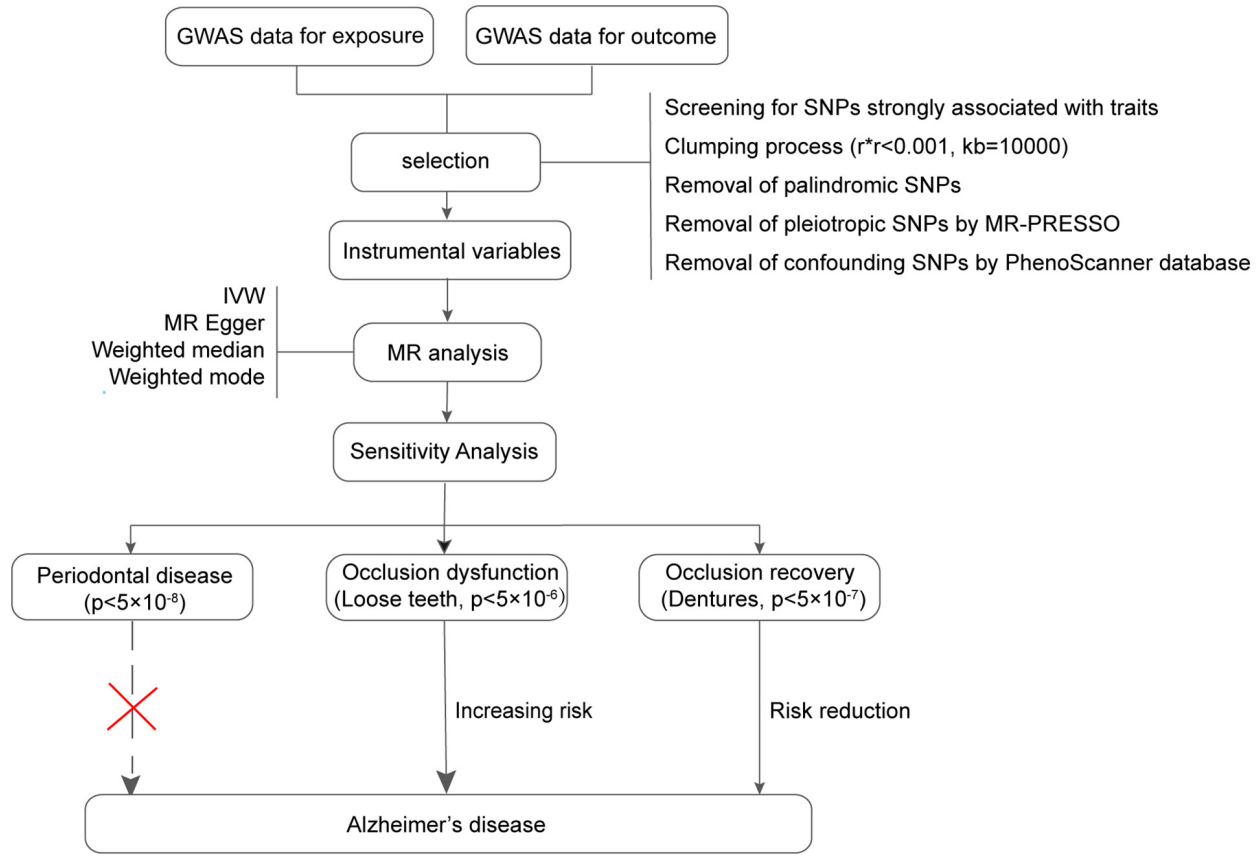

FIGURE 1
Flowchart of the Mendelian randomization process in this study. GWAS, Genome-wide association study; MR, Mendelian randomization.

TABLE 1 Detailed information on GWAS summary data.

Trait	Sample size	Population	Sex	Attribute	GWAS ID/Cohort
Periodontal Disease-related phenotype (Socransky)	975	European	mix	exposure	ebi-a-GCST003484
Occlusion Dysfunction (Loose Teeth)	461113	European	mix	exposure	ukb-b-12849
Occlusion Recovery (Dentures restoration)	498812	European	mix	exposure	UKB
Alzheimer's Disease (Late onset)	54162	European	mix	outcome	ebi-a-GCST002245
Alzheimer's Disease (Early onset)	171743	European	mix	outcome	FinnGen

The GWAS IDs provided in the table can be accessed on the IEU OpenGWAS website. UKB, UK Biobank.

palindromic SNPs, outlier SNPs, or confounding SNPs were detected. Our MR analysis revealed no causal association between PD and AD, as indicated by the MR results (P = 0.3950, IVW, Table 4).

Loose teeth

After applying screening criteria, we obtained a set of 13 instrumental variables (SNPs). This was achieved by removing 2 palindromic SNPs and 3 SNPs that were associated with confounding factors. Our MR-PRESSO and leave-one-out analyses did not identify any outlier SNPs (Figure 2).

Based on the results of the Weighted median method (p = 0.0275, OR = 747.4632, 95%CI = 2.08E+00 - 2.68E+05) and IVW method (p = 0.0171, OR = 187.3567, 95%CI = 2.54E+00−1.38E+04), we found a significant causal relationship between loose teeth and AD. Such a high OR (187.3567) implies a robust risk correlation between loose teeth and AD (Figure 3). To provide a comprehensive overview of the MR analysis, we have included the results of different methods in Table 4.

Furthermore, the Cochran's Q test (Q_pval = 0.3774, MR Egger; Q_pval = 0.46, IVW) and MR-Egger (p [between intercept and 0] = 0.9564) did not reveal any evidence of heterogeneity or horizontal pleiotropy.

TABLE 2 SNPs associated with known confounders.

Exposure	Sort	SNP	confounding factor	Reference (PMID)
Loose teeth	1	rs1117062	Diastolic blood pressure	33766239
Loose teeth	2	rs312989	hypertension	33766239
Loose teeth	3	rs72720396	Alcohol usually taken with meals	32230811
Dentures restoration	1	rs11084095	loose teeth	NA
Dentures restoration	2	rs12521680	Seen doctor for nerves, anxiety, tension or depression	21537355
Dentures restoration	3	rs148158713	Smoking	24924665
Dentures restoration	4	rs1794514	Cancer	32382138
Dentures restoration	5	rs2046850	hypertension	33766239
Dentures restoration	6	rs362270	Alcohol intake frequency	32230811
Dentures restoration	7	rs4795386	Rheumatoid arthritis	36198219
Dentures restoration	8	rs55958997	Smoking	24924665
Dentures restoration	9	rs6058638	Weight	19358976
Dentures restoration	10	rs72982972	Body mass index	19358976
Dentures restoration	11	rs7620314	Body mass index	19358976

By using PMID, the relevant literature on confounders can be accessed on the PubMed website. SNP, single nucleotide polymorphism.

Dentures restoration

Following the removal of 11 SNPs associated with confounding factors, we included a total of 22 SNPs for our MR analysis. Our analysis did not identify any SNPs as outliers (Figure 2).

Using the IVW analysis, we found a significant protective effect of dentures restoration against AD risk, with an OR of 0.0234 (95%CI = 1.13E-03—0.485) and a *p*-value of 0.0152 (Table 4, Figure 3).

We have also conducted tests to evaluate heterogeneity and horizontal pleiotropy. Both the IVW test (Q_pval = 0.8618) and the MR-Egger test (Q_pval = 0.8296, p [between intercept and 0] = 0.6932) did not provide evidence of heterogeneity or horizontal pleiotropy.

Discussion

Recently, the prevalence of OD in AD patients and its significant impact on brain health have been increasingly recognized. This condition not only arises from the mobility and cognitive impairments in AD patients but also contributes to the characteristic neurodegeneration and brain damage associated with the disease (Nakamura et al., 2021). In this study, we conducted a systematic evaluation of the causal relationships between PD, OD, occlusion recovery, and AD using a two-sample MR analysis. Our study yielded three key findings. Firstly, PD does not directly cause AD. Secondly, OD is a risk factor for AD. Lastly, occlusion recovery can reduce the risk of AD. These findings are in line with previous studies in the field.

AD patients usually suffer from PD. Previous studies have consistently shown a link between PD and AD (Borsa et al., 2021). Pathogenic bacteria associated with PD can lead to brain nerve damage and cognitive impairment through their proteins and DNA (Chen et al., 2017; Long and Holtzman, 2019). However, due to the limitations of epidemiologic studies, such as confounding factors and reverse causation, evidence for a causal relationship between PD and AD remains limited (Noble et al., 2009). Previous studies cannot provide evidence to support PD as a risk factor for AD (Sun et al., 2020). Accordingly, we re-evaluated and validated this result by utilizing stronger correlated instrumental variables ($p < 5.0 \times 10^{-8}$). Meanwhile, oral dysfunction (including OD) may contribute to cognitive impairment, such as the progression of AD (Takahashi et al., 2023). As not a direct factor in AD development, PD can indirectly influence the disease by causing certain intermediate signs. Severe PD can result in tooth loosening and eventual loss, which are frequently associated with malocclusion in patients. Additionally, numerous studies have indicated the association between occlusal function and the maintenance of brain nerve health.

To verify the role of occlusal function in AD, we performed MR analysis utilizing GWAS summary data from the UKB on loose teeth as a proxy for OD. The results indicated a significant causal relationship between OD and AD, supporting our initial hypothesis.

Tooth loss correlates with the decline of cognition-related brain regions (Kobayashi et al., 2018). Occlusion dysfunction reduces sensory input from receptors around the teeth, subsequently resulting in degeneration of primary nerve cells involved in brain neurotransmission (Kubota et al., 1988). A study confirmed that tooth loss results in the denervation of nerve endings at the root apex of the apical trigeminal nucleus Vmes (Goto et al., 2020). Vmes is the only primary sensory neuron located within the central nervous system. Recent studies suggest that this alteration may permit the activation of inflammatory microglia, which, in turn, activate pathways involving pro-phosphorylating kinases and oxidative stress. This leads to tau hyperphosphorylation and aggregation, and consequent degeneration of the locus coeruleus (LC) located near Vmes (Matsumoto et al., 2023). Additionally, the LC is primarily responsible for the release of norepinephrine, which has been shown to have an inhibitory effect on inflammation. Therefore, the degradation of the LC enhances the inflammatory

TABLE 3 Instrumental variables for MR analysis.

Exposure	Sort	SNP	EA	OA	Beta	SE	*P*-value
PD	1	rs1156327	C	T	−1.452	0.230	3.01E-10
PD	2	rs1633266	T	C	−0.932	0.168	3.09E-08
PD	3	rs17184007	C	T	1.346	0.232	6.86E-09
PD	4	rs17718700	C	T	1.217	0.223	4.58E-08
PD	5	rs3811273	G	A	1.216	0.203	2.06E-09
Loose teeth	1	rs11049359	C	T	0.003	0.0005	2.60E-08
Loose teeth	2	rs11220245	G	A	0.002	0.0005	2.70E-07
Loose teeth	3	rs279743	C	T	−0.002	0.0004	3.70E-06
Loose teeth	4	rs2947122	A	G	0.003	0.0006	1.20E-06
Loose teeth	5	rs34438171	T	C	0.003	0.0006	4.30E-06
Loose teeth	6	rs3763469	C	T	−0.003	0.0005	6.80E-07
Loose teeth	7	rs4801882	A	G	0.002	0.000	1.00E-07
Loose teeth	8	rs61823158	G	A	−0.004	0.0008	4.10E-07
Loose teeth	9	rs6586364	T	G	0.003	0.0007	1.80E-06
Loose teeth	10	rs7028167	C	A	0.002	0.0005	4.00E-06
Loose teeth	11	rs714962	G	A	0.002	0.0004	2.60E-06
Loose teeth	12	rs72664597	G	A	0.004	0.0008	4.80E-07
Loose teeth	13	rs982894	G	A	0.002	0.0004	4.20E-06
Dentures restoration	1	rs10048146	G	A	0.008	0.001	3.50E-13
Dentures restoration	2	rs10956340	C	A	−0.005	0.001	8.06E-08
Dentures restoration	3	rs10987017	G	A	0.005	0.001	8.28E-08
Dentures restoration	4	rs111659883	T	C	−0.005	0.001	3.55E-07
Dentures restoration	5	rs1122171	T	C	0.012	0.001	4.55E-44
Dentures restoration	6	rs117737827	T	C	0.007	0.001	1.61E-09
Dentures restoration	7	rs121908120	A	T	−0.022	0.003	3.54E-17
Dentures restoration	8	rs1482698	C	G	0.005	0.001	4.89E-10
Dentures restoration	9	rs2238651	T	C	0.005	0.001	2.61E-07
Dentures restoration	10	rs2270764	G	A	0.008	0.001	7.80E-20
Dentures restoration	11	rs2421616	G	A	−0.004	0.001	4.75E-07
Dentures restoration	12	rs2514310	G	A	−0.005	0.001	2.43E-07
Dentures restoration	13	rs4233366	T	C	0.005	0.001	4.52E-07
Dentures restoration	14	rs4445705	T	A	−0.007	0.001	1.65E-07
Dentures restoration	15	rs62254667	G	A	0.030	0.005	2.03E-08
Dentures restoration	16	rs72694438	A	G	0.006	0.001	1.39E-08
Dentures restoration	17	rs7367207	T	C	0.006	0.001	1.01E-10
Dentures restoration	18	rs77083638	G	A	0.007	0.001	2.18E-07
Dentures restoration	19	rs7864794	T	G	0.007	0.001	7.26E-08
Dentures restoration	20	rs924394	A	G	−0.006	0.001	1.86E-09
Dentures restoration	21	rs933292	A	G	0.006	0.001	2.21E-07
Dentures restoration	22	rs9831002	G	T	0.005	0.001	9.96E-11

PD, Periodontal Disease; EA, effect_allele; OA, other_allele; SE, standard error.

response, further increasing the number of inflammatory microglia and creating a vicious cycle. Additionally, other studies show that OD contributes to decreased expression of brain-derived neurotrophic factor (BDNF) (Takeda et al., 2016) and affects neurotransmitter release, such as the dopamine and acetylcholine in the hippocampus (Makiura et al., 2000;

TABLE 4 MR estimates for the association between exposures and outcome.

Exposure	MR method	No. of SNP	OR	95% CI	*P*-value	SE
PD	MR Egger	5	1.083	0.757 - 1.550	0.691	0.183
PD	Weighted median	5	0.979	0.913 - 1.049	0.538	0.035
PD	IVW	5	0.977	0.927 - 1.030	0.395	0.027
PD	Weighted mode	5	0.986	0.900 - 1.081	0.778	0.047
Loose teeth	MR Egger	13	331.197	4.29E-07 - 2.56E+11	0.590	10.442
Loose teeth	Weighted median	13	747.463	2.08E+00 - 2.68E+05	0.028	3.001
Loose teeth	IVW	13	187.357	2.54E+00 - 1.38E+04	0.017	2.194
Loose teeth	Weighted mode	13	3978.370	1.19E-01 - 1.33E+08	0.145	5.317
Dentures restoration	MR Egger	22	0.135	1.52E-05 - 1.19E+03	0.670	4.638
Dentures restoration	Weighted median	22	0.024	2.33E-04 - 2.566	0.118	2.375
Dentures restoration	IVW	22	0.023	1.13E-03 - 0.485	0.015	1.547
Dentures restoration	Weighted mode	22	0.018	6.90E-05 - 4.912	0.176	2.850

IVW, Inverse-Variance Weighted; OR, odds ratio; SE, standard error; CI, confidence interval.

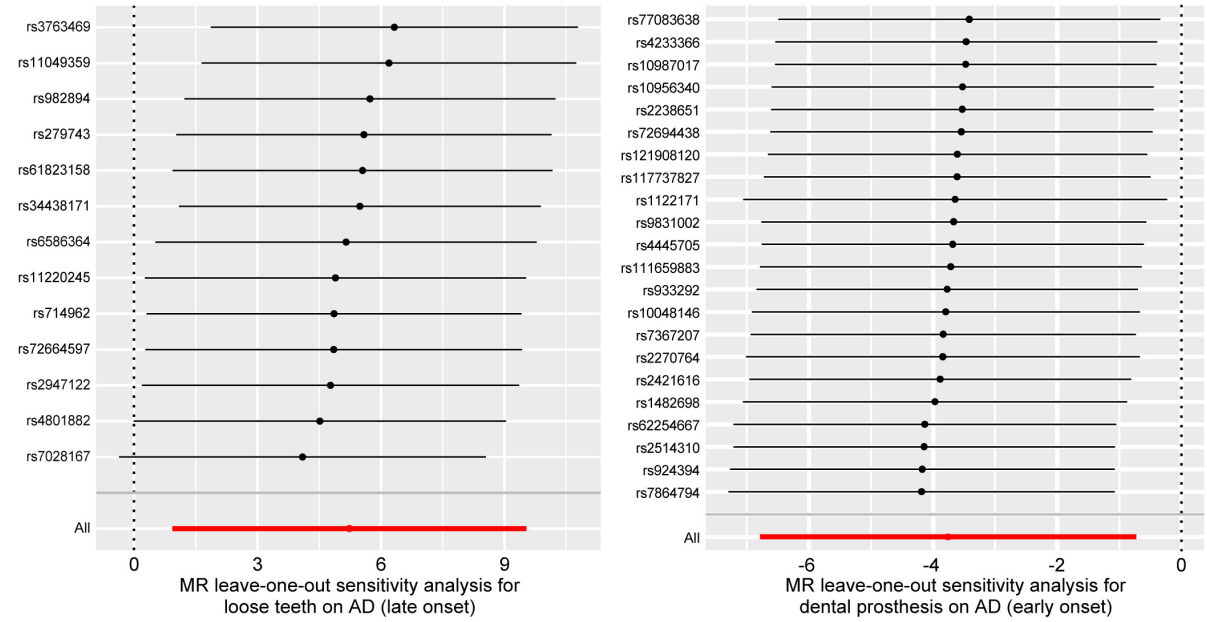

FIGURE 2
Forest plots for leave-one-out analysis in sensitivity analyses. MR analysis after removing SNPs one by one. AD, Alzheimer's disease.

Kushida et al., 2008). As reduced brain volume and dysfunction are observed in AD patients (Teipel et al., 2006; Wang et al., 2020), OD can contribute to the development of AD through mechanisms such as Tau deposition, reduced neurotransmitter secretion, and decreased BDNF expression, all resulting from neurodegeneration. Additionally, it has been shown that chewing dysfunction may contribute to the development of AD by decreasing blood flow to the brain and affecting diet (Blazer, 2022).

As the effective therapeutic for occlusion recovery, dentures restoration significantly improved occlusal function in individuals with tooth loss (Campos et al., 2017). In addition, the MR analysis results indicate a significant reduction in the risk of AD associated with occlusion recovery, which is consistent with a controlled clinical trial (Okamoto, 2011). In which, improved occlusion function facilitates neurostimulation into the brain, promotes neurotransmitter transmission, and prevents the atrophy of cerebral nerves. Consequently, dental prostheses and occlusion recovery can slow down the progression of AD. This finding corroborates the idea that OD contributes to the progression of AD and emphasizes the importance of oral care or occlusal function for AD patients (Gao et al., 2020).

In this study, we utilized SNPs strongly associated with exposure and outcome to achieve randomization, bypassing the limitations of traditional RCTs. The heritability of exposure and outcome is crucial for determining if SNPs are robust

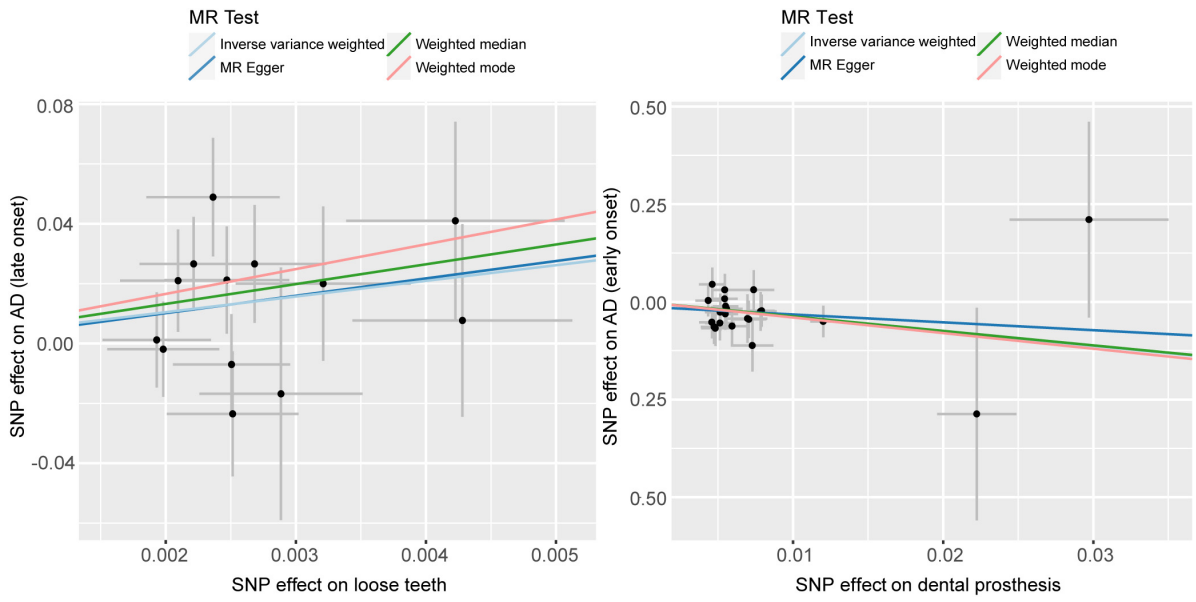

FIGURE 3
Scatter plots of causality. Perform linear regression on the results of the four different methods in MR analysis. The slope is equal to the beta. AD, Alzheimer's disease.

proxies. Research indicates that AD (Loy et al., 2014; Quan et al., 2023) and PD (Loos and Van Dyke, 2020; Shaddox et al., 2021) are strongly hereditary, and loose teeth, a marker of advanced PD, have a clear genetic relationship (Morelli et al., 2020). Given the correlation between dentures restoration and occlusal function recovery, we use dentures restoration as a proxy. Occlusion function, influenced by genetic factors affecting teeth characteristics, can be compromised by genes increasing susceptibility to PD bacteria, leading to teeth loosening and dysfunction (Esberg et al., 2019). These genetic factors also affect the feasibility of occlusal function recovery, indicating a strong genetic correlation with dentures restoration.

While our study follows a rigorous logic and the results are cross-validated, there are limitations to be considered. The AD GWAS data obtained from the UK Biobank relied on self-reports, which may introduce inaccuracies due to self-cognitive biases. Nevertheless, a meta-analysis by Marioni et al. (2018) has suggested that self-reported AD can accurately represent a clinical diagnosis (Marioni et al., 2018). Additionally, as our study is based on a European population, the generalizability of our findings to other populations may be limited, and further validation in other races is needed in future research.

Conclusion

Overall, our study provides important insights into the relationships between PD, OD, occlusion recovery, and AD. These findings contribute to a better understanding of the role of OD in AD development and emphasize the significance of occlusion recovery in the prevention of AD. Importantly, the preservation of optimal occlusion function represents a viable strategy to safeguard neurologic integrity.

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

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

Author contributions

QW: Writing—review and editing, Writing—original draft, Formal analysis, Data curation. WZ: Writing—review and editing, Writing—original draft, Formal analysis, Data curation. RH: Writing—review and editing, Writing—original draft, Resources, Data curation. ZW: Writing—review and editing, Investigation, Formal analysis. YS: Writing—review and editing, Resources. WS: Writing—review and editing, Data curation. CH: Writing—review and editing, Supervision, Funding acquisition, Conceptualization. JX: Writing—review and editing, Supervision, Funding acquisition, Conceptualization. HZ: Writing—review and editing, Supervision, Funding acquisition, Conceptualization.

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Conflict of interest

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

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The impact of education and occupation on cognitive impairment: a cross-sectional study in China

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Background and objectives: Education, occupation, and cognitive activity are key indicators of cognitive reserve and are thought to influence cognitive impairment. However, the individual and combined impacts of these factors are not fully understood. This study aims to investigate the roles of education and occupation in cognitive impairment while controlling for brain reserve and cognitive activity.

Methods: This cross-sectional study involved 369 participants aged 50 years or older from urban outpatient clinics in Jilin Province, China. Cognitive impairment was assessed using neuropsychological scales and brain imaging. Cognitive activity was evaluated with the Cognitive Reserve Scale (CRS). Covariance analysis and logistic regression models were used to analyze the associations, adjusting for age, sex, education, and occupation.

Results: Higher education was significantly associated with a lower risk of cognitive impairment ($p < 0.001$), regardless of occupation. In contrast, occupational complexity and cognitive activity did not show a significant relationship with cognitive impairment ($p > 0.05$).

Conclusion: Education, rather than occupation or cognitive activities, is a significant predictor of cognitive impairment, highlighting the importance of educational attainment in cognitive health.

KEYWORDS

cognitive reserve, education, occupation, cognitive activity, cognitive impairment

1 Introduction

Cognitive reserve (CR) has become a cornerstone in understanding the resilience observed in individuals who exhibit minimal cognitive decline despite significant brain pathologies such as Alzheimer's disease and other neurodegenerative conditions (Cavedo et al., 2012; Staff, 2012). The concept of CR explains the disparity between the extent of neuropathology and its clinical manifestations. CR is thought to be facilitated by lifelong intellectual engagement, encompassing formal education, challenging occupations, and leisure activities (Stern, 2012; Lövdén et al., 2020). This study aims to investigate the specific roles of education, occupation, and cognitive activity in contributing to CR and their individual and combined impacts on cognitive impairment. We hypothesize that higher education and intellectually demanding

occupations will be associated with higher CR and better cognitive outcomes.

A newly published white paper used CR to refer to an adaptive force that helps explain differences in sensitivity among individuals when coping with aging or lesions (Stern et al., 2020). CR is defined within this study as the brain's capacity to resist neurodegenerative damage due to its cognitive and neural flexibility. This section aims to expand on this operational definition by exploring the mechanisms through which intellectual engagements–such as education, challenging occupations, and leisure activities–contribute to CR. These activities are believed to enhance neural efficiency and cognitive flexibility, thereby allowing individuals to better manage the cognitive demands imposed by brain pathology.

Building on the definition of CR, our study particularly emphasizes the role of education and occupation. We posit that higher educational attainment and engagement in intellectually demanding occupations bolster cognitive reserve by enhancing synaptic density, network connectivity, and overall neural plasticity (Li et al., 2021; Ekdahl et al., 2023). This segment delves into how these components interact with lifelong cognitive activities to mitigate the effects of neurodegenerative lesions, providing a more detailed examination of the pathways through which education and occupational complexity influence cognitive health.

Research into CR has significantly advanced; however, critical gaps remain regarding the quantification of how educational and occupational engagements individually and collectively impact cognitive decline (Sherman-Wilkins and Thierry, 2019; Corbo et al., 2023). Our study seeks to address these gaps by employing advanced statistical models to quantify the relationship between CR components and cognitive outcomes. These models aim to refine our understanding and prediction of cognitive decline, paving the way for more targeted preventive and therapeutic interventions. Specifically, we introduce predictive modeling as a methodological approach to assess how educational attainment and occupational complexity contribute to cognitive reserve in aging populations.

This study proposes to test two primary hypotheses: (1) higher levels of educational attainment and (2) more complex occupational tasks are independently and synergistically associated with greater cognitive reserve. Furthermore, this cognitive reserve is hypothesized to influence cognitive performance among elderly subjects. We assess cognitive performance using standard neuropsychological assessments rather than direct measures of brain pathology. This approach allows us to infer the protective effects of cognitive reserve against cognitive decline without directly measuring neurodegenerative markers, providing insights into how lifelong educational and occupational engagements contribute to resilience against cognitive impairment.

2 Methods

2.1 Study participants and design

This cross-sectional study recruited participants from urban outpatient clinics of Jilin Province, China, reflecting diverse socio-economic conditions. Individuals undergoing medical examination were recruited from the largest regional medical center in the city. The inclusion criteria were as follows: aged 50 years or older, native Chinese speaker (able to communicate without barriers), and a Mini-Mental State Examination (MMSE) score of>24 points (primary: >20 points; illiteracy: >17 points). Written informed consent was obtained from all participants. Recruitment began in October 2022 and concluded in March 2023. Neurologists interviewed all subjects, and any individuals with a history of psychiatric or central nervous system disorders, hearing loss, learning disabilities, or any other conditions that could impact their performance on the neuropsychological test battery were excluded. Interviewers were trained to recognize when information on one questionnaire contradicts another, and we excluded participants with any signs of inconsistency found during the interview. This study was performed per the ethical standards in the 1964 Declaration of Helsinki, and the Ethics Committee of the School of Nursing, Jilin University approved the study and registered it with the China Clinical Registry (ChiCTR2200055112). A total of 378 participants were recruited, of which nine did not meet the inclusion and exclusion criteria or withdrew from the survey.

2.2 Cognitive reserve assessment

Cognitive Reserve was quantitatively assessed using the Cognitive Reserve Scale (CRS), a tool specifically designed to evaluate lifetime cognitive activities across diverse domains (Leon et al., 2011; León et al., 2014; Roldán-Tapia et al., 2017; León et al., 2018). This scale systematically gathers data on education, work complexity, and leisure activities, producing a composite score that reflects each participant's overall cognitive reserve.

The CRS is structured into four categories: daily activities, training, hobbies, and social life, with items rated on a 5-point Likert scale ranging from 0 (never) to 4 (three or more times per week). This method highlights the cumulative cognitive capacity of individuals, focusing on sustained cognitive engagement rather than transient cognitive activities. It addresses three critical life stages: youth (18–35 years), middle age (36–64 years), and old age (≥65 years). Participants complete the subscale corresponding to their current age stage. Each item's score is summed to derive a total CRS score, which can range from 0 to 96. Higher scores indicate more frequent engagement in cognitive reserve-building activities across the assessed life stages, reflecting higher levels of cognitive reserve.

2.3 Neuropsychological evaluation

To thoroughly assess the cognitive performance of participants, our study employed a comprehensive neuropsychological test battery that included well-established cognitive assessments alongside additional tests aimed at covering a broad spectrum of cognitive functions. Key instruments used were the MMSE (Katzman et al., 1988) and the Montreal Cognitive Assessment (MoCA) (Lu et al., 2011), both highly regarded for their utility in identifying cognitive impairments across various cognitive domains. Importantly, in order to ensure accuracy and relevance to our demographic, the raw scores for both the MMSE and MoCA were adjusted for age and educational level based on Chinese normative data. This adjustment is crucial as it accounts for the significant impact that these demographic factors can have on cognitive testing outcomes, thereby allowing for a more

Abbreviations: CR, cognitive reserve; CI, cognitive impairment.

precise evaluation of cognitive health relative to the normative standards of the Chinese population.

Furthermore, the study incorporated the Activities of Daily Living (ADL) scale to evaluate functional capabilities (Lawton and Brody, 1969; Graf, 2008), the Auditory Verbal Learning Test (AVLT) (Dong et al., 2023) for memory and learning abilities, and the Memory and Executive Screening (MES) test (Guo et al., 2012) to probe executive functions and memory recall. These assessments are especially sensitive to cognitive changes potentially related to varying levels of cognitive reserve.

Additionally, our neuropsychological evaluation featured tasks aimed at assessing verbal fluency, abstract reasoning, and complex problem-solving capabilities, such as the Animal Naming Test (ANT) (Huang et al., 2023) and the Clinical Dementia Rating (CDR) scale (Morris, 1993), which assesses six cognitive and functional domains including memory, orientation, judgment and problem-solving, community affairs, home and hobbies, and personal care (Howell et al., 2022). This robust approach aids in effectively detecting cognitive impairments, defining cognitive impairment as a CDR score of 0.5 or greater.

These tests, conducted under standardized conditions, were designed to collect detailed data on the cognitive health of participants, with results thoroughly documented and analyzed. By correlating cognitive performance with Cognitive Reserve Scale scores, our research aims to explore how cognitive reserve levels influence individuals' vulnerability or resilience to cognitive impairments.

This comprehensive evaluation serves to elucidate the intricate relationship between cognitive reserve and cognitive performance, offering deeper insights into cognitive reserve's potential to protect against cognitive decline.

2.4 Measurement of brain reserve

Brain reserve refers to the brain's ability to tolerate pathology without exhibiting clinical symptoms, a concept that is supported by varying individual resilience to similar levels of brain pathology (Satz, 1993; Hachinski and Avan, 2022). Recent research underscores the importance of brain reserve in mediating the effects of neurological changes, particularly in the context of aging and neurodegenerative diseases (Chen et al., 2020; Stern et al., 2020). This variability can be explored through proxy measures when direct neuroimaging is not feasible.

While advanced neuroimaging techniques have offered deep insights into brain reserve by measuring aspects such as cortical thickness and white matter integrity, not all studies have the resources to employ such methods. In this context, simpler, more accessible proxy measures like head circumference have been used as indicators of brain reserve (Chen et al., 2020; Yang et al., 2020). Head circumference is thought to correlate with brain volume, which is a critical component of brain reserve (Yang et al., 2020). Larger brain volumes are hypothesized to provide a greater buffer against the cognitive impairments resulting from brain pathologies, such as those seen in Alzheimer's disease.

This study utilizes head circumference as a proxy for brain reserve, drawing on methodologies that, while less direct than neuroimaging, still offer valuable insights into the structural capacities that might underpin cognitive resilience.

2.5 Statistical analysis

Data were analyzed using IBM SPSS Statistics 25 (IBM Corp, Armonk, NY, United States). Descriptive statistics were computed for all primary variables, reported as mean ± SD or median (Q1–Q3) for numerical data and N (%) for categorical data. To address the issue of unbalanced age groups, weights were applied in all analyses to adjust for disproportionate sample sizes across age categories. This adjustment ensures a more accurate representation and analysis of the data. Categorical variables were compared using chi-square tests, and continuous variables were assessed using unpaired t-tests.

Categorical variables were compared using chi-square tests, and continuous variables were assessed using unpaired t-tests to evaluate differences between participants with and without cognitive impairment in sociodemographic and clinical variables. Additionally, a variance inflation factor (VIF) analysis was conducted to check for multicollinearity among predictors before running the regression models.

The relationship between cognitive reserve (quantified by CRS total scores) and neuropsychological outcomes was examined using multiple regression models. These models included adjustments for age, sex, and educational level, as well as other potential confounders identified during the multicollinearity analysis. Additionally, a factorial ANOVA was conducted to explore the interactions between education and occupation on CRS scores, with age as a covariate. The significance threshold for all tests was set at $\alpha < 0.05$.

3 Results

3.1 Demographic and clinical characteristics

The demographic and clinical characteristics of the 369 participants are summarized in Table 1. The average age of participants was 61.5 years (SD = 7.9). The cohort included 156 males (42.3%) and 213 females (57.7%). Significant differences were noted in the rates of cognitive impairment among participants, which varied by age, educational level, waistline, thigh circumference, and family history of stroke. Older adults and those with less education were more likely to exhibit signs of cognitive impairment, with statistical significance observed across these groups ($p < 0.05$).

3.2 Distribution of cognitive impairment

The analysis explored the distribution of cognitive impairment rates across various demographic and occupational groups within our study cohort. Figure 1 depicts this distribution, highlighting significant disparities in cognitive impairment rates based on age, education level, and type of occupation.

The findings demonstrate that cognitive impairment was most prevalent among older adults, those with a lower level of education, and individuals engaged in physically demanding occupations. Specifically, over 60% of participants in these groups exhibited cognitive impairment, underscoring the pronounced impact of socio-economic and demographic factors on cognitive health.

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TABLE 1 Characteristics of the sample according to the presence of cognitive impairment ($n = 369$).

Sociodemographic variable	All	Cognitive impairment		t/χ^2-Value	*p*-Value
	(n = 369)	No(n = 240)	Yes(n = 129)		
Age (years), mean ± SD*	61.5 ± 7.9	60.0 ± 7.9	64.3 ± 7.2	−5.018	<0.001
Age group, *n* (%)†				15.369	<0.001
<65 years	251 (68.0)	180 (75.0)	71 (55.0)		
≥65 years	118 (32.0)	60 (50.8)	58 (49.2)		
Male sex, n(%)†				0.973	0.377
Male	156 (42.3)	97 (62.2)	59 (37.8)		
Female	213 (57.7)	143 (67.1)	70 (32.9)		
Education level, *n* (%)†				18.949	<0.001
Lower education	91 (24.7)	42 (46.2)	49 (53.8)		
Higher education	278 (75.3)	198 (71.2)	80 (28.8)		
Occupation, *n* (%)†				2.150	0.177
Physical	76 (20.6)	44 (57.9)	32 (42.1)		
Intellectual	293 (79.4)	196 (66.9)	97 (33.1)		
Cognitive activity total, mean ± SD*	42.6 ± 12.0	43.2 ± 11.5	41.5 ± 12.8	1.254	0.211
Cognitive activity stage, mean ± SD*					
Youth (score)	44.5 ± 12.9	45.4 ± 11.8	42.8 ± 14.6	1.770	0.078
Middle age (score)	41.4 ± 13.2	41.4 ± 13.1	41.4 ± 13.5	−0.029	0.977
Old age (score)	40.3 ± 13.0	41.2 ± 13.3	39.5 ± 12.8	0.699	0.486
Cognitive activity grade, *n* (%)†				0.829	0.676
Low	99 (26.8)	67 (67.7)	32 (32.3)		
Medium	171 (46.3)	112 (65.5)	59 (34.5)		
High	99 (26.8)	61 (61.6)	38 (38.4)		
Circumference of body parts (cm), mean ± SD*					
Head circumference	55.1 ± 2.5	55.0 ± 2.5	55.3 ± 2.4	−1.306	0.192
Height	164.4 ± 7.6	164.4 ± 7.9	164.4 ± 7.2	−0.022	0.982
Waistline	84.3 ± 11.0	82.8 ± 11.7	87.1 ± 9.1	−3.861	<0.001
Hipline	99.9 ± 7.7	100.0 ± 8.2	99.7 ± 6.7	0.374	0.709
Upper limb circumference	29.1 ± 3.9	28.8 ± 3.9	29.6 ± 3.7	−1.897	0.059
Thigh circumference	50.1 ± 6.8	49.5 ± 6.7	51.0 ± 6.9	−2.074	0.039
Calf circumference	35.6 ± 3.8	35.4 ± 4.0	36.0 ± 3.5	−1.654	0.099
Weight (kg), mean ± SD*	66.5 ± 11.5	66.6 ± 11.9	66.4 ± 10.8	0.167	0.867
Regular exercise habit, *n* (%)†				0.329	0.548
No	57 (15.4)	35 (61.4)	22 (38.6)		
Yes	312 (84.6)	205 (65.7)	107 (34.3)		
Social activities, *n* (%)†				1.351	0.521
Low	126 (34.1)	87 (69.0)	39 (31.0)		
Medium	170 (46.1)	107 (62.9)	63 (37.1)		
High	73 (19.8)	46 (63.0)	27 (37.0)		
Family history, *n* (%)†					
Dementia	52 (14.1)	36 (15.0)	16 (12.4)	0.467	0.534
Stroke	85 (23.0)	65 (27.1)	20 (15.5)	6.346	0.014
Hypertension	160 (43.4)	110 (45.8)	50 (38.8)	1.709	0.226
Diabetes	97 (26.3)	63 (26.3)	34 (26.4)	<0.001	0.982
Dyslipidemia	65 (17.6)	49 (20.4)	16 (12.4)	3.713	0.062
CHD	96 (26.0)	69 (28.7)	27 (20.9)	2.666	0.108
Cancer	68 (18.4)	51 (21.3)	17 (13.2)	3.636	0.067

*Unpaired *t* test. †Chi-squared test.

Statistical analysis revealed that individuals with lower educational attainment faced a higher risk of cognitive impairment, irrespective of their occupation being intellectually or physically oriented in Table 2. The rates of cognitive impairment were significantly higher in individuals with lower education levels working in physical roles ($p < 0.001$) and those in intellectual roles ($p = 0.018$), suggesting that education level plays a crucial role in mitigating cognitive decline, beyond the nature of occupational activities.

Intriguingly, among the lower age population, differences in education levels significantly influenced the likelihood of experiencing cognitive impairment, with those attaining higher education faring better ($p < 0.001$). However, in the elderly population, this protective effect of higher education appeared diminished, with no statistically significant differences in cognitive impairment rates observed across educational levels. This pattern suggests that while higher education can delay the onset of cognitive impairments during earlier stages of adulthood, its protective effects may wane as individuals age.

3.3 Cognitive reserve and neuropsychological outcomes

Multivariable regression analysis detailed in Table 3 demonstrates that higher CRS scores significantly enhance neuropsychological performance, particularly in the MoCA and MES tests. Before conducting the final analysis, the VIF was used

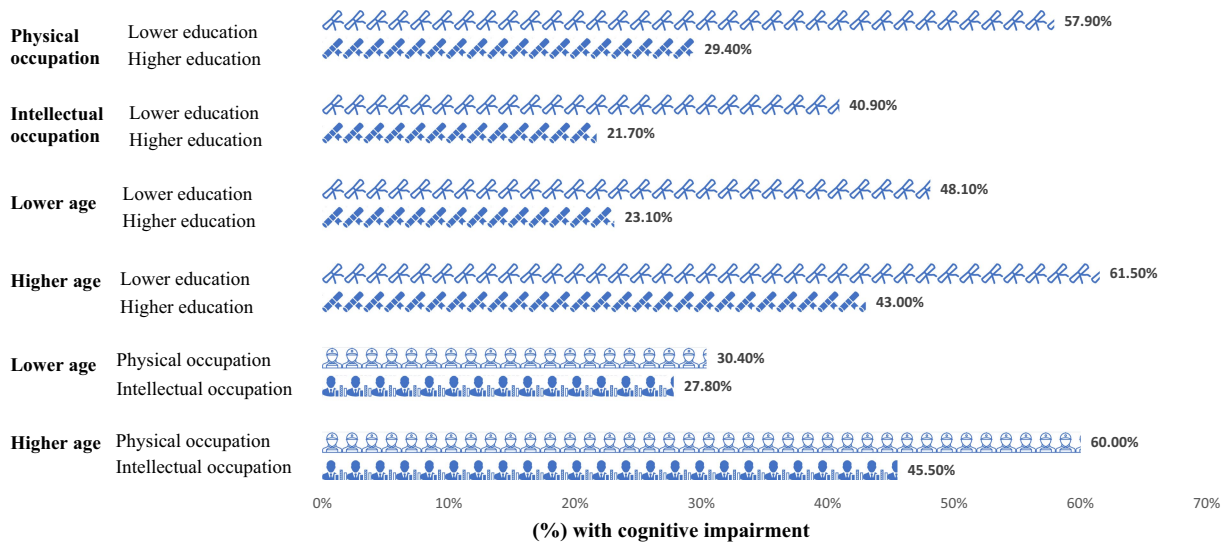

FIGURE 1
Proportion of cognitive impairment across different participant groups ($N = 369$). Lower education = years of education≤12 years; Higher education: university degree or above; Physical occupation: occupation predominated by physical strength; Intellectual occupation: occupation predominated by intellectual skills; Lower age: <65 years; Higher age: ≥65 years.

TABLE 2 Association of cognitive impairment with education level and occupation ($n = 369$).

Group	Subgroup	*n*	Cognitive impairment			χ2-Value	df	*p*-value
			No	Yes	%			
Physical occupation	Lower education	38	16	22	57.90%	12.115	1	0.001
	Higher education	255	180	75	29.40%			
Intellectual occupation	Lower education	53	26	27	40.90%	5.612	1	0.018
	Higher education	23	18	5	21.70%			
Lower age	Lower education	52	27	25	48.10%	12.663	1	<0.001
	Higher education	199	153	46	23.10%			
Higher age	Lower education	39	15	24	61.50%	3.576	1	0.059
	Higher education	79	45	34	43.00%			
Lower age	Physical occupation	46	32	14	30.40%	0.128	1	0.720
	Intellectual occupation	205	148	57	27.80%			
Higher age	Physical occupation	30	12	18	60.00%	1.894	1	0.169
	Intellectual occupation	88	48	40	45.50%			

df, Degrees of Freedom.

TABLE 3 Cognitive reserve and neuropsychological outcomes ($n = 369$).

Variable	Adjustment	*R*	B Coefficient (β)	Standard Error (SE)	*t*-value	*p*-value	95% Confidence Interval
CRS score impact on MMSE	Unadjusted	0.136	0.021	0.008	2.627	0.009	[0.005, 0.037]
	Adjusted	0.284	0.011	0.008	1.363	0.174	[−0.005, 0.027]
CRS score impact on MoCA	Unadjusted	0.186	0.050	0.014	3.625	<0.001	[0.023, 0.077]
	Adjusted	0.387	0.027	0.014	2.015	0.045	[0.001, 0.054]
CRS score impact on ANT	Unadjusted	0.148	0.072	0.025	2.868	0.004	[0.022, 0.121]
	Adjusted	0.311	0.042	0.025	1.661	0.098	[−0.008, 0.092]
CRS score impact on MES	Unadjusted	0.221	0.202	0.047	4.347	<0.001	[0.111, 0.294]
	Adjusted	0.425	0.121	0.045	2.672	0.008	[0.032, 0.211]
CRS score impact on ADL	Unadjusted	0.131	−0.015	0.006	−2.530	0.012	[−0.027, −0.003]
	Adjusted	0.291	−0.011	0.006	−1.848	0.065	[−0.023, 0.001]
CRS score impact on HAMA	Unadjusted	0.095	−0.034	0.019	−1.831	0.068	[−0.071, 0.003]
	Adjusted	0.127	−0.027	0.020	−1.384	0.167	[−0.065, 0.011]
CRS score impact on HAMD	Unadjusted	0.050	−0.015	0.016	−0.961	0.337	[−0.046, 0.016]
	Adjusted	0.110	−0.008	0.017	−0.458	0.647	[−0.040, 0.025]

The adjusted variables ware age, gender, and education level.

to check for multicollinearity among predictors to ensure the validity of the results. After adjusting for age, gender, and education level, each incremental increase in CRS scores yielded a 0.027-point increase in MoCA scores [$p = 0.045$, 95% CI (0.001, 0.054)] and a 0.121-point increase in MES scores [$p = 0.008$, 95% CI (0.032, 0.211)]. These findings underscore the substantial role of cognitive reserve in improving overall and specific cognitive domains. Nonetheless, CRS's influence was not statistically significant for other assessments, including MMSE, ADL, Hamilton Anxiety (HAMA), and Depression (HAMD) scales, after factoring in confounding variables. These findings underscore the importance of cognitive reserve in enhancing cognitive function, particularly in memory and executive domains, highlighting potential targets for cognitive intervention.

3.4 Association of cognitive reserve with age, education level, and occupation

The analysis underscores a significant association between higher CRS scores and younger age, higher education levels, and intellectual occupations. Detailed findings in Table 4 reveal that both education and occupation levels significantly correlate with CRS scores after adjusting for age ($p < 0.001$). However, when further adjusting for education, the association between occupation type and CRS diminishes, indicating no significant differences in cognitive reserve between individuals in intellectual versus physical occupations ($p = 0.118$). Conversely, higher education remains a strong predictor of higher CRS scores, even after adjusting for age and occupation ($p < 0.001$), highlighting the robust impact of educational attainment on cognitive reserve.

Additionally, factorial ANOVA results presented in Table 5 illustrate the effects of education and occupation on CRS, with age as a covariate. The interaction between education and occupation does not significantly affect CRS ($p = 0.529$), further emphasizing the predominant influence of education level over occupational type in contributing to cognitive reserve.

3.5 Association of cognitive impairment with education level and occupation categories

The study findings reveal a significant association between cognitive impairment and education-and-occupation combinations, with higher education and physical occupation [OR = 0.316 (0.153,0.654), $p = 0.002$] or intellectual occupation [OR = 0.211 (0.063,0.710), $p = 0.012$] displaying lower risks of cognitive impairment than low education and physical occupation combinations in Table 6. The results also indicate that occupation has a notable influence on scores on overall assessments of cognition (MMSE, $p = 0.013$ and MoCA $p = 0.002$) and some assessments of specific cognitive domains such as memory and language cognition domain (MES $p < 0.001$ and ANT $p < 0.001$). However, no significant effect of occupation was observed on scores on the ADL, HAMA or HAMD ($p > 0.05$). These findings are presented in Supplementary Table S1.

4 Discussion

Our study underscores the significant role of educational attainment in reducing the risk of cognitive impairment, highlighting that higher education is associated with better cognitive activity and lower risk, irrespective of occupational complexity. Contrary to initial assumptions, intellectually demanding occupations did not correlate with reduced cognitive impairment risk or enhanced cognitive activity. Analysis of cognitive function assessments revealed that occupation impacts global cognition scores (MMSE, MoCA) and specific cognitive

TABLE 4 Association of CRS with education level and occupation ($n = 369$).

Variable	*n*	CRS Score	Univariate *p*	Adjusted-1 *p*	Adjusted-2 *p*	Adjusted-3 *p*
Age group, %*			0.031	–	–	–
<65 years old	251	45.54 (12.17)				
>=65 years old	118	40.65 (11.41)				
Education, %*			<0.001	<0.001	–	<0.001
Lower education	91	36.49 (10.96)				
Higher education	278	44.62 (11.65)				
Occupation, %*			<0.001	<0.001	0.118	–
Physical	76	37.38 (12.45)				
Intellectual	293	43.97 (11.51)				

*CRS Score as the dependent variable. The adjusted-1 p-values were education and occupation as independent variables, age as covariate. The adjusted-2 P-values were occupation as independent variables, age and education as covariate. The adjusted-3 p-values were education as independent variables, age, and occupation as the covariate.

TABLE 5 Factorial ANOVA for effects of education and occupation on CRS, with age as a covariate ($n = 369$).

Source of variation	DF	Sum of squares	Mean square	*F*-Value	*p*-Value	Effect size (η^2)
Education	1	2049.255	2049.255	15.56	<0.001	0.041
Occupation	1	321.548	321.548	2.441	0.119	0.007
Education × Occupation	1	52.396	52.396	0.398	0.529	0.001
Age (Covariate)	1	80.425	80.425	0.611	0.435	0.002

DF, Degrees of freedom.

TABLE 6 Association of cognitive impairment with education level and occupation categories ($n = 369$).

Education/ Occupation	Univariate OR (95% CI)	*p*-value	Model 1 OR (95% CI)	*p*-value	Model 2 OR (95% CI)	*p*-value	Model 3 OR (95% CI)	*p*-value
Higher/Physical ($n=255$)	0.303 (0.151, 0.609)	0.001	0.347 (0.170, 0.710)	0.004	0.347 (0.170, 0.710)	0.004	0.316 (0.153, 0.654)	0.002
Lower/Intellectual ($n=53$)	0.755 (0.326, 1.749)	0.512	0.743 (0.314, 1.757)	0.499	0.743 (0.314, 1.757)	0.499	0.719 (0.301, 1.717)	0.457
Higher/Intellectual ($n=23$)	0.755 (0.326, 1.749)	0.008	0.228 (0.068, 0.758)	0.016	0.228 (0.068, 0.758)	0.016	0.211 (0.063, 0.710)	0.012

CI, Confidence Interval. Reference: lower education and physical occupation ($n = 38$). Model 1: Logistic regression model adjusted for age, sex, and ethnicity. Model 2: Logistic regression model adjusted for age, sex, ethnicity, and CRS score. Model 3: Logistic regression model adjusted for age, sex, ethnicity, CRS score, and brain reserve (head circumference).

domains (MES, ANT), with intellectual occupations linked to superior verbal skills, delayed recall, and visuospatial abilities compared to physical occupations. Notably, individuals with higher education exhibited lower cognitive impairment risks across both physical and intellectual occupations, emphasizing education as a pivotal factor in cognitive health. These findings suggest that while occupation influences certain cognitive skills, education remains a more critical determinant of overall cognitive resilience.

4.1 Education is associated with cognitive impairment

We found a strong association between education level and cognitive impairment. Similar to the findings of a Brazilian study on the association between education level and cognition ($n=1,023$), in the present study, education predicted better cognitive abilities even after adjusting for age and cognitive activity (Suemoto et al., 2022). Low education had the highest contribution to dementia risk in China among nine modifiable risk factors, with 10.8% of dementia cases attributable to low education (Mukadam et al., 2019). Moreover, research conducted in China has shown that low education is one of the highest contributing factors to the risk of dementia. In fact, a significant proportion of dementia cases in China have been attributed to low education levels. This is particularly noteworthy given that China has historically had a high illiteracy rate, with as much as 80% of the population being illiterate in 1949 (Wang et al., 2020). It is widely accepted that education level is considered an early contributor to the cognitive reserve previously shown to protect against cognitive impairment independent of the brain reserve. These findings underscore the importance of education in promoting cognitive health and reducing the risk of cognitive decline.

It is worth noting that previous research has suggested that the relationship between cognitive impairment and cognitive reserve may be modified by education level (Wang et al., 2020). Notably, a recent study conducted by the Religious Orders Study and Memory Aging Project (ROSMAP) involving 752 participants found that education level was only associated with baseline cognitive function, and was not related to slower rates of cognitive decline, later onset of decline, dementia onset or death, or residual cognitive decline not attributable to the neuropathologic burden. These findings contradict many of the tenets of cognitive reserve theory (Wilson et al., 2019).

4.2 Occupation type is not associated with cognitive impairment

The present study aimed to investigate the relationship between occupation type and cognitive function. While previous research has yielded mixed results on the matter, recent studies have shown that individuals with intellectual occupations tend to exhibit higher cognitive performance than those with physical occupations. The current research further explored this relationship and found that scores on cognitive domains such as language, delayed recall, and visuospatial/executive function were indeed higher in individuals with intellectual occupations.

It is worth noting, however, that the link between occupation and cognitive function is complex. While some studies suggest that occupational complexity protects against dementia (Dekhtyar et al., 2015; Ojagbemi et al., 2016), others have found no such association (Chapko et al., 2018). Occupational complexity is a downstream representative of cognitive reserve, which is directly influenced by educational attainment in childhood and early adulthood. The reduced risk of dementia in individuals with specific careers may be related to exposure to stressful work-related events, rather than solely to the effects of cognitively stimulating activities on cognitive reserve (Hülür et al., 2020).

In this study, we found that occupation was not related to cognitive reserve and cognitive impairment, and that intellectual occupations tended to be associated with higher levels of cognitive reserve through higher education. These findings suggest that individuals with intellectually stimulating occupations may have greater cognitive reserve, resulting in better cognitive performance in later life. Further exploration of the relationship between occupation and cognitive function is warranted.

The results of our study align with those of a previous study conducted in Cuba, the Dominican Republic, Venezuela, Peru, Mexico, and China (Prince et al., 2012), which found that education level, but not occupation, protected against dementia. However, another cross-sectional study in China (Ma et al., 2022) found that low occupational complexity explained a significant proportion of the variation in dementia cases, when both education level and occupation were considered. It is important to note that neither of these studies evaluated brain reserve. To our knowledge, our study is the first to investigate the association between education level and occupation, while also considering brain reserve information. Our study provides strong evidence for the role of education level as a cognitive reserve agent and for its ability to predict cognitive impairment. We examined data from 369 physical examination participants in a developing country (China) and administered a complete neuropsychological assessment. This association between socioeconomic status and cognitive function differs from previous studies examining cognitive reserve over the lifespan (Chapko et al., 2018).

5 Limitations and conclusions

However, the limitations of the study also need to be highlighted. This study was cross-sectional study; thus, participants were not followed over time. We obtained education level and occupation data across the lifespan and used multiple cognitive domain assessments to achieve a complete assessment of cognitive function, cognitive activity, and brain reserve. The CRS was also used to divide cognitive activity into multiple periods, providing a longitudinal perspective regarding the association between cognitive reserve and cognitive ability. Despite all precautions regarding the quality of clinical information provided by participants, recall bias was unavoidable; we reduced recall bias to some extent by training our interviewers to spot conflicting answers to questionnaires and seeking confirmation from family members about areas of doubt. Although selection bias was another threat to study validity, we contacted the regional medical supervisor, who confirmed that the demographics of our sample were similar to his perceptions of the local population, which suggests that our sample was representative of the local context. In addition, residual confounding persisted even after model adjustments for sociodemographic variables. Another area for improvement is the possibility of poor participant compliance and incorrect questionnaire responses due to the lengthy neuropsychological tests conducted in this study. We considered this issue and provided a refreshment room with coffee, food, and automatic massage chairs to alleviate fatigue. Finally, occupation significantly influenced some overall cognitive scores and individual cognitive domains but not rates of cognitive impairment, suggesting that larger sample sizes are needed to confirm our findings.

In conclusion, our study of 369 participants predominantly with higher education levels and physical occupations demonstrates that educational attainment significantly influences cognitive activity throughout life and is linked to reduced cognitive impairment risk. Conversely, occupational complexity does not appear to impact cognitive impairment or cognitive activity. Future longitudinal studies in developing countries with detailed lifestyle and cognitive activity measurements are essential to further elucidate the role of cognitive reserve in preventing cognitive impairment and 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 humans were approved by the Ethics Committee of the School of Nursing, Jilin 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

TZ: Writing – original draft, Writing – review & editing, Data curation, Software. SL: Writing – original draft, Writing – review & editing, Data curation. PL: Data curation, Writing – original draft, Writing – review & editing. YW: Resources, Writing – original draft, Writing – review & editing. LC: Project administration, Supervision, Writing – original draft, Writing – review & editing.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2024.1435626/full#supplementary-material

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Platycodin D and voluntary running synergistically ameliorate memory deficits in 5 × FAD mice via mediating neuromodulation and neuroinflammation

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Introduction: Alzheimer's disease (AD) is the leading cause of dementia, and currently, no effective treatments are available to reverse or halt its progression in clinical practice. Although a plethora of studies have highlighted the benefits of physical exercise in combating AD, elder individuals often have limited exercise capacity. Therefore, mild physical exercise and nutritional interventions represent potential strategies for preventing and mitigating neurodegenerative diseases. Our research, along with other studies, have demonstrated that platycodin D (PD) or its metabolite, platycodigenin, derived from the medicinal plant *Platycodon grandiflorus*, exerts neuroprotective effects against amyloid β (Aβ)-induced neuroinflammation. However, the combined effects of PD and physical exercise on alleviating AD have yet to be explored. The current study aimed to investigate whether combined therapy could synergistically ameliorate memory deficits and AD pathology in 5 × FAD mice.

Methods: Five-month-old 5 × FAD mice were randomly assigned to four groups, and received either PD (5 mg/kg/day, p.o.), voluntary running, or a combination of both for 47 days. Nest building test, locomotion test, and Morris water maze test were used to evaluate the cognitive function. Immunohistochemical and ELISA analysis was performed to determine Aβ build-up, microglia and astrocytes hyperactivation, and survival neurons in the hippocampus and perirhinal cortex. Real-time quantitative PCR analysis was used to assess the polarization of microglia and astrocytes. HPLC analysis was performed to measure monoamine neurotransmitters in the hippocampus.

Results and discussion: The combination of PD and voluntary running synergistically restored nest-building behavior, alleviated recognition and spatial memory deficits, and showed superior effects compared to monotherapy. In addition, the PD and voluntary running combination reduced Aβ build-up, decreased hyperactivation of microglia and astrocytes in the hippocampus and perirhinal cortex, promoted the polarization of inflammatory M1 microglia and reactive astrocytes toward beneficial phenotypes, and lowered systemic

circulating pro-inflammatory cytokines while increasing anti-inflammatory cytokines in 5 × FAD mice. Furthermore, combined therapy effectively protected neurons and increased levels of 5-hydroxytryptamine (5-HT) and dopamine (DA) in the hippocampus of 5 × FAD mice. In conclusion, the combination of PD and voluntary running holds great potential as a treatment for AD, offering promise for delaying onset or progression of AD.

KEYWORDS

Alzheimer's disease, voluntary running, platycodin D, neuroinflammation, monoamine neurotransmitter

1 Introduction

Alzheimer's disease (AD) is a primary neurodegenerative disorder predominantly affecting the elderly. It is characterized by persistent disturbances in higher neurological activities, including consciousness, emotion, memory, analytical judgment, thinking, and spatial recognition (McKhann et al., 2011). A key pathological hallmark of AD is the accumulation of beta-amyloid (Aβ) plaques. Aβ contributes to neurotoxicity by inducing neuroinflammation, promoting hyperphosphorylation of tau proteins, and sustaining neuronal hyperexcitability (Maestú et al., 2021).

Neuroinflammation, a component of the innate inflammatory response of the central nervous system (CNS), initially benefits to eliminate pathogens and maintain brain homeostasis (Gorji, 2022). However, during the pathological progression of AD, neuroinflammation becomes hyperactivated, leading to Aβ accumulation, neuronal damage, and ultimately cognitive deficits (Li et al., 2023). M1 microglia and reactive neurotoxic astrocytes exhibit a pro-inflammatory phenotype, releasing a variety of pro-inflammatory cytokines and accelerating neuronal death, whereas M2 microglia and S100a10^{+} astrocytes are neuroprotective, producing neurotrophic factors and anti-inflammatory cytokines (Liddelow et al., 2017; Wei and Li, 2022). Therefore, prompting astrocytes and microglia to adopt a beneficial polarization is a crucial strategy for AD treatment.

Aβ fibrils and hyperphosphorylated tau proteins can act as toxins, disrupting synaptic plasticity and neurotransmitter release, which leads to learning and cognitive dysfunction (Guerrero-Muñoz et al., 2015). Reduced levels of monoamine neurotransmitters such as dopamine (DA), norepinephrine (NE), and serotonin (5-HT) have been observed in the brains of various AD models and are associated with impaired cognitive memory (Chalermpalanupap et al., 2013; Rodríguez et al., 2012). Thus, modulating monoamine neurotransmitter levels through pharmacological interventions has shown efficacy in restoring cognitive memory capacity (Castellano et al., 2016). Several anti-AD drugs targeting neurotransmitters are either completed or in phase III clinical trials, including escitalopram, brexpiprazole, AVP-786, and nabilone (Cummings et al., 2023). However, there remains a significant gap between clinical trials and widespread clinical applications.

Platycodon grandiflorum has been used as a medicine food homology plant in China for centuries, and *Platycodon grandiflorum* pickle is a specialty in Korea. Our previous studies have proved that platycodigenin is effective in ameliorating LPS-induced inflammation and Aβ-induced axonal atrophy and neuronal death (Yang et al., 2019b). Platycodin D (PD) has been shown to improve learning and memory by enhancing neurite outgrowth and synaptogenesis in the mouse hippocampus, as well as ameliorating memory deficits by regulating PI3K/Akt/GSK3β signaling in type 2 diabetes mellitus mice (Kim et al., 2017; Lu et al., 2024). In addition to nutritional interventions, physical exercise is a crucial way to improve cognitive ability in AD. Prolonged sedentary behavior contributes to cognitive decline in the elderly (Edwards and Loprinzi, 2017), whereas planned or voluntary exercise has been shown to enhance cognitive performance in both mice and humans with AD (Kemoun et al., 2010; Mehla et al., 2022). Exercise can also significantly reduce medication-induced side effects in AD treatment. Thus, combining dietary supplement with regular physical exercise may be a more effective strategy for delaying AD progression. We hypothesize that the combination of PD with voluntary exercise could synergistically ameliorate cognitive deficits in 5 × FAD mice more effectively than monotherapy. Hence, the present study investigates the combined effects of these strategies on cognitive abilities and AD-related pathologies in 5 × FAD mice, and examines the underlying molecular mechanisms by assessing monoamine neurotransmitters, inflammatory cytokines, and the polarization of microglia and astrocytes.

2 Materials and methods

2.1 Animals experiment design

The experimental 5 × FAD mice were purchased from Aniphe BioLab (Jiangsu, China). These mice were maintained as hemizygotes by crossing 5 × FAD males with wild-type C57BL/6 F1 females. All care and experimental protocols were performed in line with the guidelines of the Animal Experimentation Committee of Guangdong Ocean University (SYXK2022-0032). Five FAD mice (5 months old, male) were utilized as treated groups and littermate wild-type C57BL/6 mice (5 months old, male, $n = 6$) were used as control (CT) group. The 5 × FAD mice were randomly assigned to 4 groups: a sedentary group (TgS, $n = 5$), a voluntary running group (TgR, $n = 5$), a PD treatment group (TgS-PD, $n = 5$), and a combined voluntary running and PD treatment group (TgR-PD, $n = 6$). Mice in the voluntary running group were housed

in a multichannel animal wheel running system (KEWBASIS, Nanjing, China), and the running distances were recorded daily. To minimize the impact of a single housing on social behavior, each mouse from each group was single caged in standard polypropylene cages throughout the experiment. The temperature was maintained at 23 ± 2° with a 12-h light/dark cycle, and the humanity was kept at 55 ± 10%, all mice had *ad libitum* access to food and water. PD was purchased from PUSH Bio-technology (Chengdu, China) with a purity exceeding 98.5% as confirmed by HPLC analysis. PD was dissolved in d-H_2O to a concentration of 0.5 mg/ml and intragastrical administered continuously for 47 days at a dose of 5 mg/kg/day. The dosage was determined based on our preliminary experimental results.

2.2 Nest building test

Each animal was provided with the same type of nesting material (16 pieces of cotton paper, each measuring 3 cm × 3 cm). These pieces were evenly distributed in the cage to prevent them from sticking together. The nesting patterns were assessed 24 h later and scored based on the following criteria: score 1–little to no nesting material was moved, score 2–nesting material was moved but did not form a distinct nest, score 3–nesting material was moved and aggregated into a flat nest, score 4–nesting material was aggregated into a distinct nest with walls above the mice, score 5–based on score 4, the nesting material was gnawed and shaped into a cozy nest (Deacon, 2006).

2.3 Open field test

The open field test was performed to assess the animals' exploratory behavior, mobility, and anxiety in a novel environment (Kraeuter et al., 2019). Prior to the experiment, the mice were acclimated to a quiet room for 1 h. The experimental chamber was a square box with 40 cm in length, width and height, made of black polyvinyl chloride. The mice were placed head-down in the center of the chamber, and the traveling paths were tracked for 5 min using a digital camera. The moved distance, rearing numbers, and number of feces were recorded with VisuTrack software (Xinruan, Shanghai, China). To prevent odor interference, the chamber was cleaned with 5% ethanol before each animal's trial.

2.4 Novel object recognition test

To assess the learning and memory abilities of mice, a novel object recognition test was performed based on their innate exploring tendency to novel objects (Schlunk et al., 2021). The experimental protocol was adapted with minor modifications from previous studies (Deng et al., 2022). During the training phase, two identical objects were placed symmetrically on opposite diagonals of the chamber. The mice were introduced into the chamber, facing the wall at the corners equidistant from the two objects, and the exploratory times with each object was recorded within 8 min. One hour later, one of the objects was replaced with a novel object, and the preferential index for the novel object was calculated.

2.5 Morris water maze test

The Morris water maze (MWM) test is commonly used to assess the spatial memory abilities of mice (Othman et al., 2022). A circular pool, 50 cm high and 120 cm in diameter, equipped with a video-tracking system (Shanghai Xinruan Information Tech, Shanghai, China) was employed. The pool was filled with water to a depth of 30 cm, mixed with titanium dioxide, and maintained at a temperature of 22 ± 1°C. Four equidistant points N, E, S, W were marked with brightly colored shapes on the wall of the pool as signposts, dividing the pool into four quadrants: NW, WS, SE, and EN. A transparent circular platform, 29 cm high and 12 cm in diameter, was submerged 1 cm below the water surface in one of the quadrants. Mice were sequentially placed in each of the four quadrants daily and allowed 1 min to locate the hidden platform. Escape latency, defined as the time taken for the mice to find the platform (3 s retention), was recorded. The mice that did not find the platform within 60 s were manually guided to it and allowed to acclimate for 15 s. Four trials per day were conducted in each different quadrant with 20 min intervals between trials over 5 consecutive days. On day 6, the platform was removed, and the mice were placed in the quadrant that is opposite to the platform. A probe trial was conducted for 1 min, during which the number of platform crossings and the time spent in the target quadrant were recorded.

2.6 Mouse tissue preparation

Voluntary running was ceased for 1 day prior to the sacrifice of the mice to minimize acute stress. The mice were deeply anesthetized with a mixture of xylazine hydrochloride (23 mg/kg), zolazepam (15 mg/kg), and salbutamol hydrochloride (15 mg/kg) administered via intraperitoneally injection. Approximately 1.5 ml of blood was collected from the abdominal aorta, centrifuged at 2,500 *g* for 15 min, and the serum was harvested. Cardiac perfusion was performed to remove the circulating blood. The left hemisphere of the brain was immediately soaked in 4% paraformaldehyde (Biosharp, Guangzhou, China) and stored at 4°C for fixation. The hippocampus and prefrontal cortices were dissected from the right hemisphere, rapidly frozen in liquid nitrogen, and stored at −80°C.

2.7 Enzyme linked immunosorbent assay (ELISA) analysis

Thirty milligrams of cortex tissue was lysed on ice for 30 min using Mammalian Protein Extraction Reagent (M-PER^{TM}, Thermo Scientific, Massachusetts, USA) containing 1× protease inhibitor mix. The lysate was then centrifuged at 12,000 *g* at 4°C for 10 min. The supernatant was collected, and total protein concentration was measured using the Pierce^{TM} 660 nm Protein Assay Kit (Thermo Scientific, Waltham, Massachusetts, USA). Levels of Aβ1-42 in the cortex and concentrations of IL-1β, TNF-α, IL-4, and IL-10 in serum were quantified using ELISA kits (Zeyu Biological, Jiangsu, China).

2.8 Immunohistochemistry analysis

The left hemisphere of the brain was picked from paraformaldehyde post 2 days of fixation. The surface liquid was removed with filter paper, and the tissue was then dehydrated through a gradient of 10, 20, and 30% sucrose solutions. The samples were embedded in Sakura Tissue-Tek® O.C.T. Compound, and 15 μm thick cryosections were made by a cryostat (Kedee, Jinhua, China). Aβ (1:500, 700254, Invitrogen), ionized calcium-binding adaptor molecule 1 (Iba1, 1:500, 019-19741, Wako), glial fibrillary acidic protein (GFAP) (1:200, MA5-12023, Invitrogen), NeuN (1:500, ab177487, Abcam) were used as primary antibodies, and goat anti-mouse (Alexa Fluor 594, 1:500, ab150116) and goat anti-rabbit (Alexa Fluor 488, 1:500, ab150081) IgG were used as secondary antibodies. Counterstaining was performed using DAPI (1 μg/ml, MCE, USA). The immunopanned slices were captured using an ECHO Revlove fluorescence microscope (ECHO, San Diego, California, USA) and quantitatively analyzed with ImageJ software (NIH, Bethesda, Maryland, USA).

2.9 High performance liquid chromatography (HPLC) analysis

Approximately 15 mg of hippocampal tissue was mixed with 150 μL of lysis buffer (0.6 mol/L perchloric acid, 0.5 mmol/L disodium ethylenediaminetetraacetic acid, and 0.1 g/L L-cysteine), homogenized, and centrifuged twice for 15 min each at 14,000 *g* and 4°C. The collected supernatant was then mixed with an equal volume of perchloric acid precipitant (1.2 mol/L dipotassium hydrogen phosphate, 2 mmol/L disodium ethylenediaminetetraacetic acid) and allowed to stand for 10 min in an ice bath. The mixture was centrifuged for 15 min at 14,000 *g* and 4°C, and the resulting supernatant was filtered through a 0.45 μm membrane. A 20 μL aliquot of the filtrate was injected into an Agilent 1260 Infinity II system (Agilent, Santa Clara, California, USA) equipped with an Agilent ZORBAX 300SB-C18 column (150 mm × 4.6 mm, 5 μm, Agilent, Santa Clara, California, USA) and an Agilent 1260 infinity fluorescence detector (excitation wavelength at 280 nm and emission wavelength and 330 nm). The mobile phase consisted of citrate sodium acetate buffer (A) containing 0.5 mM $C_7H_{15}O_3SNa$, 0.5 mM Na_2-EDTA, and 5 mM $C_6H_{15}N$, and methanol (B) at an isocratic elution with 87% A. The flow rate was set at 1.0 mL/min. The contents of dopamine (DA), dihydroxyphenylacetic acid (DOPAC), 5-hydroxytryptamine (5-HT), 5-hydroxyindoleacetic acid (5-HIAA), norepinephrine (NE), and 3-methoxy-4-hydroxyphenylglycol (MHPG) were quantified according to standard curve (Yang et al., 2021).

2.10 Real-time quantitative PCR analysis

Total RNA was extracted from 10 mg of mouse hippocampal tissue using AG RNAex Pro Reagent (Accurate Biology, Hunan, China). The tissue was thoroughly ground, left to stand for 15 min at room temperature, then mixed with 200 μL of chloroform, vortexed for 30 s, and centrifuged at 12,000 *g* for 15 min at 4°C post an additional 15-min standing period. The supernatant was collected, mixed with an equal volume of isopropanol, left to stand for 10 min, and then centrifuged at 12,000 *g* for 10 min at 4°. The RNA pellets were washed twice with 75% ethanol, air-dried, and then resuspended in 15–20 μL of DEPC water. RNA concentration was measured using a DS-11 Ultramicro spectrophotometer (DeNovix, USA). cDNA was synthesized from RNA using the HiScript II Q Select RT SuperMix for qPCR (+gDNA wiper) (Vazyme, China) kit. PCR amplification was performed with ChamQ Universal SYBR qPCR Master Mix Kit, and mRNA expression levels were measured using a CFX96Touch TM Real-Time Fluorescent Quantitative PCR System (Bio-Rad, Hercules, California, USA) with initial activation at 95°C for 30 s, subsequently by 40 cycles of amplification (5 s at 95°C and 30 s at 60°C). Primer sequences for mouse CD11b, CD206, C3, S100a10, and actin (Sango Biotech, Shanghai, China) were as follows: CD11b forward: TATGGAGCATCAATAGCCAGCCT, CD11b reverse: GAGAT CCTTACCCCCACTCAGAGAC; CD206 forward: TCTTTGCC TTTCCCAGTCTCC, CD206 reverse: TGACACCCAGCGG AATTTC, C3 forward: AGCTTCAGGGTCCCAGCTAC, C3 reverse: GCTGGAATCTTGATGGAGACGC; S100a10 forward: GTTTGCAGGCGACAAAGACC, S100a10 reverse: ATTTTGTCCACAGCCAGAGG; Actin forward: CATCCGTAAAGACCTCTATGCCAAC, Actin reverse: ATGGAGCCACCGATCCACA.

2.11 Statistical analysis

Results from behavioral and molecular experiments were processed using GraphPad Prism 9 (GraphPad Software, California, USA) or "rcompanion" package (for the Scheirer-Ray-Hare test) of R version 4.2.3. Data are presented as mean ± SEM. For multigroup comparisons involving data characterized by non-normal distribution, heteroscedasticity, or small sample sizes, the Kruskal–Wallis test followed by Dunn's *post-hoc* test was employed for one-factor designs. In the case of two-way designs, the Scheirer-Ray-Hare test, an extension of the Kruskal–Wallis test, was utilized, followed by Dunn's *post-hoc* test. The $p < 0.05$ was indicated as statistical significance.

3 Results

3.1 Voluntary exercise and PD synergically ameliorated memory deficits in 5 × FAD mice

To determine the optimal dosage of PD, we conducted a preliminary experiment. PD was administered orally to 5 × FAD mice (6–8 months old, half male and female) at doses of 5 and 15 mg/kg for 20 days. Behavioral tests, including the locomotion test, object recognition test (ORT), elevated maze test, and object location test (OLT) were performed on days 14, 15, 18, and 19, respectively (Supplementary Figure 1A). Compared to vehicle-treated 5 × FAD mice, PD-treated mice showed a trend toward decreased body weight (Supplementary Figure 1B). The 5 × FAD mice displayed significantly reduced spontaneous activity

compared to wild-type mice (Supplementary Figure 1C), while vehicle-treated 5 × FAD mice spent more time in the central zone compared to wild-type and PD-treated mice (Supplementary Figure 1D), indicating PD improved exploratory behavior. No significant differences were observed in the ratio of open and closed arm entries between groups (Supplementary Figure 1E). Vehicle-treated 5 × FAD mice failed to recognize novel or novel-placed objects compared to wild-type mice, whereas PD-treated mice showed significantly increased preferential index for novel object or novel-placed object (Supplementary Figures 1F, G). We also evaluated the impact of voluntary running on memory function in 5 × FAD mice. Experiments were performed using 5 × FAD mice (2.5–3 months old, half male and female, $n = 8$) and littermate wild-type C57BL/6 mice (2.5–3 months old, half male and female, $n = 8$). They were randomly assigned to 4 groups: sedentary 5 × FAD, sedentary wild-type, voluntary running 5 × FAD, and voluntary running wild-type. Even a month of voluntary running significantly improved spatial memory in 5 × FAD mice (Supplementary Figure 2A–G). To further assess the combined effects of voluntary exercise and PD treatment on memory deficits, we orally administered PD (5 mg/kg/d) with voluntary excise to 5 × FAD mice for 47 consecutive days (Figure 1A). The running distance for the TgR group averaged approximately 5 km per day, while the TgR-PD showed a marked decrease to 2 km per day (Figure 1B). We monitored the changes of body weight during voluntary running and/or PD treatment, the TgR-PD group had significantly reduced body weight compared to the TgS and TgR groups (Figure 1C and Supplementary Figure 3). The TgR or TgS-PD groups also showed decreased body weight compared to the TgS 5 × FAD mice (Figure 1C), indicating that the combination of PD and physical exercise more efficiently reduced body weight than either treatment alone. Nest-building behavior, a natural indicator of overall health and cognitive function in mice, was assessed. Compared to wild-type mice, sedentary 5 × FAD mice exhibited severely impaired nest-building ability. The TgR-PD group demonstrated significantly improved nest-building ability compared to the TgS group, and showed slightly better scores than the TgR and TgS-PD groups (Figure 1D).

The open field test was used to evaluate the mice's exploratory behavior and mobility. PD administration tended to decrease spontaneous activity in the mice (Figure 1E), which corresponded with the voluntary running distance shown in Figure 1B. The number of rearing was dramatically lower in the TgS group compared to the CT group, while the TgR group exhibited a rebound effect, and the TgR-PD group showed an increased trend compared to the TgS-PD group (Figure 1F), indicating that voluntary running enhanced exploratory behavior. The number of feces did not exhibit any significance among groups (Figure 1G). In the object recognition test, mice were equal to explore the two identical objects during the training session. During the test session, TgS mice failed to recognize the novel objects compared to CT mice ($^{**}p < 0.01$, TgS vs. CT), whereas the preferential index for novel objects was significantly increased in the TgR-PD group ($^{*}p < 0.05$, TgS vs. TgR-PD), displaying the best discrimination between old and novel objects (Figure 1H). In the MWM test, the escape latency for the TgS group was significantly higher than that of the other groups, with the TgR-PD group showing the shortest escape latency from day 4 (Figure 1J). To further assess the memory retention following exercise and PD intervention, a spatial probe trial was conducted on day 6. Compared to TgS mice, the number of platform crossings was significantly increased in the TgR-PD, TgR, and TgS-PD groups (Figures 1I, K), with a similar trend observed in the time spent in the target quadrant (Figure 1L). In conclusion, the combination of PD and voluntary exercise synergistically ameliorated cognitive deficits in 5 × FAD mice, demonstrating superior efficacy compared to monotherapy.

3.2 PD and voluntary exercise attenuated Aβ plaques build-up in 5 × FAD mice

Extracellular Aβ aggregation, which forms senile plaques, is one of the main pathological features of AD. We performed Aβ immunofluorescence staining and ELISA assays in the hippocampus and perirhinal cortex. The analysis revealed a significant increase in plaque sizes (diameter < 20 μm, 20–40 μm, and > 40 μm) and plaque areas in both the hippocampus (Figures 2A–C) and perirhinal cortex compared to CT mice (Figures 2D–G). In 5 × FAD mice, the majority of Aβ plaques were in the < 20 μm diameter range (Figures 2C, G). The TgR-PD group showed a reduction in Aβ plaques compared to the PD or voluntary running alone groups (Figures 2B, E). No plaques were detected in the wild-type CT mice. In addition, an ELISA kit was used to examine $A\beta_{1-42}$ levels in the prefrontal cortex (Figure 2F). $A\beta_{1-42}$ levels were unambiguously upregulated in TgS mice compared to CT mice, but PD treatment or physical running significantly reduced Aβ accumulation. The TgR-PD group exhibited a decreasing trend in $A\beta_{1-42}$ levels compared to the other two single interventions.

3.3 PD and voluntary exercise modulated neuroinflammation in 5 × FAD mice

Hyperactivated microglia and astrocytes, marked by Iba1 and GFAP, respectively, were remarkably upregulated in the hippocampus (Figures 3A–C) and perirhinal cortex (Figure 3D–F) of sedentary 5 × FAD mice compared to CT mice. TgR-PD treatment significantly reduced Iba1 expression in the hippocampus and cortex (Figures 3C, F) and was more effective at suppressing GFAP compared to TgR or TgS-PD alone (Figures 3B, E).

To assess microglia and astrocyte polarization toward beneficial phenotypes, we conducted qRT-PCR analysis for markers C3 and S100a10 (reactive astrocytes), and CD11b and CD206 (M1 and M2 microglia, respectively) (Miyamoto et al., 2020; Yang et al., 2019a). CD11b expression was significantly up-regulated in the TgS group compared to the CT group, while it was down-regulated in the TgR-PD group (Figure 4A). CD206 expression was significantly up-regulated in the TgR-PD group and the wild-type CT group compared to sedentary 5 × FAD mice (Figure 4B). C3 mRNA expression was up-regulated while S100a10 was down-regulated in the TgS group compared to CT mice, PD combined with voluntary running effectively restored the imbalance of reactive astrocytes (Figures 4C, D). These findings suggest that PD combined with voluntary running synergistically promotes

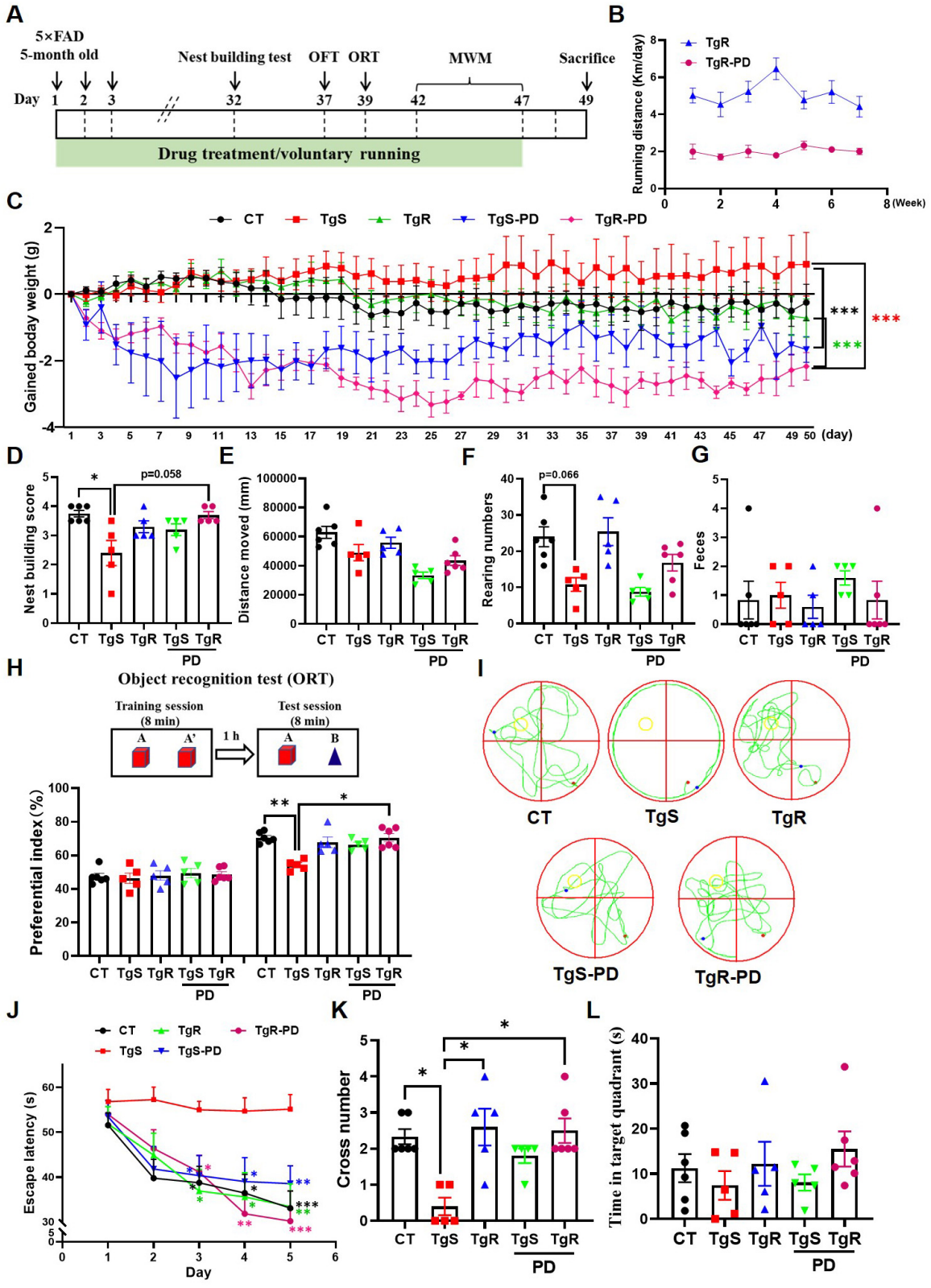

FIGURE 1
PD and voluntary running ameliorated cognitive deficits in 5 × FAD mice. **(A)** The experimental schedule. **(B)** Running distance of TgR and TgR-PD mice. **(C)** The gained body weight. **(D)** Score in the nest building test. **(E)** Total distance moved in the open field test. **(F)** Rearing numbers in the open field test. **(G)** The number of feces in the open field test. **(H)** Novel object recognition (NOR) memory test. **(I)** Representative swimming paths on the 6th day of the MWM. **(J)** Escape latency in the MWM. **(K)** Platform crossing numbers on the 6th day in the probe trial test. **(L)** Time spent in target quartant on the 6th day in the probe trial test. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ vs. TgS group. The Kruskal–Wallis test followed by Dunn's *post-hoc* test was used for one-factor designs, and the Scheirer-Ray-Hare test (an extension of the Kruskal–Wallis test) followed by Dunn's *post-hoc* test was used for experiments with two-way designs (mean ± SEM, $n = 5–6$).

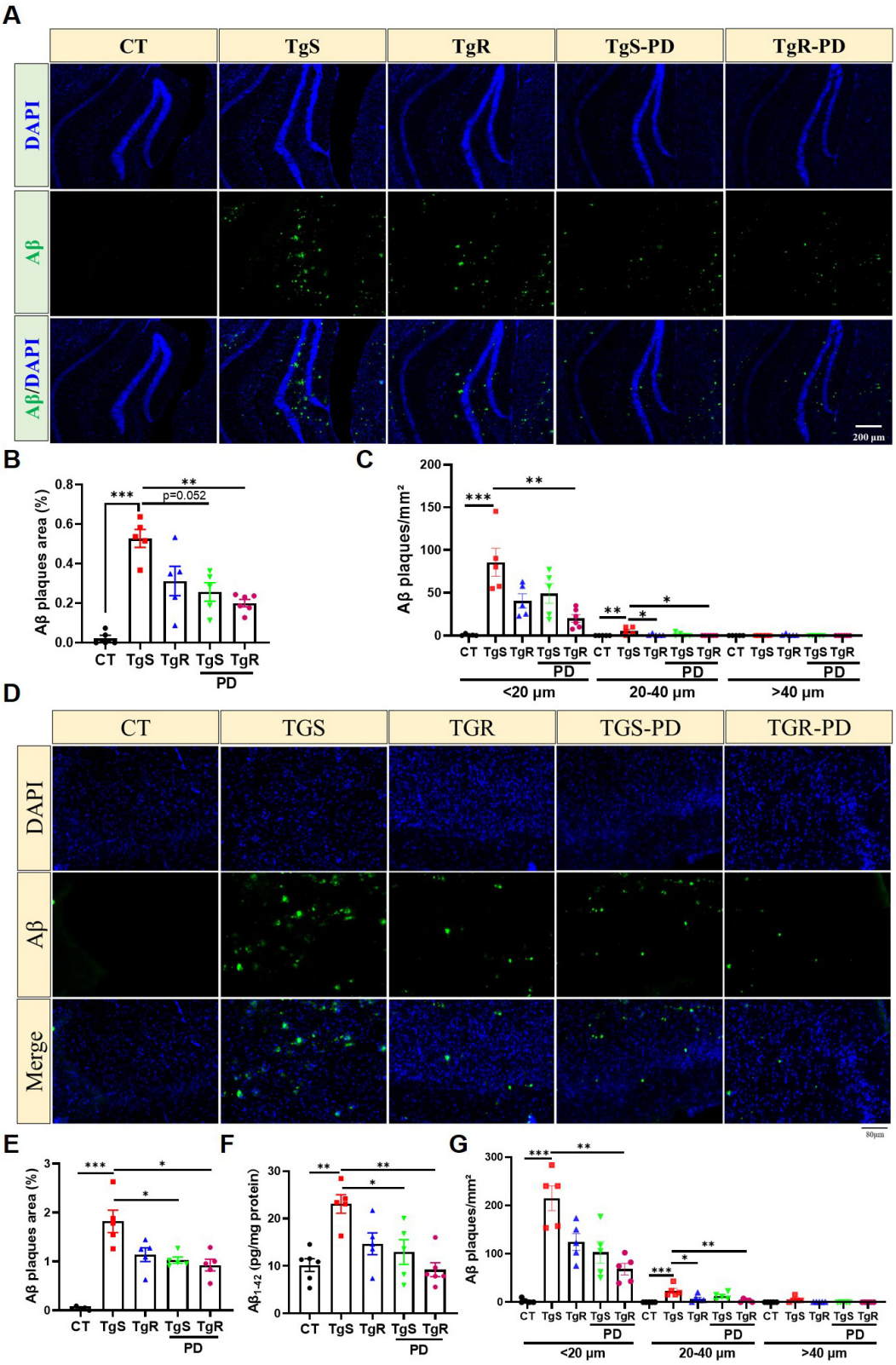

FIGURE 2
PD and voluntary running reduced Aβ deposition in the brain of 5 × FAD mice. **(A)** Representative Aβ immunopanned photos in the hippocampus. **(B)** The percentage of plaque total area in the hippocampus. **(C)** Number of Aβ1-42 plaques in different sizes (diameter < 20 μm, 20–40 μm, > 40 μm) per mm^2 in hippocampus. **(D)** Representative Aβ immunopanned photos in perirhinal cortex. **(E)** The percentage of plaque total area in perirhinal cortex. **(F)** Relative expression of Aβ1-42 in perirhinal cortex measured by ELISA analysis. **(G)** Number of Aβ1-42 plaques in different sizes (diameter < 20 μm, 20–40 μm, > 40 μm) per mm^2 in perirhinal cortex. *p < 0.05, **p < 0.01, ***p < 0.001 vs. TgS group. The Kruskal–Wallis test followed by Dunn's *post-hoc* test was used (mean ± SEM, n = 5–6).

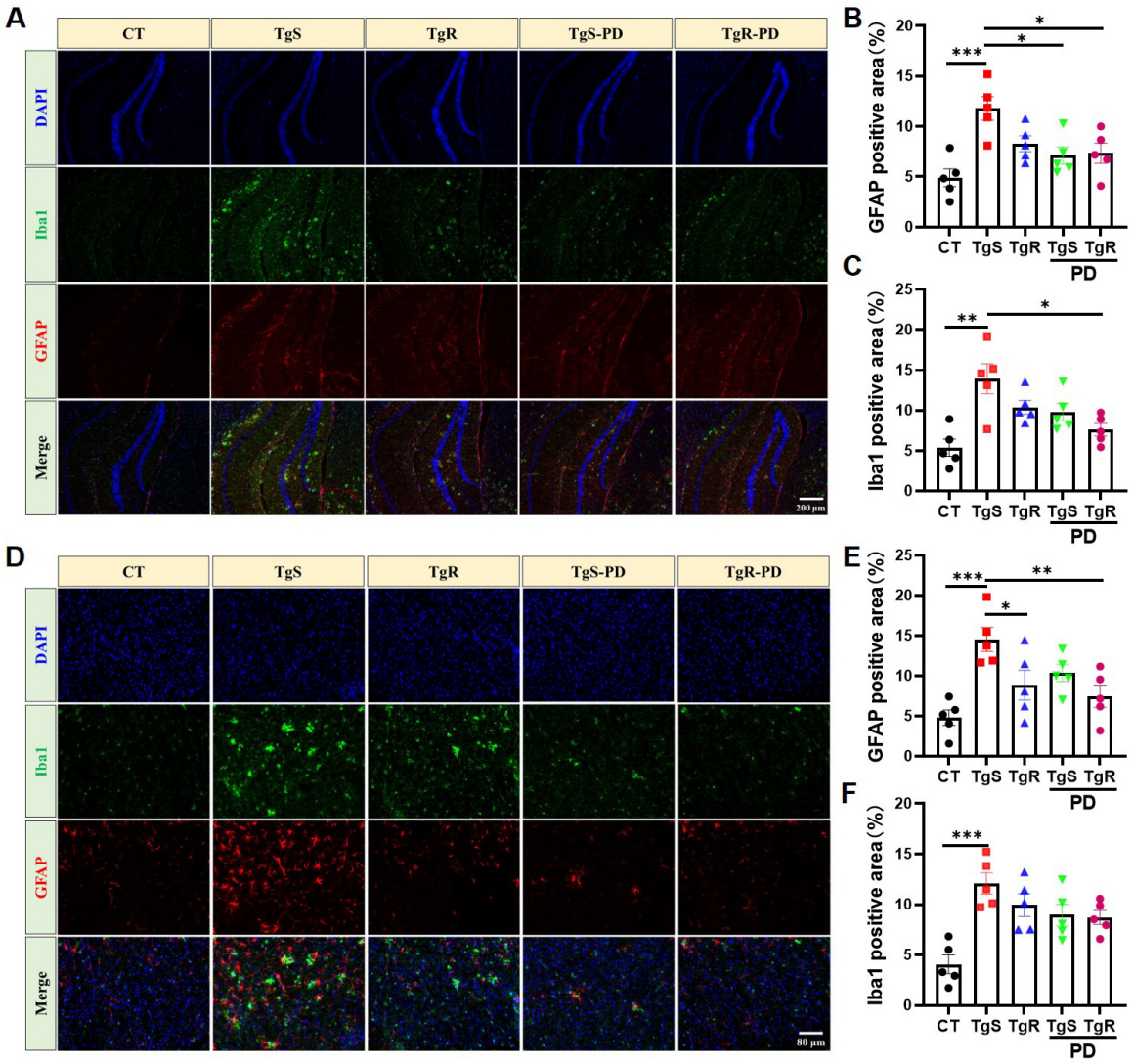

FIGURE 3
PD and voluntary running suppressed microglia and astrocytes hyperactivation in 5 × FAD mice. **(A)** Representative Iba1 and GFAP immunostaining images in the hippocampus of mice. **(B)** Fluorescence expression of GFAP in the hippocampus. **(C)** Fluorescence expression of Iba1 in the hippocampus. **(D)** Representative Iba1 and GFAP immunostaining images in the perirhinal cortex of mice. **(E)** Fluorescence expression of GFAP in the perirhinal cortex. **(F)** Fluorescence expression of Iba1 in the perirhinal cortex. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ vs. TgS group. The Kruskal–Wallis test followed by Dunn's *post-hoc* test was used (mean ± SEM, $n = 5$).

the polarization of microglia and astrocytes toward an anti-inflammatory phenotype. ELISA analysis of serum inflammatory cytokines revealed significant increases in TNF-α and IL-1β compared to CT mice (Figure 4E–H), which were markedly reversed by TgR-PD and TgR treatments (Figure 4E, F). The level of IL-4 was significantly increased in TgR-PD and TgR groups compared to the TgS group (Figure 4G), while IL-10 levels remained unchanged among groups.

3.4 PD and voluntary running modulated neuronal activity in 5 × FAD mice

The neurotransmitter system is closely linked to learning and memory. To investigate how PD and/or physical running affect neurotransmitter levels, we analyzed the expression of DA, 5-HT, NE, and their metabolites DOPAC, 5-HIAA, and MHPG in the hippocampus via HPLC analysis (Figure 5). Results showed that levels of 5-HT and DA were significantly increased in the TgR-PD group and the CT group compared to the TgS group, with trends toward increased levels also observed in the TgR and TgS-PD groups (Figures 5A, C). However, expression levels of DOPAC, 5-HIAA, NE, and its metabolite MHPG were not dramatically changed among groups (Figures 5B, D–F).

To assess the impact of PD and/or physical running on neuronal apoptosis, we performed immunohistochemical staining with the NeuN antibody. The results revealed that the combined treatment effectively reduced neuronal apoptosis in both the hippocampal DG and perirhinal cortex compared to the TgS group (Figure 6). Specifically, the number of NeuN-positive neurons was significantly higher in the TgR-PD group than in the TgS-PD group (Figures 6A, B). In conclusion, the combined intervention

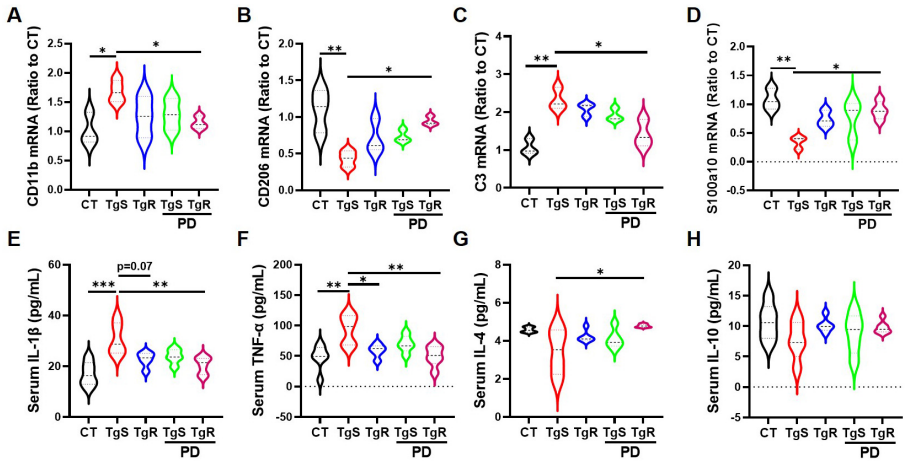

FIGURE 4
PD and voluntary running promoted the polarization of microglia and astrocytes to beneficial phenotypes in the hippocampus. **(A)** mRNA expression of M1 microglia marker CD11b. **(B)** mRNA expression of M2 microglia marker CD206. **(C)** mRNA expression of A1 astrocyte marker C3. **(D)** mRNA expression of reactive astrocyte marker S100a10. **(E–H)** IL-1β, TNF-α, IL-4, and IL-10 expression level in serum by ELISA analysis. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$ vs. TgS group. The Kruskal–Wallis test followed by Dunn's *post-hoc* test was used (mean ± SEM, $n = 3–4$).

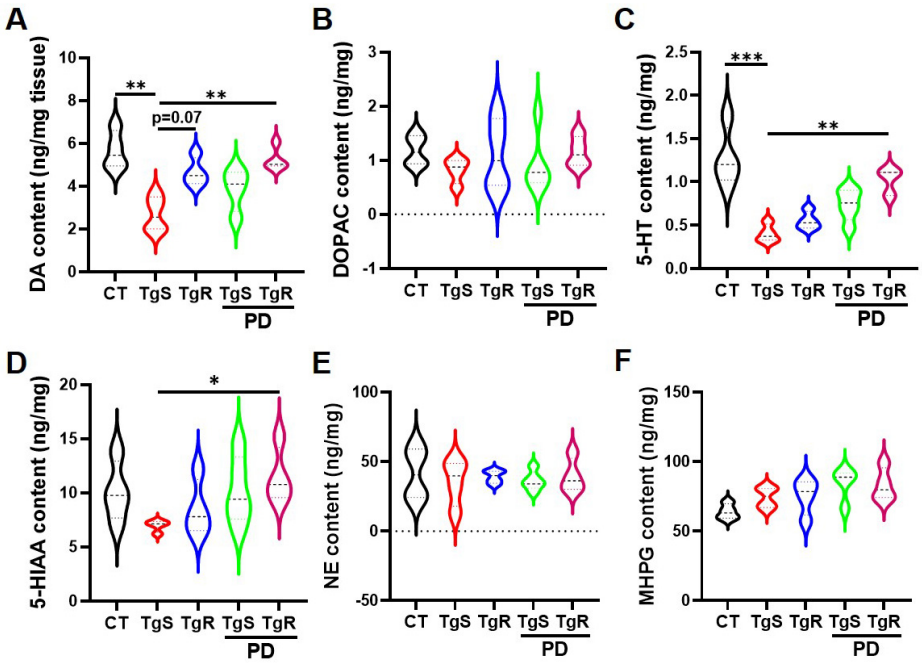

FIGURE 5
PD and voluntary running modulated monoamine neurotransmitters in the hippocampus. **(A–F)** Contents of DA, DOPAC, 5-HT, 5-HIAA, NE, and MHPG determined by HPLC analysis. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$ vs. TgS group. The Kruskal–Wallis test followed by Dunn's *post-hoc* test was used (mean ± SEM, $n = 4$).

of PD and voluntary running appears to induce 5-HT and DA upregulation and offers neuronal protection, likely contributing to improvements in memory function.

4 Discussion

In the present study, we examined the effects of PD nutritional intervention and physical exercise on memory deficits in 5 × FAD mice, an APP/PS1 transgenic model of AD. We found that the combination of PD and voluntary running dramatically inhibited hyperactivation of glial cells, shifted microglia and astrocytes toward beneficial phenotypes, alleviated systemic inflammatory cytokines, promoted Aβ plaque clearance, and restored hippocampal neurotransmitters 5-HT and DA, which ultimately attenuated memory deficits in the 5 × FAD mice. To our knowledge, this is the first study to demonstrate the impact of PD

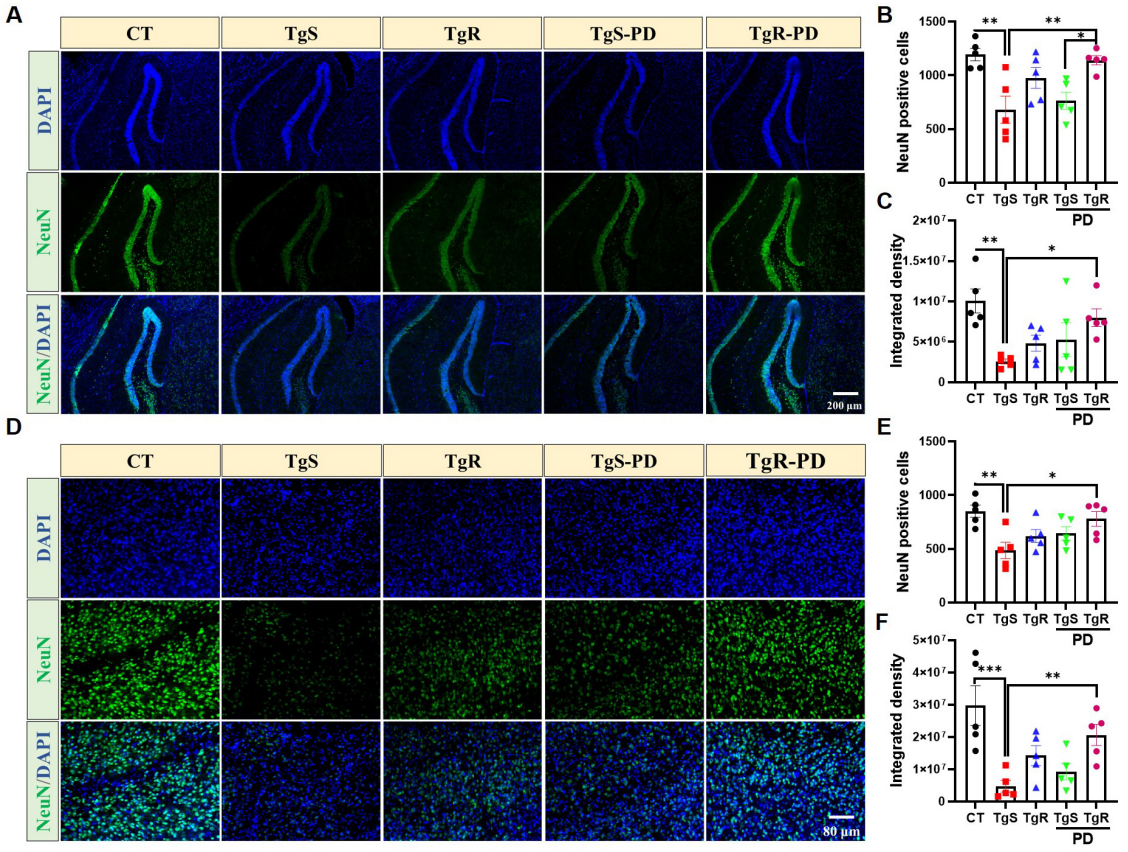

FIGURE 6
PD and voluntary running protected neurons in the hippocampus and perirhinal cortex. **(A)** Representative NeuN immunostaining images in the hippocampal DG of mice. **(B)** NeuN positive cells in hippocampal DG. **(C)** Integrated density of NeuN in hippocampal DG. **(D)** Representative NeuN immunostaining images in the perirhinal cortex of mice. **(E)** NeuN positive cells in the perirhinal cortex. **(F)** Integrated density of NeuN in the perirhinal cortex. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ vs. TgS group. The Kruskal–Wallis test followed by Dunn's *post-hoc* test was used (mean ± SEM, $n = 5$).

nutritional intervention and physical exercise on learning and memory in AD.

Report has indicated that PD inhibits Aβ-induced oxidative stress and inflammatory response in BV2 cells via activating the Nrf2/HO-1 pathway and suppressing the TLR4/NF-κB signaling pathway (Zhang et al., 2021). In addition, PD ameliorates memory impairment induced by $AlCl_3$ and D-galactose via AMPK activation, which mediates the suppression of mitochondrial ROS, inhibition of neuroinflammation, and reduction of neuronal apoptosis (Zhang et al., 2023). However, whether PD modulates glial polarization and neurotransmitter levels in 5 × FAD mice remain elusive. A network meta-analysis noted that short bursts of aerobic exercise improved cognitive performance more effectively than donanemab, lecanemab, aducanumab, or placebo in AD patients, with better tolerability and acceptability (Terao and Kodama, 2024). Although the cognitive benefits of physical exercise in AD model animals are well documented, the involved signaling pathways such as CNS neurogenesis (Norevik et al., 2024), cerebral neuroinflammation modulation (Zhao, 2024), and non-amyloidogenic AβPP processing (Elsworthy et al., 2022), few studies have examined the combination of exercise and medication. For example, swimming combined with clove oil treatment restored Aβ1-42-induced memory deficits by increasing α7nAChR and decreasing NLRP1 and dark cells (Karaji et al., 2023). Similarly, combining luteolin with wheel exercise reduced Aβ levels, glial cell activation, and autophagy in Aβ1-42-induced AD model rats, which was superior to monotherapy (Tao et al., 2023). Moreover, combined aerobic exercise and crocin treatment yielded a more profound effect on cognitive performance, nerve growth factor expression, and tau gene expression in trimethyltin-induced AD rats (Moghadasi et al., 2024). Despite these findings, the impact of PD combined with voluntary exercise on AD remains unexplored. Thus, this study was designed to explore the impact of combined PD supplementation and physical exercise on cognitive ability in 5 × FAD mice. The results highlighted that the synergistic interventions hold great potential to improve memory function.

Research has shown that levels of Aβ40 and Aβ42 were robustly increased from 4 to 8 months in 5 × FAD mice, correlating with elevated reactive $GFAP^+$ astrocytes and neurotoxic $Iba1^+$ microglia (Forner et al., 2021). Mass spectrometry and bioinformatics analyses demonstrate that the microglial inflammatory response occurs prior to Aβ accumulation (Boza-Serrano et al., 2018). In addition, activated microglia exacerbate AD by triggering reactive astrocytes through the secretion of Il-1α, TNFα, and C1q (Liddelow et al., 2017). Six months old 5 × FAD mice exhibit a significant increase in brain Aβ plaques, an upsurge in neuroinflammatory

cytokines, and cognitive decline in behavioral experiments (Girard et al., 2013). Thus, we utilized 5-month-old 5 × FAD mice and comprehensively assessed cognitive changes after a 1.5-month synergistic intervention. A toxicity test revealed that a single oral dose of 2,000 mg/kg PD had no obvious effect on organ weights or histopathological changes (Lee et al., 2011). Our pre-experiments have demonstrated that 5 and 15 mg/kg (p.o.) PD treatment for 2 weeks significantly improved memory deficits in 6–8 months old 5 × FAD mice. Intriguingly, PD treatment slightly reduced body weight, though not significantly, aligning with reports that PD exerts anti-obesity effects in *db/db* mice (Kim et al., 2019). Mild exercise combined with PD treatment markedly decreased body weight, opening up a potential new strategy for anti-obesity. In the open field and water maze tests, a reduction in locomotor activity was observed following PD treatment, likely due to its sedative effects. Previous study has demonstrated that oral administration of platycodon crude saponin effectively prolongs sleep duration in pentobarbital sodium-injected mice (Choi et al., 2004), and PD may be one of the active components contributing to this effect. Additionally, voluntary exercise appeared to counteract the sedative effects of PD.

Despite the fact that clinical trials targeting Aβ have largely been unsuccessful, Aβ plaque aggregation in the brains of AD patients remains one of the key pathological hallmarks of AD (Nehra et al., 2024). Aβ interacts with and activates dynamin related protein 1 (Drp1), which is expressed in the mitochondrial membrane and is important for normal mitochondrial division. This interaction induces mitochondrial dysfunction and synaptic loss (Qi et al., 2019). In addition, Aβ triggers oxidative stress through a variety of pathways, including the activation of nicotinamide adenine dinucleotide phosphate oxidase (Nox) and the production of reactive oxygen species (ROS). This leads to an influx of Ca^{2+}, resulting in neuronal injury, apoptosis, or necrosis (Oguchi et al., 2017). Phagocytosis of Aβ by microglia activates the NLRP3 inflammasome and caspase-1, causing the release of IL-1β and inflammatory responses, which further deteriorate AD pathology. Hyperactivated astrocytes, triggered by microglia, produce a large number of pro-inflammatory cytokines such as IL-1β and TNF-α, which suppress astroglial autophagy and block the clearance of Aβ in the brain (Gui et al., 2020). The deposition rate of Aβ1-42 was significantly accelerated in 5 × FAD mice, and reducing Aβ1-42 levels in the brain or serum of AD model rats is highly correlated with cognitive improvement (Oakley et al., 2006). The current study demonstrated that combining PD with physical running dramatically reduced Aβ plaque load in both the hippocampus and cortex of 5 × FAD mice, particularly decreasing the number of small-diameter plaques. Importantly, the TgR-PD group was more efficacious in eliminating 20–40 μm-diameter plaques compared to the TgS-PD group, as well as reducing the total amount of cortical Aβ1-42.

A large number of reactive microglia and astrocytes are observed around Aβ plaques in AD patients, indicating a strong association between Aβ deposition and neuroinflammation (Fakhoury, 2018). Under normal conditions, resting microglia are responsible for removing neuronal debris or remnants via phagocytosis, regulating neuronal homeostasis, maintaining synaptogenesis, and secreting neurotrophic factors (Cserép et al., 2020). Astrocytes, on the other hand, are involved in blood-brain barrier maintenance, synaptogenesis regulation, and neuronal activation (Sofroniew, 2015). Neuroinflammation disrupts these essential functions. Our results indicate that physical exercise combined with PD treatment can inhibit the hyperactivation of astrocytes and microglia in the brains of 5 × FAD mice. Pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 were significantly increased, while anti-inflammatory cytokines IL-4 and IL-10 were significantly reduced in AD models (Kaur et al., 2019). ELISA results revealed that physical exercise and PD intervention synergistically decreased serum levels of pro-inflammatory cytokines and increased levels of anti-inflammatory cytokines. Under certain conditions, microglia can differentiate into the M1 phenotype, which secretes high levels of pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1β, or into the M2 phenotype, which produces increased amounts of anti-inflammatory factors like transforming growth factor-β (TGF-β), IL-4, and IL-10 (Liu et al., 2024). Similarly, reactive astrocytes can polarize into either pro-inflammatory phenotype and anti-inflammatory phenotypes. Hyperactivated microglia secrete IL-1α, TNF-α, and C1q, which together induce neurotoxic reactive astrocytes, promoting neuronal death in AD (Liddelow et al., 2017). We demonstrated that physical exercise and PD intervention synergistically promoted the polarization of microglia and astrocytes toward beneficial phenotypes.

Neuronal viability and the neurotransmitter-involved neural networks are crucial for memory formation, consolidation, and retrieval. Aβ-induced neuronal death and disruption of neurotransmitter systems impair neural networks, ultimately leading to memory deficits (Deng et al., 2022). In the present study, we observed a significant reduction in NeuN-positive neurons in 5 × FAD mice. However, combined physical exercise and PD intervention restored hippocampal and cortical neurons. The neurotransmitter 5-HT regulates learning and memory via modulating dopaminergic, cholinergic, and GABAergic signaling. Studies have indicated that 5-HT promotes activation of 5-HT1A receptor, increasing the level of DA in the marmoset brain and enhancing the DA neuronal pathway (Baba et al., 2015). Additionally, activation of the 5-HT4 receptor promotes acetylcholine (Ach) release (Segu et al., 2010). Furthermore, 5-HT activates the 5-HT7 receptor, which increases the release of GABA in the hippocampal CA1 region, enhancing the inhibitory GABA pathway and ultimately improving learning and memory abilities. Investigations have revealed that DA levels are decreased in AD patients, animal models, and those with Parkinson's disease, resulting in impaired long-term potentiation (LTP) and cognitive decline (Papenberg et al., 2014). DA plays a critical role in regulating neural network activities involved in learning and memory in young animals, but its levels decrease with age. We found that 5-HT and DA levels were significantly reduced in 5 × FAD model mice, but were restored by combined physical exercise and PD intervention. An inverted U-shaped relationship exists between DA levels and synaptogenesis. DA activates the cAMP-PKA pathway via binding to D1/D5 receptors, which promotes the phosphorylation of NMDA and AMPA receptors, improving synaptic plasticity and LTP (Flores-Barrera et al., 2014), and on the other hand, leads to the phosphorylation of DA and cAMP-regulated phosphoprotein (DARPP-32), inhibiting protein phosphatase 1 (PP-1) and activating CREB to induce LTP, thereby enhancing learning and memory functions (Srivastava et al., 2018). However, excessive DA can overactivate

D1 receptors, inhibit NMDA receptors, reduce intracellular Ca^{2+} levels below the threshold required for LTP, and induce long term depression (LTD), thereby impairing learning and memory functions (Thirugnanasambandam et al., 2011). DOPAC levels in TgR-PD treated 5 × FAD mice showed an increased tendency compared to the TgS group, suggesting that regulating DA metabolic homeostasis may be a potential strategy for restoring memory ability.

The current study has several limitations. Firstly, as group housing did not permit predictions about the running wheel use of individual animals, and to evaluate whether physical activity alone has beneficial effects, each mouse from each group was singly caged in standard polypropylene cages. Report has shown that single housing exacerbates cognitive impairment by increasing Aβ and calpain activity (Hsiao et al., 2018). While, other studies have demonstrated that long-term voluntary exercise can ameliorate cognitive impairment in singly housed AD mice, future research should aim to minimize the stress associated with prolonged isolation (Belaya et al., 2020; Zhang et al., 2022). As suggested by previous studies, mice could be housed in cages with running wheels for 3 h daily and returned to their original cages for the remaining 21 h (Choi et al., 2018). Secondly, the limited number of mice used in the current study limits its conclusions. Although additional pre-experiments were conducted to confirm the effects of PD or voluntary running on AD using 5 × FAD mice, larger scale, validated studies are needed to improve statistical power and result reliability. Furthermore, questions remain about the direct targets of PD, the role of physical running mediated peripheral-CNS interactions in the amelioration of AD pathologies, and why the combination of PD and voluntary running is superior to monotherapy? Addressing such issues will be an essential task for future research.

Collectively, the present study demonstrated that the combination of PD and voluntary running attenuated cognitive deficits in 5 × FAD mice that is superior to monotherapy. However, our investigation is currently limited in exploring changes in pathological features, and further studies are needed to elucidate the underlying molecular mechanisms. In addition, further clinical and pre-clinical research is required to confirm the efficacy of PD and physical running in AD. Our results highlight that nutritional and physical exercise synergistic interventions hold great potential to treat AD.

Data availability statement

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

Ethics statement

The animal study was approved by the Animal Experimentation Committee of Guangdong Ocean University. The study was conducted in accordance with the local legislation and institutional requirements.

Author contributions

JL: Writing – original draft, Validation, Methodology, Investigation, Formal analysis. JJ: Writing – original draft, Methodology, Investigation. CH: Writing – review & editing, Investigation. LZ: Writing – review & editing, Formal analysis. YZ: Writing – review & editing, Formal analysis. SZ: Writing – review & editing, Formal analysis. ZY: Writing – review & editing, Supervision, Resources, Funding acquisition, Conceptualization.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2024.1451766/full#supplementary-material

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Bibliometric analysis of research trends on factors affecting older adults with mild cognitive impairment

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Background: In recent years, the problem of cognitive impairment in the elderly has become increasingly prominent. Understanding the research trend of influencing factors of mild cognitive impairment, and provide reference for medical staff to early screening of the elderly with mild cognitive impairment.

Objective: Through the visual analysis of the influence factors of the elderly with mild cognitive impairment, the current research status was discussed.

Methods: The relevant literature in the field of influencing factors of mild cognitive impairment in the elderly included in the Web of Science core collection database from 2013 to 2022 was searched. Using software such as Cite Space and VOS viewer to visually analyze literature citations, country, keywords, and development trends.

Results: A total of 547 relevant literatures were included, and the number of publications showed an increasing trend in the past ten years. The United States ranked first in both the number of published papers (157) and centrality (0.34), and the United States and China had a greater influence on the influencing factors of mild cognitive impairment. Alzheimer's disease, cognitive decline, the elderly, risk factors, are the research hotspot in this field.

Conclusion: Cognitive decline will affect the autonomy of the elderly. Cognitive frailty, MRI is the forefront of MCI research, to understand the research hotspots and frontiers in this field, to conduct early screening and intervention guidance for people with mild cognitive impairment, so as to delay the occurrence of Alzheimer's disease, and reduce the pressure on family caregivers and society.

KEYWORDS

mild cognitive impairment, elderly, influencing factors, bibliometrics, visual analysis

1 Introduction

In the context of global aging, population aging has become a serious problem for countries around the world. According to the World Health Organization, Alzheimer's disease is the seventh leading cause of death in the world. It is a degenerative disease of the central nervous system with an insidious onset and progressive progression (1). A recent cross-sectional study shows that there are 15.07 million cases of dementia in people over 60 years of age in China, including 9.83 million cases of Alzheimer's disease, the prevalence of MCI in people over 60 years of age is 15.5%, and the number of people with mild cognitive impairment

reaches 38.77 million, and the incidence rate is constantly rising (2). At present, there is no specific drug for the treatment of AD, and the basic research and clinical research focus more on the pre-clinical stage of dementia, that is, the stage of mild cognitive impairment. Mild cognitive impairment is a transitional state between normal aging and dementia, a clinical syndrome in which cognitive or memory impairment is present but the ability to perform daily life is normal (3). Mild cognitive impairment not only jeopardizes the mental and physical health of older persons, but also imposes a more serious socio-economic burden. It is estimated that by 2030, the cost of mild cognitive impairment in China will reach 2.54 trillion US dollars (4).

Each year, roughly 5–10% of patients with mild cognitive impairment will develop dementia. Understanding the influencing factors of MCI is beneficial for the early identification and intervention of MCI, and slows down the progression of MCI to AD (5). Among the socio-demographic factors, studies have shown that gender, age and education are among the factors affecting cognitive functioning in older adults. Zhang found that being male and having an education level of junior high school and above were protective factors for MCI, while age 70 and above was a risk factor for MCI (6). Similarly, while economic level has a direct impact on cognitive functioning in older adults, economic level can also indirectly affect cognitive functioning by influencing factors such as social support. Lu's study found differences in cognitive functioning and social support across economic income groups, more pronounced in higher income groups (7). In lifestyle, there are also associations between different dietary patterns and cognitive function, and some studies have found that n-3 PUFA supplementation has a positive effect on cognitive performance in older adults (8). The Araya-Quintanilla F study found no effective results of short-term n-3 polyunsaturated fatty acid supplementation on cognitive performance in Alzheimer's patients (9).

At present, more and more researchers pay more and more attention to MCI, but there are still many problems in the field of MCI. Due to the lack of clear and systematic diagnostic criteria, the assessment of cognitive function by medical workers will be biased, and the prevalence of cognitive impairment in the elderly in different regions is affected by gender, age, education level and so on (10). The development of mild cognitive impairment has been explored and researched in various fields of study, including biology, physiology, and psychology. However, there is a lack of systematic review on the factors affecting mild cognitive impairment. This study analyzed the field of MCI by searching the Web of Science database and using bibliometric software. The current status of research, research hotspots and frontiers in the field internationally were demonstrated using visualization to provide a reference for in-depth research on mild cognitive impairment in China.

2 Materials and methods

2.1 Data sources

A ten-year search of the Web of Science Core Collection for literature published between January 1, 2013, and December 31, 2022, on relevant influencing factors in the mild cognitive impairment population of community-dwelling older adults. The data retrieval strategy is as follows: TS = ("mild Cognitive Impairment*" or "mild cognitive disorder*" or "MCI") AND ("elderly" or "aged") AND ("influence factor*" or "risk factor*"). The inclusion criteria for cognitive impairment in this study include amnestic cognitive impairment and non-amnestic cognitive impairment. Literature type was set to article, online publications, conference proceedings and conference abstracts were excluded, and English was selected as the language type, resulting in 896 bibliographic records. In order to obtain more accurate analysis results, after reading the literature titles and abstracts, two researchers independently screened and discussed, manually excluding literature unrelated to mild cognitive impairment. Finally, the remaining 547 documents were recorded. The title, year of publication, country or region, institution, journal, references and keywords of each bibliographic record were collected as basic data.

2.2 Statistical methods

This study using the https://bibliometric.com/websitedescribes the number of publications in different countries or regions. VOS viewer software generates easy-to-understand bibliometric analysis mapping (11). The screened literature was imported into Cite Space 6.2.R2 visual analysis software in plain text format. Set the time span as 2013 to 2022, time slice as 1, and node type as institution, journal, keyword, and reference for visualization and analysis (12, 13). To obtain a clear view of the network, the clipping approach selects Pathfinder and Pruning sliced networks to eliminate the less visually appealing networks and nodes. Other settings keep the default algorithm.

3 Results

3.1 Annual publication distribution

This study analyzed 547 publications on factors affecting mild cognitive impairment in older adults published between 2013 and 2022. The citation report function of Web of Science was used to count the number of citations retrieved each year, and the citation data was independently verified using the repeat removal function of Cite Space software. Starting in 2019, the number of annual publications on this area of mild cognitive impairment is at a high level and on an upward trend, reaching a maximum in 2022. Figure 1 shows the number of publications per year for the last ten years.

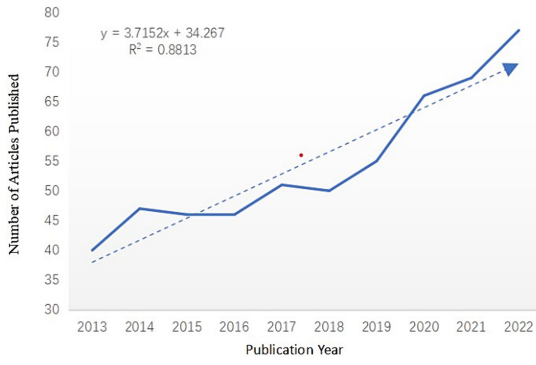


FIGURE 1
Annual number of publications on MCI influencing factors from 2013 to 2022.

3.2 Countries or regions

Retrieve published literature related to this field in all countries/regions, independently screen and discuss by two researchers, exclude literature unrelated to this field, and finally use bibliometric to analyze the publication volume and cooperation relationship of each country, with a total of 62 countries/regions were mentioned in the citations. The color-block areas in Figure 2 represent the proportion of publications by countries, and the different colored connecting lines represent the partnerships between countries. Compared to other color block areas, the United States, represented by light blue, and China, represented by dark blue, have the highest number of posts. The lighter blue areas have more connecting lines to the other color blocks, suggesting that the U.S. is working more frequently with other countries in the area of MCI impact factors. Table 1 shows the top five countries with the highest number of publications in the field of MCI impact factors, which are the United States (157), China (140), the United Kingdom (43), Japan (41), and South Korea (33). At present, research on the influencing factors of mild cognitive impairment mainly focuses on the United States and China. Some countries in Africa and South Asia, such as Tanzania, Morocco, Nepal, Kazakhstan, etc., have relatively few publications in this field and insufficient cooperation with other countries/regions. With the increasing international exchanges, the multi country cooperation model is gradually advancing.

3.3 Institutional cooperation distribution

Use Cite Space software to visualize and analyze the collaborative relationships and publication volumes between different institutions. As shown in Figure 3, a total of 288 organizations are involved in research in the area of MCI influencing factors during the period 2013–2022. This network graph generates a total of 288 nodes, 231 shortest paths of network nodes, each label represents an agency node, the connectivity between nodes represents the cooperation between agencies, and the size of the node represents the number of the number of messages sent by the agency. As shown in Table 2, the top ten institutions in terms of the number of publications in this field are Capital Medical University (18), Karolinska Institutet of Medicine (11), Shanghai Jiao Tong University (10), Fudan University (10), Tianjin Medical University (9), Boston University (8), Albert Einstein College of Medicine (8), Mayo Clinic (8), and National University of Singapore (8), Seoul National University (8 articles). In terms of institutional partnerships, Capital Medical University and Tianjin Medical University have more connecting lines with other nodes

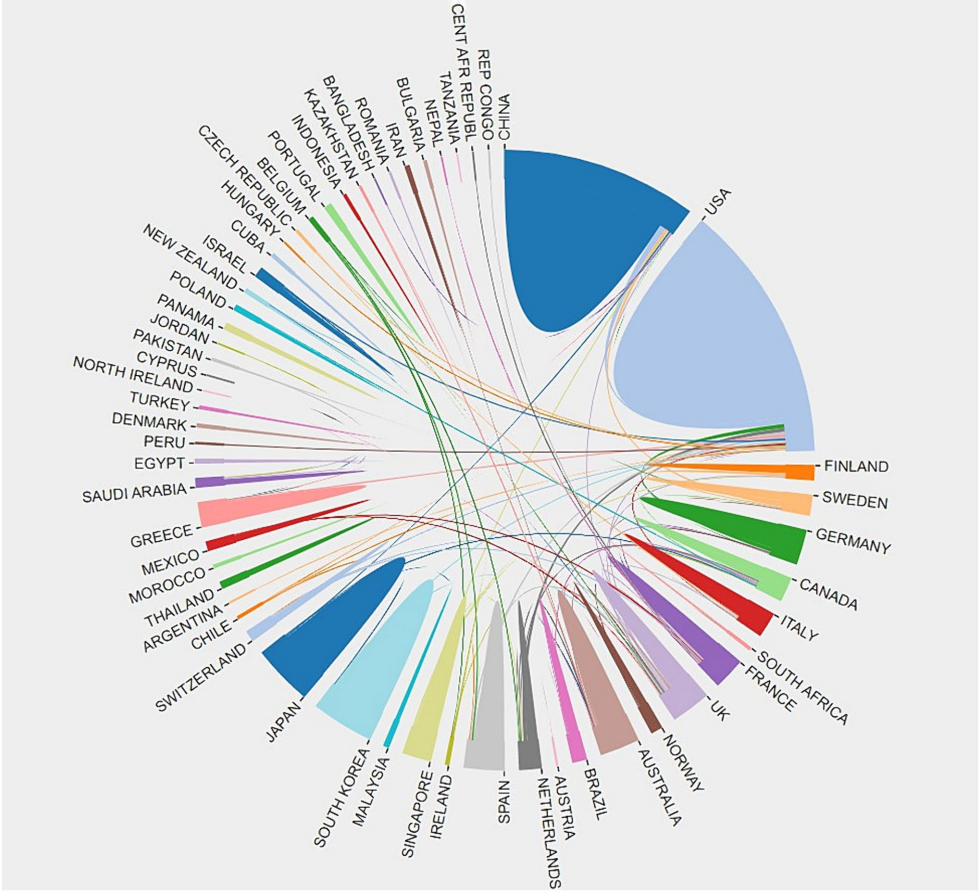


FIGURE 2
Cooperation among countries involved in the publication of MCI influencing factors, 2013–2022. Different colored areas represent various countries. The connection between different color blocks represents the countries' cooperative relationship.

compared to other university institutions in the country, suggesting that the institution is working more closely with foreign institutions. However, relative to foreign countries such as Boston University and Mayo Clinic, China's research in this field still needs to learn from foreign countries and strengthen exchanges and cooperation with foreign institutions to promote the development of this field.

3.4 Cited journals

Through the analysis of the map of the cited journals published by the international MCI influencing factors from 2013 to 2022. As shown in Table 3, the most cited journal among the top 10 journals is NEUROLOGY with 439 citations in the last 10 years. The journal with the highest impact factor among the cited journals in the field is The Lancet, with an impact factor of 98.4 in 2024, which is of high quality and represents a high level of attention to the field of MCI impact factors. In order to have a more intuitive understanding of the relationship between the citing journal and the cited journal, this study uses Cite Space software to make the double-image overlay atlas of the journal. Figure 4 displayed the dual-map overlay of journals, the left and right sides corresponded to the citation map and the cited journal map, respectively. The color curve depicts the citations of journals from various disciplines. The arrow points to the cited publications from various disciplines that are typically referred to by citing journals. There were four citation paths. The yellow path shows articles in the research fields of MOLECULAR/BIOLOGY/IMMUNOLOGY that are more likely to cite articles in the field of GENETICS/EDUCATION/SOCIAL. The green path shows articles in the research fields of MEDICINE/MEDICAL/CLINICAL that are more likely to cite articles in the field of NURSING/PSYCHOLOGY/MOLECULAR. The pink path shows articles in the research fields of NEUROLOGY/SPORTS/OPHTHALMOLOGY that are more likely to cite articles in the field of BIOLOGY/PSYCHOLOGY/SOCIAL. The blue path shows the subject fields of BIOLOGY/GENETICS/SOCIAL, which are probably cited by PSYCHOLOGY/EDUCATION/HEALTH.

TABLE 1 Top 5 countries with published papers on MCI influencing factors 2013–2022.

Rank	Country	Counts	Centrality	Percentage
1	America	157	0.34	28.70%
2	China	140	0.05	25.59%
3	England	43	0.31	7.86%
4	Japan	41	0.02	7.49%
5	Korea	33	0.01	6.03%

3.5 Analysis of keywords

In this study, high frequency keywords were analyzed using Vos viewer software. To eliminate redundancy in the mapping, synonyms as well as abbreviated keywords were merged, such as Alzheimer-disease, Alzheimers-disease, AD, etc. into Alzheimer disease. The minimum threshold of keyword frequency was chosen as 11 and 80 keywords were visualized and analyzed. As shown in Figure 5A, the color of keyword labels with higher frequency of occurrence is closer to yellow, and the color of keyword labels with lower number of

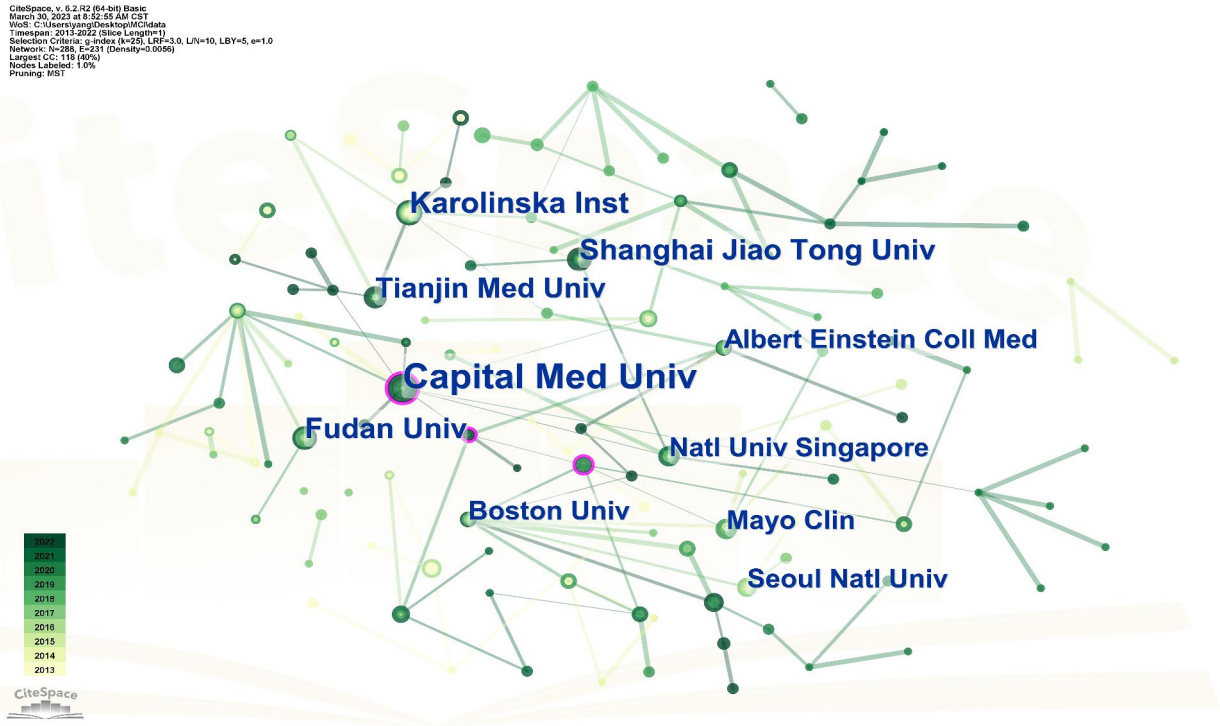


FIGURE 3
The chart of cooperation between institutions publishing papers in the field of MCI influencing factors from 2013 to 2022. Each label in the figure is a research institution. The connecting line between labels indicates the cooperative relationship between institutions.

TABLE 2 The top 10 institutions in the field of MCI influencing factors published in 2013–2022.

Rank	Institutions	Country	Counts	Centrality
1	Capital Medical University	China	18	0.19
2	Karolinska Institute	Sweden	11	0.05
3	Shanghai Jiao Tong University	China	10	0.02
4	Fudan University	China	10	0.01
5	Tianjin Medical University	China	9	0.01
6	Boston University	America	8	0.08
7	Albert Einstein College of Medicine	America	8	0.04
8	Mayo Clinic	America	8	0.02
9	National University of Singapore	Singapore	8	0.04
10	Seoul National University	Korea	8	0.01

TABLE 3 Top 10 journals cited in the field of MCI influencing factors from 2013 to 2022.

Rank	Cited journals	Counts	2024 journal impact factor
1	NEUROLOGY	439	7.7
2	J ALZHEIMERS DIS	333	3.4
3	ALZHEIMERS DEMENT	318	13.0
4	J AM GERIATR SOC	316	4.3
5	DEMENT GERIATR COGN	243	2.2
6	INT J GERIATR PSYCH	213	3.6
7	LANCET NEUROL	212	46.5
8	PLOS ONE	211	2.9
9	LANCET	211	98.4
10	JAMA—J AM MED ASSOC	209	63.1

citations and frequency of occurrence is closer to blue. In research in the area of MCI influencing factors during the last 10 years, mild cognitive impairment, Alzheimers disease, dementia, risk factor, decline are high-frequency key words. Further Cite Space software was used to generate a table of emergent keywords, Figure 5B lists 12 emergent keywords from the timeline, observing the emergent words gives an idea of the high frequency keywords that appeared in different time-years, and thus the research hotspots in the field in each year.

3.6 Analysis of co-cited references

By analyzing the co-citation timeline graphs of the literature, it is possible to understand the research themes and development of the research field in different time dimensions. The co-cited literature was clustered with keywords using the default algorithm in Cite Space, and a total of 15 clusters were generated, using the modularity index to measure the modularity of the network. The higher the modularity Q the better the clustering of the network. The graph clustering module value (Q-value) is 0.7336, the Q-value is more than 0.3, which implies that the clustering structure is significant; the average profile value (S-value) of the clusters is 0.8799, if the S-value is more than 0.5, it implies that the clustering is reasonable. As shown in Figure 6, the co-citation relationship of references on the timeline axis of different clustering groups changes with time and the citation heat, where the size of the nodes indicates the citation frequency of the literature. As can be seen in Figure 6, #cognitive frailty and #magnetic resonance imagine are important clusters and are hotly researched until 2022.

4 Discussion

4.1 Analysis of annual publications, countries, institutions, and journals

Articles on MCI's influencing factors have increased dramatically since 2019. This may be related to the fact that more researchers are increasingly focusing on the field of geriatric MCI as the World Health Organization (WHO) officially releases guidelines for the prevention and control of cognitive decline and dementia risk in 2019. In the same year, Prof. Jia Jianping of Xuanwu Hospital of Capital Medical University published a study on the current situation of dementia patients in China in a Lancet sub issue (2). The proposed intervention programs and prevention and control strategies for dementia in China are of great significance in the prevention of dementia and cognitive impairment, and provide important scientific and technological references for researchers in the field of MCI. In terms of national cooperation, researchers in the United States and the United Kingdom are more closely involved with other countries in this area of cooperation and exchange. The U.S. has the most publications in this area and has the highest centrality of 0.34, and in Cite Space, a node with a centrality of more than 0.1 indicates that the node occurs more often on the shortest path in the overall network. The higher the centrality, the more important and influential the keyword is in the research area. Although China's share of publications in this field is 25.59%, second only to the United States, its node centrality is only 0.05, and its influence in the field of MCI is relatively small, and it should strengthen cooperation and exchange with other countries to promote China's research development in the field of MCI. In terms of institutional cooperation, Capital Medical University and Boston University have led the development of MCI in China and the United States, respectively, but the inter-institutional cooperation is in a small-scale and regionalized cooperation, while the international cooperation is less, and the institutions in China have not yet formed an obvious cooperation network in this field. Analyzing the research areas of the citing and cited journals, in the area of MCI influencing factors, more researchers are focusing on the cutting-edge areas of clinical medicine, neurology, immunology, and biology, which provide

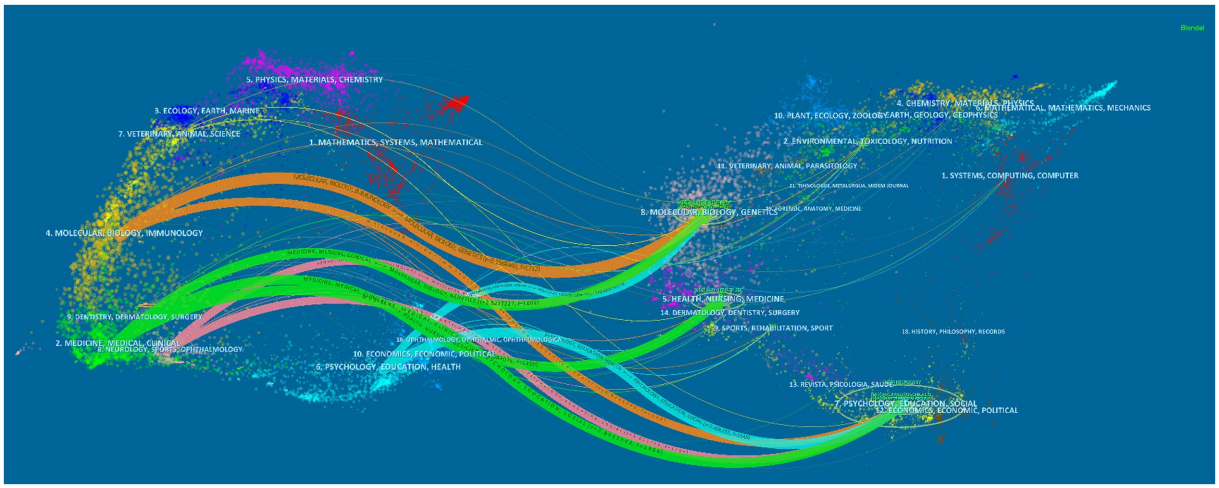


FIGURE 4
Double-graph overlay map of journals in the field of MCI influencing factors from 2013 to 2022. The left side correspond to the citation map and the right side represent the cited journal map. These labels represented the disciplines covered by the journal.

important scientific references for further dissecting the pathological changes of mild cognitive impairment and subsequent interventions.

4.2 Analysis of research hotspots

Keywords condense the core vocabulary of the subject matter of the literature and are a high level summary of the content of the literature, and high-frequency keywords are often used to identify hot issues in a field of study (14). Current research frontiers can be identified using emergent keyword analysis. Through the analysis of the keyword heat map generated by VOS viewer software and the co-citation time graph generated by cite space software, this study found that from 2013 to 2022, the research in the field of MCI influencing factors mainly included Alzheimer's disease, risk factors, cognitive frailty and magnetic resonance imaging. The research focuses on the screening and effective prevention of cognitive function of the elderly in the community, so as to delay the development of MCI population towards AD.

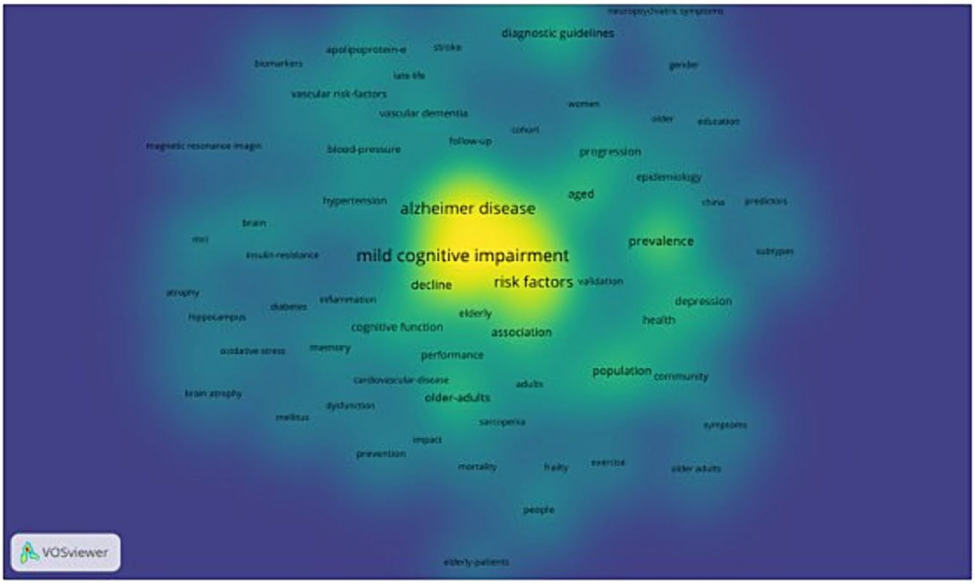
4.2.1 Cognitive frailty

Decrease in physiological reserve function of the elderly, leading to increased vulnerability of the body and causing debilitation of the elderly body (15). In contrast, cognitive debility is a subtype of debilitation with both physical debility and mild cognitive impairment. There are common risk factors for frailty and mild cognitive impairment, and frailty and mild cognitive impairment interact with each other (16, 17). Old age, low education, poor sleep quality and depression are common risk factors for frailty and mild cognitive impairment (18–20). There is a vicious cycle of interaction between mild cognitive impairment and frailty, which makes older adults with organic frailty more susceptible to mild cognitive impairment. Shimada H's study explored the relationship between cognitive decline and the prevalence of dementia in community-dwelling older adults and found that community-dwelling older adults with cognitive decline had a higher prevalence of dementia than older adults with mild cognitive impairment alone or older adults with debility (21). Frail older adults have reduced visuospatial ability, executive ability, and lower delayed memory scores compared to older adults in the normal community (22). The common risk factors and high-risk groups of mild cognitive impairment and frailty are gradually clear, but there is a lack of large-scale experimental studies, and the relevant mechanism of frailty leading to cognitive changes in various dimensions still needs to be further explored. In conclusion, healthcare professionals should pay high attention to the status of organic weakness and cognition in the elderly in order to recognize and prevent cognitive weakness in the elderly at an early stage.

4.2.2 Alzheimer's disease

Alzheimer's disease is one of the most common forms of dementia, severely affecting the central nervous system of the brain, resulting in cognitive dysfunction and mental behavior abnormalities (23). After a diagnosis of mild cognitive impairment, most older adults with mild cognitive impairment will transition to dementia within 4–6 years without intervention (24). At present, most studies focus on the influential factors of mild cognitive impairment and Alzheimer's disease in the elderly, and few studies have explored the influential factors of the transformation of patients with mild cognitive impairment into Alzheimer's disease. The Berezuk researchers investigated the risk factors for the conversion of MCI to AD, and the results showed that advanced age, female gender, hypertension, diabetes, residential status, neuropsychiatric symptoms, and cerebrovascular disease were risk factors for the conversion of MCI patients to AD (25–27). Kewcharoen's study found that patients older than 75 years of age with MCI were more likely to develop AD (28). Udeh-Momoh C's study found that in the elderly population with MCI, women are more likely to develop AD than men, which may be related to the greater changes in estrogen levels in women in old age (29, 30). Neuropsychiatric symptoms are one of the risk factors for the conversion of MCI to AD, which may be related to the development of negative

(A)



(B)

Top 12 Keywords with the Strongest Citation Bursts

Keywords	Year	Strength	Begin	End	2013 - 2022
diagnostic criteria	2013	3.9	2013	2015	
vascular dementia	2013	3.76	2013	2014	
apolipoprotein e	2013	3.19	2013	2014	
mri	2013	3.02	2013	2015	
late life	2013	2.87	2013	2014	
brain atrophy	2014	2.75	2014	2017	
cohort	2015	4.4	2015	2017	
dysfunction	2014	2.87	2017	2019	
white matter hyperintensity	2019	3.36	2019	2020	
cognitive dysfunction	2020	3.6	2020	2022	
impact	2020	3.01	2020	2022	
older	2020	2.71	2020	2022	

FIGURE 5
(A) Keywords popularity in literatures related to MCI influencing factors from 2013 to 2022. A keyword with higher frequency counts forms a yellow region, and those with lower frequency counts form a blue region. **(B)** Map of emerging keywords on MCI influencing factors from 2013 to 2022.

emotions (31), and depression is the most common symptom of MCI progression to AD (32). Through the graph analysis of the cited journals in the international MCI research hotspots in the past decade, it is found that the literatures in the fields of psychology and nursing are more frequently cited in medical and clinical journals. More and more researchers pay attention to the neuropsychiatric symptoms of MCI and improve the cognitive function of patients through psychological intervention. Analysis of risk factors for the development of AD patients in older adults with mild cognitive impairment, early screening and individualized clinical management of patients with mild cognitive impairment are beneficial for improving cognitive function and reducing the incidence of MCI to AD (33, 34).

4.2.3 Magnetic resonance imaging

Neuroimaging techniques provide an important diagnostic basis for exploring structural and functional changes in the brain of older adults with mild cognitive impairment, and play an

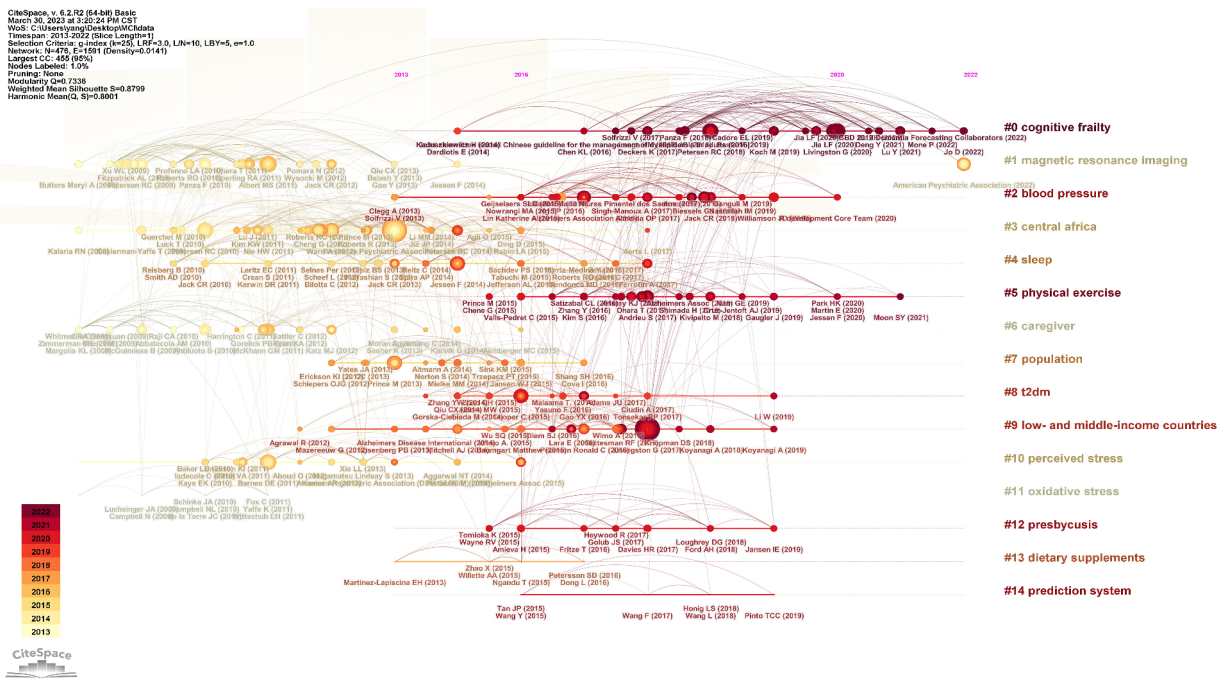


FIGURE 6
Co-citation time diagram of references on MCI influencing factors from 2013 to 2022. The clustering label of the co-cited literature may be found on the right side of the image.

important role in the early diagnosis and risk prediction of mild cognitive impairment (35). Amnestic mild cognitive impairment is mainly characterized by memory loss (36), which is closely related to hippocampal atrophy (37). Amnestic mild cognitive impairment declines more rapidly relative to other subtypes of cognitive functioning and progresses more rapidly to AD (38). The Montreal Cognitive Assessment Scale is a widely used instrument for assessing cognitive functioning in older adults, with good levels of content and structural validity (39). Through MRI, Knudsen LV found that brain structural abnormalities in patients with mild cognitive impairment have a higher correlation with clinical test scores, and MRI can more accurately identify different types of MCI, which is convenient for early intervention and treatment of MCI in elderly people (40). Resting-state functional MRI has the advantages of being noninvasive, high spatial resolution, and comparability. Cai investigated the mechanism of progression of aMCI to AD by using MRI and found that patients with aMCI have diminished functional connectivity in default network brain regions such as the hippocampus, medial prefrontal and inferior parietal lobes (41). MRI is widely used to detect and understand the development of neurodegenerative diseases such as MCI, with high detection accuracy and generalization ability, and it is possible to differentiate between stable and progressive mild cognitive impairment by analyzing magnetic resonance imaging images (42). In observing the extent of volume changes in hippocampal subregions and the functional connectivity characteristics among subregions, MRI can provide more detailed and accurate reference value for MCI diagnosis and disease progression.

5 Limitations

There are limitations to this visualization analysis, which currently only includes literature published in the last decade from 2013–2022; some studies are ongoing but not yet published. Secondly, the analysis of this study only included literature data in Web of Science and lacked analysis of different databases such as PubMed and Cochrane. Subsequent studies can add databases to expand the scope of searching, while supplementing Chinese databases to compare and analyze domestic and foreign studies, identify differences, and analyze them in depth.

6 Conclusion

This study objectively analyzes the research hotspots and research frontiers in the field of MCI influencing factors in older adults through the use of bibliometric methods. The results show that the research focus in this field is mainly on Alzheimer's disease and risk factors in recent ten years. The clinical therapeutic medications for AD can only alleviate psychological and behavioral symptoms to a certain extent, and cannot prevent the progression of AD. Therefore, more and more researchers' attention is focused on MCI, and understanding the risk factors that impair cognitive functioning during this period is beneficial in slowing down the progression of MCI to AD. In addition, cognitive decline and MRI are at the forefront of research in the MCI field, and community healthcare workers should focus on older adults with decline and screen for cognitive function at an early stage.

Author contributions

LY: Writing – original draft, Writing – review & editing, Methodology. RY: Writing – review & editing, Data curation, Formal analysis. BW: Writing – review & editing, Validation. TL: Validation, Writing – review & editing. ZW: Writing – review & editing, Conceptualization, Visualization.

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Conflict of interest

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

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Disparities in structural brain imaging in older adults from rural communities in Southern Nevada

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Introduction: Identifying the associations between rural-living or neighborhood disadvantage and neurobiology may clarify rural–urban disparities in older adults with cognitive impairment related to Alzheimer's disease.

Methods: We examined rural–urban differences and neighborhood disadvantages in brain cortical thickness (CT) measures among 71 rural and 87 urban-dwelling older adults. Analysis of covariance was used to test each FreeSurfer-derived CT measures' associations with rural–urban living, clinical impairment status, and their interactions. Post-hoc linear regressions were used to test the association between CT measures and neighborhood disadvantage index.

Results: Rural-dwelling older adults had thinner cortices in temporal and inferior frontal regions compared to urban participants, especially among clinically normal participants, where the thinner temporal cortex further correlated with higher neighborhood disadvantage. Conversely, rural participants had thicker cortices in superior frontal, parietal and occipital regions.

Discussion: Our results suggest a complex interplay between community contexts and neurobiology. For memory-related regions, rural-living and neighborhood disadvantage might be negatively associated with subjects' brain structures.

KEYWORDS

rural–urban differences, cortical thickness, neighborhood disadvantage, rural–urban commuting area, dementia, Alzheimer's disease

1 Introduction

Older adults living in rural communities and disadvantaged neighborhoods are at a heightened risk for Alzheimer's Disease (AD) than those living in urban areas and advantaged neighborhoods (Majoka and Schimming, 2021; Rahman et al., 2021; Liu et al., 2022; Wiese et al., 2023). This risk difference parallels other place-based disparities in health behaviors and mortalities, and is rooted in the neighborhood demographic, social, cultural, economic, and physical conditions in which human beings live and age (Meilleur et al., 2013; Aggarwal et al., 2021; Cross et al., 2021; Turecamo et al., 2023). Given the fact that rural areas often have a higher proportion of elderly individuals that are under-represented in AD-related studies, there is an emerging demand to include participants from rural and less advantaged neighborhoods in AD research to understand the factors contributing to these disparities and more inclusively promote healthy aging.

Cognitive decline is one of the major clinical symptoms in AD, and neurobiological changes precede and contribute to these clinical impairments (Aisen et al., 2017; Jack et al., 2018). Various socio-demographic, socio-cultural and socio-economic factors may shape residents' cognition and neurobiology (Aisen et al., 2017; Majoka and Schimming, 2021). Currently, how exactly these factors impact cognitive functioning and brain structures in AD remains unclear. Recent studies investigate such factors individually, in terms of sex-gender, education and socio-economic status (Stern, 2012; Hill et al., 2015; Caldwell et al., 2017, 2019; Cieri et al., 2022). Compared to these individual factors, integrative measures such as residency status and neighborhood disadvantage, offer an opportunity to comprehensively study the complex interplay among the above factors and the cognitive and neurobiological changes relevant to AD.

Rural living in early life could be a risk factor for lower levels of cognitive functioning (Herd et al., 2021). Better verbal memory performances have also been reported in rural-dwelling older adults (Miller et al., 2023). Investigating neurobiological changes associated with neighborhood contexts might help elucidate these mixed findings. To this end, neighborhood disadvantage has been associated with AD-specific patterns of neurodegeneration such as hippocampal volume loss (Hunt et al., 2020, 2021) and AD-related neuropathological changes (Powell et al., 2020) across lifespan. To date, these studies have been primarily conducted in clinically normal adults living in urban communities. It remains an open question how rural residency or disadvantaged neighborhood will be associated with AD biomarkers, such as brain regional structures, in both cognitively normal and impaired older adults.

In an effort to bridge this gap, we explore (1) rural–urban differences in brain structures and (2) the association between neighborhood disadvantage and these brain structures in both clinically normal and impaired participants. We particularly seek to examine the association of rural residency or neighborhood disadvantage with brain cortical thickness (CT) measures, hypothesizing that living in rural or a more disadvantaged area could be associated with thinner cortex in regions related to AD.

2 Materials and methods

2.1 Participants

Data for this project were drawn from participants enrolled in the Nevada Exploratory Alzheimer's Disease Research Center (NVeADRC)[1] and the Nevada Center for Neurodegeneration and Translational Neuroscience (CNTN).[2] Both studies have been reviewed and approved locally by the Cleveland Clinic Institutional Review Board and all participants gave written, informed consent prior to participation.

Details of these cohorts have been previously reported (Ritter et al., 2018; Sabbagh et al., 2021; Miller et al., 2023). Briefly, the NVeADRC is actively enrolling community-dwelling adults over the age of 50 that maintain a primary and current residency in a non-metropolitan area surrounding Las Vegas, NV. CNTN is a longitudinal, natural history study that is actively enrolling the clinical population at the Cleveland Clinic Nevada in Las Vegas. In both studies, following the aligned protocols, annual visits were conducted at the same single site, including a clinical examination, neuropsychological assessment based on the Uniform Data Set (v3) (Weintraub et al., 2018), and brain magnetic resonance imaging (MRI) acquisition. Demographic information including age, sex, years of education (YOE), race and ethnicity were self-reported and collected during each clinical visit.

2.1.1 Rural–urban status and neighborhood disadvantage

Based on participants' primary and current addresses, Rural–urban commuting area (RUCA) code (USDA ERS – Rural-Urban Commuting Area Codes, 2010) was utilized to characterize their residency status and area deprivation index (ADI) state decile (i.e., ranking within Nevada) (Kind and Buckingham, 2018; University of Wisconsin School of Medicine and Public Health, 2023) was used to characterize their neighborhood disadvantage. Details about RUCA and ADI were included in Supplementary method 1.

Briefly, a higher ADI indicates a more disadvantaged neighborhood and is linked to various negative health outcomes (Mora et al., 2021; Rangachari et al., 2022). In addition, following the guidance from the Health Resources and Services Administration (HRSA) (Health Resources and Services Administration, 2024), NVeADRC participants whose address was associated with RUCA $\geq$4 were included as the rural cohort; and CNTN participants with RUCA<4 were included as the urban cohort.

2.1.2 Demographic and clinical characteristics

Demographic variables, RUCA, ADI state decile, and clinical diagnoses [cognitively normal, mild cognitive impairment (MCI) or dementia] were obtained for each participant. Given the limited number of individuals with dementia, we collapsed those with MCI and dementia into a unified clinically impaired group. The Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005), Clinical Dementia Rating (CDR) (Hughes et al., 1982) sum of boxes, and Rey Auditory Verbal Learning Test (RAVLT) (Schmidt, 1996) immediate (sum of trial1-5) and delayed-recall scores were used to assess overall cognitive and memory function.

2.1.3 Structural MRI

MRI scans were collected locally for both studies on a Siemens 3 T scanner with a standard MPRAGE sequence at the same visit as the clinical examination. Details of MRI acquisitions and processes (Fischl, 2012) were included in Supplementary method 2.

Our analyses focused on 68 regional CT measures from subject-specific whole-brain anatomical labeling (Desikan et al., 2006) and 2 average CT measures of the two hemispheres, without any a prior selection.

2.2 Statistical analysis

All statistical analyses were conducted in matrix laboratory (MATLAB) 2022b.[3] Confidence intervals for effect-sizes were computed using the MBESS package in R (Kelley, 2007). If not

1 https://nvadrc.org/

2 https://nevadacntn.org/

3 https://www.mathworks.com/

otherwise stated, statistical significance levels were established at uncorrected $p \leq 0.05$.

2.2.1 Demographic comparison

Differences between rural and urban participants were explored using a two-sample t-test for continuous variables and a Chi-square test for categorical variables.

2.2.2 Analysis of covariance (ANCOVA)

Our primary analysis was to investigate rural–urban differences of each CT measure and examine whether these differences would differ between clinically normal and impaired stages. To this end, an ANCOVA with main effects of residency (rural vs. urban) and clinical impairment status (normal vs. impaired), along with their interactions was used. Age, sex, and YOE were included as covariates.

Since ANCOVA was conducted on each of the 70 CT measures, uncorrected p-values were corrected for 70×3 comparisons for both main and interaction effects using the false discovery rate (FDR) method. Statistical significance levels were established at $p_{FDR} \leq 0.05$. For the following post-hoc analyses, each CT measure was adjusted for sex, age, and YOE using coefficients estimated in the ANCOVA.

2.2.3 Post-hoc effect-sizes

Cohen's d (d) between rural and urban groups (i.e., rural–urban) of CT measures were computed for the overall samples, and for clinically normal and impaired participants, respectively. Effect-sizes between normal and impaired groups (i.e., normal-impaired) were calculated to approximate the relative degree of CT differences between different clinical stages in rural cohorts relative to urban cohorts.

2.2.4 Post-hoc association between CT and ADI

For CT measures with a significant interaction effect, we performed a linear regression analysis to determine whether there was an association between neighborhood disadvantage and CT measures in clinically normal and impaired cohorts. CT measures adjusting for covariates were used as the dependent variable, and ADI state decile was considered as the independent variable. We also tested whether the slope obtained through linear regression model between CT measures and ADI would differ between clinically normal and impaired groups. Due to the relatively limited sample-sizes, this association analyses were conducted in the post-hoc manner; and given the cohort relevance to AD, we extended this post-hoc association analyses to all temporal regions.

3 Results

3.1 Participants' demographics

Participants' demographic information is summarized in Table 1. Briefly, we assessed 71 rural-dwelling (62.0% women, 71.13 ± 6.45 years old, primarily non-Hispanic (88.5%) White (93.1%), 56.3% clinically normal) and 87 urban-dwelling (43.7% women, 72.16 ± 6.88 years old, primarily non-Hispanic (97.6%) White (88.7%), 52.1% clinically normal) older adults. The ADI state decile was significantly higher in rural than urban cohort, with distributions skewed toward 3–10 in the rural and 1–2 in the urban cohorts, respectively (Supplementary Figure 1).

In all participants, there were no significant differences in age, YOE, or race (1st column in Table 1). Rural cohort had less Hispanic participants ($\chi^2(1) = 6.14$, $p = 0.01$) and more women ($\chi^2(1) = 5.24$, $p = 0.02$) than urban cohort. Clinical impairment status, MoCA and CDR sum of boxes scores did not differ between rural and urban participants. However, the rural cohort demonstrated a better memory performance on RAVLT immediate [$t(156) = 2.45$, $p = 0.02$] and delayed recall [$t(156) = 3.12$, $p = 0.002$].

After stratifying by impairment status, there were no significant rural–urban differences for any demographic or cognitive variables expect the RAVLT scores. Rural dwelling order adults still demonstrated better verbal memory performances than urban-dwelling participants (2nd and 3rd column in Table 1).

3.2 ANCOVA analyses: structural brain cortical thickness (CT) measures

Table 2 summarizes the residency, clinical impairment and interaction effects in the ANCOVA model for 70 CT measures. Significant FDR-corrected p-values ($p_{FDR} \leq 0.05$) are listed (1st big column). Post-hoc effect-sizes (Cohen's d) for residency (rural–urban, 2nd big column) and clinical diagnoses (normal-impaired, 3rd big column) are listed for all participants, and for participants in each group, respectively.

3.2.1 Main effect

Our results showed that 32 out of 70 CT measures demonstrated significant residency effects ($p_{FDR} \leq 0.05$, Table 2), and these regions could be divided into two categories.

First, the inferior frontal and temporal regions demonstrated significantly thinner cortices in rural than urban participants on the post-hoc effect-size (d) maps (blue in Figure 1A). Stratified analyses in clinically normal and impaired participants further showed that these differences were more pronounced in clinically normal than impaired participants (Supplementary Figure 2, left).

In contrast, cortex in parietal, occipital, and superior part of the frontal regions were thicker in rural than urban participants (red in Figure 1A). Stratified analyses suggested that these differences were less predominant in clinically normal than impaired participants (Supplementary Figure 2, right).

For clinical impairment effect, 16 out of 70 CT measures, mainly encompassing temporal and parietal regions, demonstrated a significantly thicker cortex in clinically normal than impaired participants ($p_{FDR} \leq 0.05$, red in Figure 1B, right). A higher CT measure was indeed observed for almost all brain regions in the clinically normal participants (red in Figure 1B, left). Stratified analyses in rural and urban participants further indicated that the clinical impairment effect on CT measures was notably smaller in rural than urban participants (Supplementary Figure 3).

3.2.2 Interaction effect

Significant ($p_{FDR} \leq 0.05$) interaction effects between impairment and residency on CT measures were found in five brain regions, including left parsopercularis gyrus, left insula, right lateral-orbito-frontal cortex, right parahippocampal gyrus and right precuneus

10.3389/fnagi.2024.1465744

TABLE 1 Demographics of all participants (big column 1), clinically normal participants (big column 2) and clinically impaired participants (big column 3).

Characteristic	Overall			Clinically normal			Clinically impaired		
	Urban	Rural	Urban–rural differences (*p*-values)	Urban	Rural	Urban–rural differences (*p*-values)	Urban	Rural	Urban–rural differences (*p*-values)
	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	
	n=87	*n*=71		*n*=49	*n*=37		*n*=38	*n*=34	
Sex [No. (%)]			0.02			0.07			
Women	38 (43.7%)	44 (62.0%)		25 (51.0%)	26 (70.3%)		13 (34.2%)	18 (52.9%)	
Men	49 (56.3%)	27 (38.0%)		24 (49.0%)	11 (29.7%)		25 (65.8%)	16 (47.1%)	
Age	72.16 (6.88)	71.13 (6.45)		70.57 (6.96)	69.33 (6.04)		74.21 (6.28)	73.10 (6.39)	
Education in years	16.05 (2.43)	15.59 (2.35)		16.10 (2.46)	16.03 (2.34)		15.97 (2.42)	15.12 (2.31)	
ADI state decile	3.32 (2.10)	5.75 (2.51)	<0.001	3.35 (2.20)	5.54 (2.38)	<0.001	3.29 (2.00)	6.00 (2.68)	<0.001
RUCA code	1.01 (0.11)	4.27 (0.92)	<0.001	1.02 (0.14)	4.28 (1.05)	<0.001	1.00 (0.00)	4.26 (0.76)	<0.001
Ethnicity [No. (%)]			0.01			0.08			0.07
Hispanic	10 (11.5%)	1 (1.4%)		4 (8.1%)	0 (0.0%)		6 (15.8%)	1 (2.9%)	
Non-Hispanic	77 (88.5%)	70 (98.6%)		45 (91.9%)	37 (100.0%)		32 (84.2%)	33 (97.1%)	
Race [No. (%)]									
American Indian or Alaska Native	0 (0.0%)	2 (0.0%)		0 (0.0%)	1 (2.7%)		0 (0.0%)	1 (2.9%)	
Asian	4 (4.6%)	2 (2.8%)		3 (6.1%)	2 (5.4%)		1 (2.6%)	0 (0.0%)	
Black	2 (2.3%)	4 (5.6%)		2 (4.1%)	3 (8.1%)		0 (0.0%)	1 (2.9%)	
Native Hawaiian or Other Pacific Islander	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	
White	81 (93.1%)	63 (88.7%)		44 (89.8%)	31 (83.8%)		37 (97.4%)	32 (94.1%)	
Other (Specify)	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	
Clinical Diagnosis [No. (%)]									
Impaired	38 (43.7%)	34 (47.9%)		0 (0.0%)	0 (0.0%)		38 (100.0%)	34 (100.0%)	
Normal	49 (56.3%)	37 (52.1%)		49 (100.0%)	37 (100.0%)		0 (0.0%)	0 (0.0%)	
MoCA	24.36 (3.75)	23.85 (4.05)		26.33 (2.68)	26.3 (2.41)		21.81 (3.39)	21.18 (3.79)	
CDR sum of boxes	1.29 (1.91)	0.89 (1.47)		0.35 (0.86)	0.14 (0.3)		2.51 (2.19)	1.72 (1.77)	
RAVLT immediate	36.94 (10.55)	41.45 (12.57)	0.02	41.82 (7.98)	48.97 (9.97)	<0.001	30.66 (10.19)	33.26 (9.69)	
RAVLT delayed-recall	5.53 (4.36)	7.77 (4.67)	0.002	7.84 (3.60)	10.78 (3.01)	<0.001	2.55 (3.33)	4.50 (3.90)	0.03

(Figure 1C and Supplementary Figure 4). All five regions except the right precuneus demonstrated thinner cortex in rural than urban participants who were clinically normal. These rural–urban differences became less prominent or even reversed in clinically impaired participants (dashed lines in Figure 1C and Supplementary Figure 4).

TABLE 2 Analysis of covariance (ANCOVA) results for cortical thickness measures.

Brain lobes	Brain regions	Significance level in ANCOVA p_{FDR}			Cohen's d: rural–urban (d [95% CI])			Cohen's d: normal-impaired (d [95% CI])		
		Residency status	Impairment status	Interaction	All participants	Normal participants	Impaired participants	All participants	Rural participants	Urban participants
Temporal	Left Entorhinal		4.96E-02					0.46 [0.14, 0.78]	0.23 [−0.24, 0.70]	0.61 [0.17, 1.04]
	Left Fusiform									
	Left Parahippocampal									
	Left Temporalpole	3.13E-02			−0.50 [−0.82, −0.18]	−0.88 [−1.32, −0.43]	−0.10 [−0.56, 0.37]			
	Left Bankssts	2.83E-03			0.60 [0.28, 0.92]	0.53 [0.09, 0.96]	0.72 [0.24, 1.19]			
	Left Inferiortemporal	3.80E-02			−0.47 [−0.79, −0.15]	−0.63 [−1.07, −0.19]	−0.29 [−0.75, 0.18]			
	Left Middletemporal		1.54E-02					0.56 [0.24, 0.87]	0.27 [−0.20, 0.74]	0.77 [0.33, 1.21]
	Left Superiortemporal		4.13E-02					0.48 [0.16, 0.80]	0.16 [−0.31, 0.62]	0.74 [0.30, 1.18]
	Left Transversetemporal									
Frontal	Left Caudalmiddlefrontal	2.65E-03			0.58 [0.26, 0.90]	0.31 [−0.12, 0.74]	0.95 [0.46, 1.44]			
	Left Lateralorbitofrontal	2.00E-03			−0.66 [−0.98, −0.34]	−0.95 [−1.40, −0.50]	−0.36 [−0.83, 0.11]			
	Left Medialorbitofrontal		4.09E-02					0.49 [0.17, 0.80]	0.15 [−0.32, 0.62]	0.80 [0.35, 1.23]
	Left Parsorbitalis									
	Left Parsopercularis			3.26E-02	0.20 [−0.12, 0.51]	−0.20 [−0.63, 0.23]	0.71 [0.23, 1.18]	0.44 [0.12, 0.75]	−0.05 [−0.51, 0.42]	0.83 [0.38, 1.27]
	Left Parstriangularis									
	Left Rostralmiddlefrontal	8.13E-03			0.51 [0.19, 0.83]	0.44 [0.00, 0.87]	0.64 [0.16, 1.11]			
	Left Superiorfrontal									
	Left Frontalpole									
	Left Paracentral									
	Left Precentral									
Parietal	Left Inferiorparietal	1.35E-04			0.76 [0.43, 1.08]	0.79 [0.35, 1.23]	0.76 [0.28, 1.24]			
	Left Postcentral	1.50E-06			0.90 [0.57, 1.23]	0.65 [0.21, 1.09]	1.29 [0.77, 1.79]			
	Left Precuneus	5.54E-05	1.77E-02		0.77 [0.44, 1.09]	0.69 [0.25, 1.13]	0.97 [0.48, 1.46]	0.46 [0.15, 0.78]	0.42 [−0.06, 0.89]	0.63 [0.20, 1.06]
	Left Superiorparietal	9.77E-08			1.06 [0.72, 1.39]	1.12 [0.66, 1.58]	1.00 [0.51, 1.49]			
	Left Supramarginal	8.13E-03			0.51 [0.19, 0.83]	0.29 [−0.14, 0.72]	0.85 [0.37, 1.33]			

(Continued)

10.3389/fnagi.2024.1465744

TABLE 2 (Continued)

Brain lobes	Brain regions	Significance level in ANCOVA p_{FDR}			Cohen's d: rural–urban (d [95% CI])			Cohen's d: normal-impaired (d [95% CI])		
		Residency status	Impairment status	Interaction	All participants	Normal participants	Impaired participants	All participants	Rural participants	Urban participants
Occipital	Left Cuneus	6.91E-04			0.68 [0.36, 1.00]	0.60 [0.16, 1.03]	0.77 [0.29, 1.25]			
	Left Lateraloccipital	1.03E-03			0.66 [0.34, 0.98]	0.67 [0.23, 1.11]	0.67 [0.19, 1.14]			
	Left Lingual	4.09E-02			0.44 [0.12, 0.75]	0.50 [0.06, 0.93]	0.39 [−0.08, 0.85]			
	Left Pericalcarine	7.98E-11	4.40E-02		1.25 [0.91, 1.59]	1.05 [0.59, 1.50]	1.50 [0.97, 2.02]	−0.39 [−0.70, −0.07]	−0.72 [−1.20, −0.23]	−0.10 [−0.53, 0.32]
Cingulate	Left Caudalanteriorcingulate	3.80E-02			−0.46 [−0.78, −0.15]	−0.56 [−1.00, −0.13]	−0.33 [−0.80, 0.14]			
	Left Isthmuscingulate									
	Left Posteriorcingulate									
	Left Rostralanteriorcingulate									
Insula	Left Insula	4.65E-02	4.16E-02	3.24E-02	−0.46 [−0.78, −0.14]	−0.85 [−1.30, −0.40]	0.04 [−0.43, 0.50]	0.49 [0.17, 0.81]	−0.01 [−0.48, 0.45]	0.86 [0.42, 1.30]
Mean	Left Meanthickness	3.13E-02	4.40E-02		0.42 [0.10, 0.74]	0.23 [−0.20, 0.66]	0.71 [0.23, 1.18]	0.44 [0.12, 0.75]	0.20 [−0.27, 0.67]	0.68 [0.24, 1.11]
Temporal	Right Entorhinal		6.77E-03					0.61 [0.28, 0.93]	0.50 [0.03, 0.97]	0.67 [0.23, 1.10]
	Right Fusiform									
	Right Parahippocampal			4.16E-02	−0.30 [−0.61, 0.02]	−0.68 [−1.12, −0.24]	0.17 [−0.29, 0.63]	0.37 [0.06, 0.69]	−0.11 [−0.58, 0.35]	0.69 [0.25, 1.12]
	Right Temporalpole		4.40E-02					0.47 [0.15, 0.79]	0.22 [−0.25, 0.69]	0.65 [0.22, 1.09]
	Right Bankssts									
	Right Inferiortemporal									
	Right Middletemporal		1.18E-03					0.71 [0.39, 1.03]	0.44 [−0.04, 0.90]	0.92 [0.48, 1.37]
	Right Superiortemporal									
	Right Transversetemporal	6.70E-04	3.80E-02		0.65 [0.32, 0.97]	0.51 [0.08, 0.95]	0.87 [0.39, 1.36]	0.43 [0.11, 0.75]	0.35 [−0.12, 0.82]	0.57 [0.14, 1.00]

(Continued)

10.3389/fnagi.2024.1465744

TABLE 2 (Continued)

Brain lobes	Brain regions	Significance level in ANCOVA p_{FDR}			Cohen's d: rural–urban (d [95% CI])			Cohen's d: normal-impaired (d [95% CI])		
		Residency status	Impairment status	Interaction	All participants	Normal participants	Impaired participants	All participants	Rural participants	Urban participants
Frontal	Right Caudalmiddlefrontal	1.34E-03			0.64 [0.32, 0.96]	0.70 [0.26, 1.14]	0.61 [0.14, 1.08]			
	Right Lateralorbitofrontal	8.13E-03		3.80E-02	−0.58 [−0.90, −0.26]	−1.00 [−1.45, −0.54]	−0.11 [−0.57, 0.36]	0.30 [−0.01, 0.62]	−0.20 [−0.66, 0.27]	0.68 [0.24, 1.11]
	Right Medialorbitofrontal									
	Right Parsorbitalis									
	Right Parsopercularis									
	Right Parstriangularis									
	Right Rostralmiddlefrontal	5.92E-04			0.68 [0.36, 1.00]	0.63 [0.19, 1.06]	0.77 [0.29, 1.25]			
	Right Superiorfrontal									
	Right Frontalpole									
	Right Paracentral									
	Right Precentral									
Parietal	Right Inferiorparietal	2.11E-04	4.09E-02		0.70 [0.38, 1.02]	0.60 [0.16, 1.03]	0.89 [0.40, 1.37]	0.42 [0.10, 0.73]	0.28 [−0.19, 0.74]	0.63 [0.19, 1.06]
	Right Postcentral	1.12E-04			0.75 [0.42, 1.07]	0.69 [0.25, 1.12]	0.87 [0.39, 1.36]			
	Right Precuneus	2.45E-06	2.83E-03	3.80E-02	0.82 [0.49, 1.14]	0.49 [0.06, 0.93]	1.38 [0.86, 1.89]	0.57 [0.25, 0.89]	0.20 [−0.27, 0.67]	1.02 [0.57, 1.47]
	Right Superiorparietal	8.96E-08			1.06 [0.72, 1.39]	1.07 [0.61, 1.52]	1.07 [0.57, 1.56]			
	Right Supramarginal	5.26E-03			0.53 [0.21, 0.85]	0.37 [−0.07, 0.79]	0.82 [0.34, 1.30]			
Occipital	Right Cuneus	1.59E-04			0.75 [0.43, 1.08]	0.59 [0.15, 1.02]	0.96 [0.46, 1.44]			
	Right Lateraloccipital	9.73E-04			0.67 [0.34, 0.99]	0.77 [0.32, 1.21]	0.59 [0.11, 1.06]			
	Right Lingual	7.22E-03			0.56 [0.24, 0.88]	0.55 [0.11, 0.98]	0.57 [0.09, 1.04]			
	Right Pericalcarine	1.21E-15			1.59 [1.23, 1.95]	1.42 [0.94, 1.90]	1.81 [1.25, 2.35]			

(Continued)

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TABLE 2 (Continued)

Brain lobes	Brain regions		Significance level in ANCOVA p_{FDR}			Cohen's d: rural–urban (d [95% CI])			Cohen's d: normal-impaired (d [95% CI])		
			Residency status	Impairment status	Interaction	All participants	Normal participants	Impaired participants	All participants	Rural participants	Urban participants
Cingulate	Right Caudalanteriorcingulate										
	Right Isthmuscingulate										
	Right Posteriorcingulate										
	Right Rostralanteriorcingulate										
Insula	Right Insula			3.13E-02		0.55 [0.23, 0.87]	0.36 [−0.07, 0.79]	0.86 [0.38, 1.35]	0.51 [0.19, 0.83]	0.32 [−0.15, 0.79]	0.65 [0.21, 1.08]
Mean	Right Meanthickness		2.83E-03	3.80E-02					0.44 [0.13, 0.76]	0.21 [−0.25, 0.68]	0.71 [0.27, 1.14]

Significant levels [false discovery rate (FDR) corrected p-values (p_{FDR})] are listed for residency effect (rural or urban), clinical impairment effect (normal or impaired) and their interaction effect in ANCOVA (big column 1). Post-hoc effect-sizes (Cohen's d) between rural and urban participants are computed using all, only clinically normal and only clinically impaired participants, respectively (big column 2). A positive effect-size indicates thicker cortex in rural-dwelling than urban-dwelling participants. Post-hoc effect-sizes (Cohen's d) between normal and impaired participants are calculated using all, only rural and only urban participants (big column 3). A positive effect-size indicates thicker cortex in normal than impaired participants. 95% confidence intervals for each post-hoc effect-size (Cohen's d) are listed in square brackets. Thickness measures used to calculate the effect-sizes have been adjusted for ags, sex and education level using coefficients estimated in the ANCOVA.

3.3 Association between neighborhood disadvantage and CT measures

For the five regions with a significant interaction effect, a significantly negative correlation was observed between the CT of right para-hippocampal gyrus and ADI state decile in normal participants (partial correlation r, [95% confidence intervals (CI)] = −0.37, [−0.54, −0.17], $p < 0.001$, Figure 2A, blue), and this correlation was significantly different from the one in impaired participants ($p = 0.003$, Figure 2A). Similar patterns of associations were observed for all 18 temporal regions (Supplementary Figure 5A), with six regions demonstrating statistical significances (Supplementary Figure 5B).

In contrast, a significant positive correlation between the CT of right precuneus and ADI was observed in impaired participants ($r = 0.25$ [0.01, 0.45], $p = 0.03$, Figure 2B, orange).

4 Discussion

Participants from rural areas and less advantaged neighborhoods are at a heightened risk for AD but are underrepresented in AD research (Rahman et al., 2021; Wiese et al., 2023). Our study is among the first to characterize rural–urban differences on brain structural measures and examine the association of neurobiology with neighborhood disadvantage, using both clinically normal and impaired older adults. Our results showed extensive rural–urban disparities on CT measures and significant negative associations between neighborhood disadvantage and CT measures in regions involved in memory and vulnerable to AD.

As we stated in the results section, the observed rural–urban disparities on CT measures could be mainly divided into two categories (summarized in Table 3).

4.1 First category: temporal and inferior prefrontal regions

Given the putative risk of dementia that rural participants are facing (Wiese et al., 2023), older adults from rural areas exhibiting lower CT measures than their urban peers in these regions (blue in Figure 1A) align with our hypotheses, suggesting disadvantages on brain measures for rural-dwelling older adults.

These rural–urban disparities tend to diminish once clinical impairment onset (red arrows in Supplementary Figure 2), as (1) both rural and urban groups showed a significantly lower CT measures in these regions in impaired participants (red arrows in Figure 1), and (2) these impairment-effect seemed to be less pronounced in rural participants (red arrows in Supplementary Figure 2). These interaction effects between residency and impairment reached statistical significance ($p_{FDR} \leq 0.05$) in three regions from this category (left parsopercularis, right lateral-orbito-frontal cortex, and right parahippocampal gyrus, Figure 1C and Supplementary Figure 4), further consolidating that rural cohort tended to have a less pronounced differences between normal and impaired participants in these regions, as compared to urban participants.

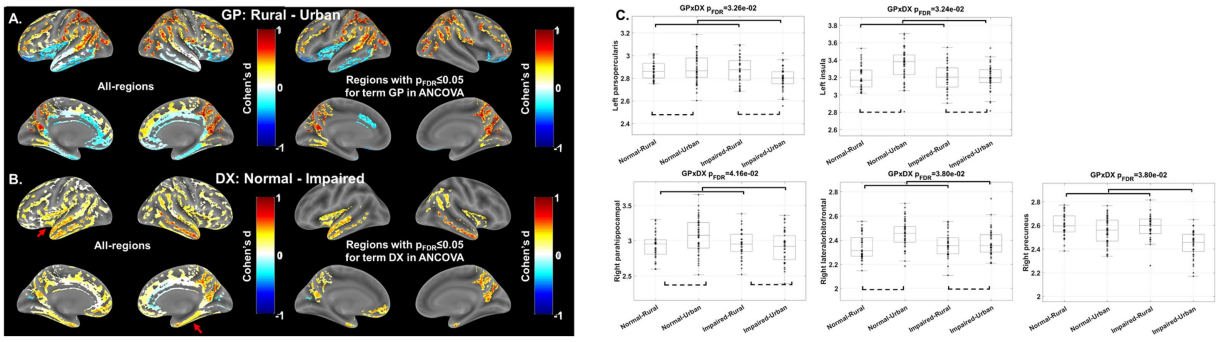

FIGURE 1
Analysis of covariance (ANCOVA) results on cortical thickness measures. **(A)** Residency effect. Post-hoc effect-sizes (Cohen's d) between groups (GP: Rural vs. urban) for whole-brain (Left) and regions with significant residency effect ($p_{FDR} \leq 0.05$, Right) in the ANCOVA. **(B)** Impairment effect. Post-hoc Cohen's d of Normal vs. impaired for whole-brain (Left) and regions with significant impairment effect in the ANCOVA ($p_{FDR} \leq 0.05$, Right). **(C)** Interaction effect. Five regions showed significant interaction effect between residency and impairment (GPxDX) in the ANCOVA analysis. Thickness measures used in the post-hoc analysis and plotted here have been adjusted for age, sex and education in the ANCOVA model. GP: Residency group (i.e., rural or urban); DX: Diagnosis (i.e., clinical impairment status); FDR: false discovery rate.

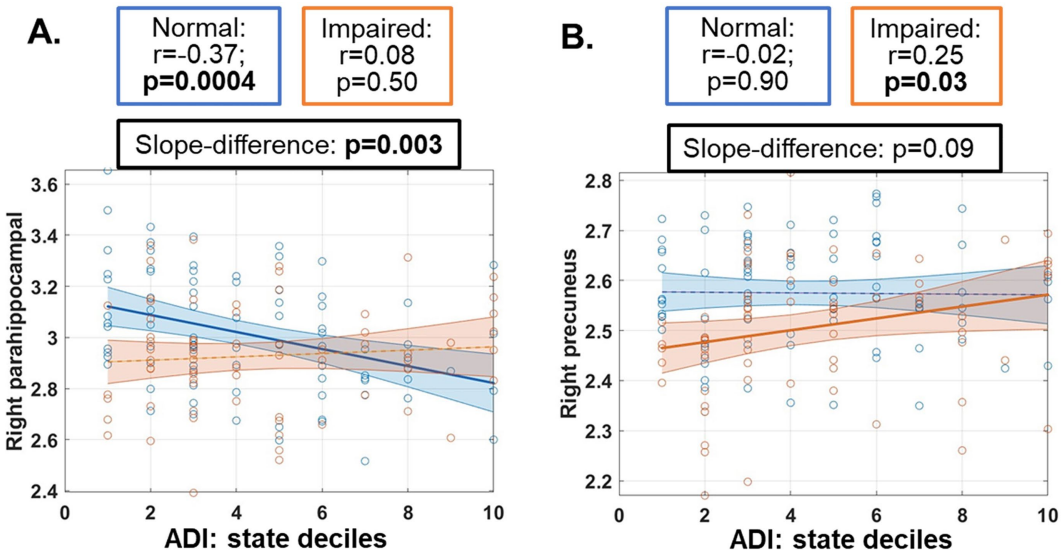

FIGURE 2
Post-hoc associations between cortical thickness measures and neighborhood area deprivation index (ADI) in both normal (blue) and impaired (orange) participants. ADI ranked within Nevada was used. Regions with significant ANCOVA results were input to this association analyses, and only regions with a significant slope ($p \leq 0.05$) were plotted here, including parahippocampal gyrus **(A)** and precuneus **(B)**. Cortical thickness measures used in this post-hoc analysis and plotted here have been adjusted for age, sex and education in the ANCOVA model. Partial correlation values (r) with 95% confidence intervals and statistical significance levels (*p*-values) were listed in boxes above the plots.

Given the implication of these temporal and frontal regions in memory processes, our findings might imply that rural-dwelling older adults who are cognitively normal may have thinner cortex than their urban peer; and decreases in their CT measures to a lesser degree could notably affect the clinical impairment status, as compared to urban participants.

Additionally for CT measures in this category, a negative association with ADI state deciles was evident in only clinically normal participants (Figure 2A and Supplementary Figure 5), indicating that for cognitively normal individuals, living in a more disadvantaged neighborhood in Nevada was associated with thinner cortex in regions that were mostly involved in memory and vulnerable to AD. These results are consistent with previous reports on ADI associations with thinner cortex in AD signature regions (mostly temporal lobe) and smaller hippocampal volumes in younger unimpaired participants from another US state (Hunt et al., 2020, 2021). Our results additionally suggested that once clinical impairment emerged, impairment effects would be more dominant than the neighborhood effects and masked these associations.

Interestingly, our exploratory analysis with hippocampal volume did not find any association with ADI (Supplementary Figure 6B). Given the vulnerability of hippocampus to aging or AD, and our cohorts were in their 70s [participants in previous studies were in their 60 s (Hunt et al., 2020, 2021)], clinical impairment effect might be again more dominant for these regions and thus masked the neighborhood effect in our analyses.

TABLE 3 Summarized residency (rural vs. urban) and clinical impairment (normal vs. impaired) effects for cortical thickness measures.

		All subjects	Normal	Impaired	All subjects	Urban	Rural
Structural MRI-derived cortical thickness measures	Temporal and inferior frontal regions	Rural < Urban (align with our hypothesis)	Rural < Urban (Larger effect size) Negatively associated with higher ADI	Rural < Urban (Smaller effect size)	Normal > Impaired	Normal > Impaired (**Larger** effect size)	Normal > Impaired (**Smaller** effect size)
	Superior frontal, parietal and occipital regions	Rural > urban	Rural > urban (Smaller effect size)	Rural > Urban (Larger effect size)			

4.2 Second category: parietal, occipital and superior and middle frontal areas

Rural-dwelling participants show thicker cortex in these regions than urban-dwelling participants (red in Figure 1A). Considering the same enhanced dementia risks in rural participants, these rural advantages in brain CT measures were less expected, indicating that a more complex interplay of residency neighborhood contexts with neurobiology may exist. A potential compensatory mechanism might partially explain these observations, as rural participants could recruit other brain regions to supplement the thinner temporal and inferior frontal cortices.

4.3 Technical perspectives

In this study, rural–urban status and neighborhood disadvantage index were used in conjunction with separate analyses. We acknowledge that RUCA codes and ADI rankings are to some degree parallel such that more rural areas are likely to be more disadvantaged. However, our interpretation of the underlying components used to derive each metric suggests that they are sufficiently distinct to be used in conjunction. In our analyses, we first evaluated the rural–urban differences in whole-brain CT measures without any prior knowledge and examined the association between CT measures and ADI in a post-hoc manner.

Since ethnicity was significantly different between rural and urban groups, we have repeated our ANCOVA with ethnicity as an additional covariate. All main findings remained the same in this repeated analysis, as revealed by the overall concordance of significance levels in ANCOVA with and without ethnicity as covariates, and the two categories of rural–urban differences on CT measures (Supplementary Figure 7).

4.4 Limitation

Several limitations should be considered when interpreting our results.

First, our cross-sectional setting and reliance on single measurement without baseline data could only infer associations between CT measures and residency and/or clinical impairment status. The small sample has further posed a threat to the generalizability of our results. However, we consider our preliminary findings as a starting point to address the underrepresentation of rural-dwelling older adults in neuroimaging research. In addition, our study is specifically designed as a longitudinal study. Future follow-up studies are planned once we have sufficient data available, to evaluate whether a significant cortical thinning exists in urban or rural participants once disease manifests, depending on different regions.

Sex was treated as a covariate in our analyses despite that brain structures could differ between men and women. The relatively small sample sizes have limited our statistical power to stratify our analyses by sex (Supplementary Figure 8). Due to the same reason of limited sample size, the association between ADI and CT measures were also analyzed in a post-hoc manner, focusing on regions with significant interaction effect in ANCOVA. Future analyses with increased sample-sizes might better evaluate the sex-stratified association between neighborhood context and brain structures.

The NVeADRC is a community-dwelling cohort whereas the CNTN recruits urban-dwelling order adults seeking active clinical care. Although these two cohorts did not differ in clinical, cognitive functioning or functional status, the differences in recruitment strategy may bias our findings. However, we observed thinner cortices in memory-related regions in community- and rural-dwelling older adults, which provided confidence to our interpretations that the status of rural-living and neighborhood disadvantage might negatively impact the neurobiology in brain regions involved in memory and vulnerable to AD. Nevertheless, future studies following individuals that have already established care in a rural-based clinical setting could further validate our findings.

In addition, the RUCA code and ADI state deciles in NVeADRC and CNTN were all based on participants' current and primary residences, thus did not consider participants' time of settlement. Moreover, besides composite RUCA or ADI scores, other detailed measures such as economic differences and living habits of each participant could also affect their brain structures. In the present study, we chose to focus on the core socio-demographic and socio-economic factors of community, and have not controlled these relevant factors due to the lack of information and the limited sample-size. Future studies evaluating full residency history with updated RUCA codes and detailed economic factors might further consolidate and clarify our results.

More importantly, the average RUCA score in our rural cohort is 4.27, and most participants live 1–2 h away from Las Vegas. Though this RUCA score and this distance confer some disadvantages in receiving healthcare, our cohort can only represent the rural and non-metropolitan areas locally in Nevada, and the disparities experienced by more rural and isolated areas representing by higher RUCA codes are not represented by our cohort. Furthermore, even under similar RUCA codes, detailed rural area characteristics and resource allocations could differ and differentially affect the brain structures of older adults who reside in them. Therefore, additional caution is advised generalizing our results to other rural areas with similar RUCA codes. Nevertheless, our study serves as an important initial step in exploring the impact of community background on brain structures.

5 Conclusion

Our cross-sectional study is among the first to characterize rural–urban differences on brain structures and associate CT measures with neighborhood disadvantage in both clinically normal and impaired populations. The results of this observational study demonstrated a complex interplay of rural living and community backgrounds with neurobiological changes in AD. Our findings could potentially aid in designing future studies to more comprehensively understand the rural–urban disparities in AD.

Data availability statement

The datasets used for this study can be found in the Nevada Exploratory Alzheimer's Disease Research Center (NVeADRC, https://nvadrc.org/) and the Nevada Center for Neurodegeneration and Translational Neuroscience (CNTN, https://nevadacntn.org/), through reasonable requests from qualifying PIs.

Ethics statement

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

Author contributions

XZ: Data curation, Formal analysis, Methodology, Visualization, Writing – original draft, Writing – review & editing. DC: Conceptualization, Data curation, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. JC: —. AB: Formal analysis, Methodology, Writing – original draft, Writing – review & editing. JM: Conceptualization, Funding acquisition, Investigation, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing.

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Conflict of interest

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

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2024.1465744/full#supplementary-material

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Effects of traditional Chinese exercises or their integration with medical treatments on cognitive impairment: a network meta-analysis based on randomized controlled trials

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Objective: This study aims to summarize and critically evaluate the effects of traditional Chinese exercises, both in isolation and in combination with medical treatments, on cognitive impairment.

Methods: A systematic search of academic databases, including PubMed, Embase, Web of Science, Cochrane Library, CNKI, Wanfang, and VIP, was conducted to identify the randomized controlled trials (RCTs) that evaluated traditional Chinese exercises and their integration with medical treatments for addressing cognitive impairment. Study quality was assessed using the Cochrane Handbook's Risk of Bias tool. A total of 24 RCTs involving 1,808 participants were included. The primary outcome measures were the Montreal Cognitive Assessment (MOCA) and the Mini-Mental State Examination (MMSE). Subgroup analyses were performed to compare the intervention effects.

Results: The network meta-analysis revealed that acupuncture combined with Tai Chi (Aandtaiji) showed the most significant improvement in MOCA scores, followed by Qigong. Tai Chi soft ball exercise (Taijiball) demonstrated the greatest improvement in MMSE scores.

Conclusion: The combination of traditional Chinese exercises with medical treatment is more effective in improving MOCA scores, while traditional exercises alone yield better results to enhance MMSE scores. The extended practice of Tai Chi and Qigong enhances cognitive function in patients with cognitive impairment.

KEYWORDS

Tai Chi, traditional Chinese exercises, Qigong, cognitive impairment, medical treatments

Introduction

As the aging continues to accelerate, cognitive impairment has become a widespread and urgent public health issue, affecting millions of people worldwide (Loss et al., 2024; Moawad et al., 2024). Cognitive impairment refers to a decline in abilities like information processing, attention, memory, language, and executive functions, which significantly

impact daily life (Arnold, 2020). Cognitive impairment is an umbrella term that encompasses a range of conditions, from mild cognitive impairment (MCI) to severe dementia (Sohn, 2018). Across the world, the care and treatment costs for Alzheimer's and related dementias are estimated at $1.3 trillion annually, covering medical, home care, long-term facilities, and caregiver services (Roth, 2022; Pandharipande et al., 2023). Low-cost treatment and healthcare strategies are urgently needed to reduce the financial strain on patients and families, slow cognitive decline, and lessen the demand for professional care and healthcare resources (Lin et al., 2024).

Traditional Chinese exercises, such as Qigong, Tai Chi, and Taijiball, combine breath control, body postures, and meditation to enhance physical and mental health (Li et al., 2001; Park et al., 2023; Duan et al., 2024). These exercises have proven effective in aiding recovery from chronic diseases, including cognitive impairment, and in reducing treatment costs (Wayne et al., 2014; Li et al., 2019; Yao et al., 2023). Traditional Chinese exercises combined with medical interventions are considered potential effective solutions due to their low cost, ease of implementation, and long-term efficacy (Navas-Otero et al., 2024; Zhang X. et al., 2024).

However, previous meta-analyses have limitations. Most studies focus mainly on Yang-style Tai Chi and a few types of Qigong (Park et al., 2023; Wang et al., 2023), such as Baduanjin Qigong (BDJqigong), Yi Jin Jing Qigong, Wuqinxi Qigong, and Liuzijue Qigong (LZJqigong), have been considered (Yao et al., 2023). Overlooking other traditional exercises and the diversity within Tai Chi and Qigong. Tai Chi includes various styles, such as Chen, Yang (including simplified forms like the 24-style; Lei et al., 2022), six-style (Lin et al., 2019), and eight-style (Meiling, 2021), Wu style, Sun style, and He style (You et al., 2021). Many commonly practiced Qigong forms, such as SEDJqigong (Jing et al., 2019; Hengjia et al., 2020), Yangfeifang Qigong (YFF Qigong) (Min and Xiaodan, 2023), and exercises like Taijiball (Yong et al., 2016), have never been included in meta-analyses.

Furthermore, combinations of traditional Chinese exercises with therapies like acupuncture and transcranial direct current stimulation (tDCS) are rarely included (Rizhen et al., 2013; Yu, 2021; Liu et al., 2022; Xu et al., 2023). However, these combinations are seldom included in the meta-analyses, and these limitations restrict the generalizability of findings. Moreover, meta-analyses have provided mixed results. Lyu et al. (2021) found Tai Chi had no significant effect on cognitive dysfunction, while Zhou et al. (2022) reported significant improvements.

Most previous studies relied on traditional meta-analysis, limited to direct comparisons between the two treatments (Lyu et al., 2021). Unlike traditional meta-analysis, network meta-analysis allows for the simultaneous comparison of multiple treatments, including traditional Chinese exercises and their combination with medical treatments, even when direct comparisons are unavailable. It ranks interventions by effectiveness, offering a more comprehensive understanding of therapeutic potential. This method is particularly useful in medical research with diverse treatment options, as it integrates both direct and indirect evidence, enhances statistical power, and reveals benefits not apparent in direct comparisons, making it a valuable tool for clinical decision-making (Mbuagbaw et al., 2017; Tian and Li, 2024).

This network meta-analysis review aims to assess the impact of various traditional Chinese exercises, alone and combined with other treatments, on cognitive function in individuals with cognitive impairment. The goal is to identify the most effective intervention strategies, providing valuable insights for clinical trials.

Methods

Study registration

The study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Network Meta-Analyses (PRISMA-NMA) guidelines and was prospectively registered with PROSPERO (CRD42024536140).

Eligibility criteria

Inclusion criteria

The inclusion criteria were formulated based on the PICOS (population, interventions, controls, outcomes, study design) framework.

Population: Patients with a confirmed diagnosis of cognitive impairment, who are in the early to early-middle stages of dementia or mild cognitive impairment (MCI), with no prior use of any medications before the intervention were included in the analysis. There were no restrictions on age, gender, race, or nationality.

Intervention: Studies focusing on traditional Chinese exercises (such as Tai Chi, Qigong, etc.) combined with other therapeutic methods (such as acupuncture, tDCS, etc.) were included for the analysis. These interventions were applied either individually or in combination.

Comparison: The control group in this study comprised participants who maintained their regular daily activities without receiving any form of intervention.

Outcome: Cognitive screening and assessment are crucial for evaluating cognitive impairment. In epidemiological studies, MOCA and MMSE are commonly used tools. Thus, the results of this study are based on these measures (Yu et al., 2012; Arevalo-Rodriguez et al., 2021; Jia et al., 2021).

Main outcome measure: Based on the results of this study, the Aandtaiji demonstrated the best effect on the MOCA scores, while Taijiball showed the most significant improvement of the MMSE scores.

Second primary outcome measure: Based on the results of this study, the intervention combining traditional Chinese exercises with other therapeutic methods was superior to all other traditional Chinese exercises in the MOCA scores when compared to the control group receiving no treatment. However, traditional Chinese exercise interventions alone were more effective in improving the MMSE scores than the integrated approach of traditional exercises with other therapeutic methods.

Study design: The study design was restricted to randomized controlled trial.

Exclusion criteria

Studies involving intervention methods unrelated to traditional Chinese exercises in the experimental group; duplicate studies or data, animal experiments, non-patient studies, studies not published in

Chinese or English, and studies unrelated to cognitive impairment were excluded from the analysis.

Data sources and search strategy

We conducted a systematic search across major academic databases, including PubMed, EMbase, Web of Science, Cochrane Library, CNKI, Wanfang, and VIP, up to April 30, 2024. The aim was to identify randomized controlled trials (RCTs) evaluating the effects of traditional Chinese exercises (e.g., Tai Chi) or their combination with other treatments on cognitive impairment. Both subject headings and free-text terms were used to capture the relevant studies. To minimize bias and errors, the search strategy followed these principles: (1) *diverse search terms*: We included a broad range of synonyms and variants, such as Tai Ji, TAIJI, Taijiquan, Baduanjin, cognitive impairment, mild cognitive impairment, dementia, and others; (2) *language restrictions*: The search was limited to English and Chinese publications to include global research within these two languages; (3) *manual and gray literature search*: Additional studies were identified by manually reviewing reference lists and including gray literature (e.g., dissertations). This strategy ensures a comprehensive collection of studies on traditional Chinese exercises and their effects on cognitive impairment, minimizing bias and enhancing the reliability of the findings.

Study selection

Based on the predetermined literature retrieval strategy, researchers Jiadong Qiu and Wanyu Shu utilized the EndNote X20 software to retrieve and eliminate duplicate documents. The remaining literature has been assessed for inclusion or exclusion based on established criteria through title and abstract review, followed by a thorough evaluation of the full texts for qualification. In cases of discrepancy, a third researcher, Liang Chen, was consulted to reach a consensus on the final selection of literature.

Data extraction

Two researchers, Jiadong Qiu and Wanyu Shu, developed a data extraction form based on the necessary information for the study and conducted independent data extraction. The included contents were as follows: (1) basic information such as title, author, year, study type, diagnostic criteria, intervention measures, treatment course, and outcome indicators; (2) demographic characteristics including sample size, age, and gender; and (3) methodology of information: Various methods such as randomization, allocation concealment, and blinding are employed in research studies. In cases where discrepancies arise in the data collected by two individuals, they engaged in a discussion to resolve the issue. If a resolution cannot be reached, further discussion and decision-making processes were undertaken.

Risk of bias in studies

Two researchers Jiadong Qiu and Wanyu Shu used the Cochrane Risk of Bias Assessment tool for RCTs to assess the risk of bias. The assessment tool contains the following seven items: generation of the random sequence, allocation concealment, blinding of subjects and intervention providers, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias, with each item assessing the outcome as low bias, high bias, or unclear (Isenberg et al., 2020).

Synthesis methods

Bayesian random effects models were employed to assess the comparative effectiveness of different interventions. The Markov chain Monte Carlo method was utilized for modeling, with four Markov chains run concurrently and annealing performed 20,000 times. Model convergence was achieved after 50,000 simulation iterations. The study utilized the bias information criterion (BIC) to assess the model fit and global consistency, employed the node splitting method to evaluate local consistency in the presence of closed-loop networks, ranked interventions according to the surface under the cumulative ranking (SUCRA) curve, and generated a league table to compare the efficacy of various interventions. We extracted data from the original 24 RCTs. Numerous original studies incorporated in the analysis conducted multi-arm studies on Tai Chi and other traditional Chinese exercises within the MOCA and MMSE indexes, categorizing subgroups based on specific exercise types. Utilizing Bayesian network meta-regression, we examined potential differences between various traditional Chinese exercises across different intervention durations compared to a control group. When the number of studies included in the outcome index exceeded 10, a funnel plot was utilized to visually represent publication bias. Statistical analyses were conducted using Stata 15.0 (Stata Corporation, College Station, TX) and R 4.2.0 (R Development Core Team, Vienna).[1] A significance level of $p < 0.05$ indicated a statistically significant difference.

Results

Study selection

The literature search and study selection process yielded a total of 3,281 records from the database (Supplementary Table 1). Through screening the references and related articles of the included studies, 1,027 duplicate articles were excluded using software, and an additional 256 duplicate articles were removed by comparing titles with authors. In total, 1,292 duplicate articles were eliminated, resulting in a final selection of 1989 articles. Following the initial screening of titles and abstracts, 700 articles were excluded, leaving a total of 1,289 articles for further review. Of these, 59 underwent full-text evaluation, resulting in the inclusion of 24 studies in the final analysis (Figure 1).

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

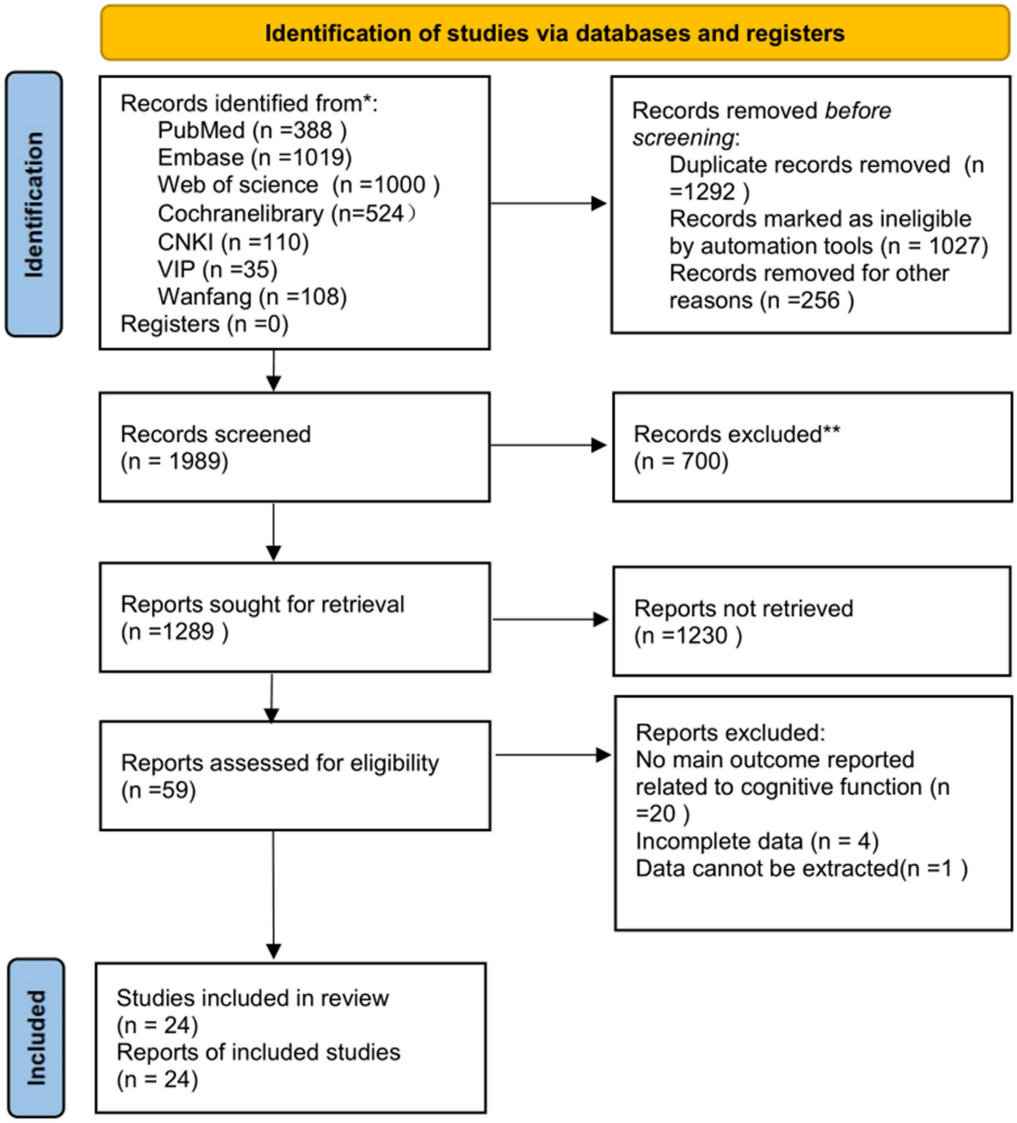

FIGURE 1
Literature screening process.

Study characteristics

This study included 24 studies (Burgener et al., 2008; Rizhen et al., 2013; Tuan and Juan, 2013; Cheng et al., 2014; Li et al., 2014; Chan et al., 2016; Yong et al., 2016; Jun and Zhongxing, 2018; Siu and Lee, 2018; tao et al., 2018; Jing et al., 2019; Lin et al., 2019; Hengjia et al., 2020; Liu et al., 2021; Meiling, 2021; Yu, 2021; Zhicheng et al., 2021; Jinping, 2022; Liu et al., 2022; Yu et al., 2022; Chen et al., 2023; Min and Xiaodan, 2023; Xia et al., 2023; Xu et al., 2023) with a total of 1808 patients. The authors were from China and the United States, and the publication time was from 2008 to 2023. Most of the studies were published in the past 5 years. The criteria of MCI mainly came from Petersen. Twenty-four studies employed the same type of traditional Chinese exercises or combined them with other medical interventions (Table 1).

Risk of bias in studies

This study reviewed 24 articles. Regarding randomization, all studies provided detailed descriptions or explicitly stated adherence to random allocation procedures, resulting in a "low-risk" classification. For allocation concealment, one study explicitly reported not implementing it (Siu and Lee, 2018), 11 studies confirmed its use, while 12 studies lacked sufficient detail and were classified as having an "uncertain risk of bias." Due to the nature of the interventions, blinding the participants was limited. Thirteen studies reported using blinding, while the others were rated as having "uncertain risk" due to inadequate reporting. For outcome assessment, data completeness, and selective reporting, all studies were deemed "low risk" as participant numbers were consistent with initial enrollments, and no selective reporting was observed. Two studies with small sample sizes (Hengjia et al., 2020; Yu et al., 2022)

TABLE 1 Characteristics of included studies in this review.

No	Title	Language	Author	Country	Time	Patient	Intervention	Number	Course	Outcome
1	Tai Ji Quan and global cognitive function in older adults with cognitive impairment: A pilot study	English	Fuzhong Li	USA and China	2014	MCI	14-week Yang style tai Ji: Moving for Better Balance (TJQMBB) program;	Taiji group ($n = 20$) Control group ($n = 20$)	14w	MMSE
2	Tai Chi versus conventional exercise to improve cognitive performance in older adults with mild cognitive impairment	English	Angus P Yu	Hong Kong, China	2022	MCI	Tai Chi group: 24 weeks of Yang-style Tai Chi training three times a week for 60 min each session; Conventional Exercise group: 24 weeks of fitness training three times a week for 60 min each session; Control group: no intervention.	Tai Chi group ($n = 10$); Exercise group ($n = 12$); Control group ($n = 0.12$)	24w	MOCA
3	Tai chi qigong as a means to improve night-time sleep quality among older adults with cognitive impairment: A pilot randomized controlled trial	English	Aileen WK Chan	Hong Kong, China	2016	MCI	Yang and Wu style tai Ji and Baduanjin, Wuqinxi, Liuzijue qigong sessions twice a week for 2 months, 60 min each session	Taiji group ($n = 27$) Control group ($n = 25$)	8w	MMSE
4	Simplified Tai Chi 6-Form Apparatus for Balance in Elderly People with Alzheimer's Disease	English	Lin, Y. C.	Taiwan, China	2020	MCI	The Yang style tai Ji group (TCGr) completed an 8-week training course for the Simplified Yang style tai Ji 6-Form Apparatus	Taiji group ($n = 11$) Control group ($n = 10$)	8w	MMSE
5	Mind–Body Exercise Modulates Locus Coeruleus and Ventral Tegmental Area Functional Connectivity in Individuals With Mild Cognitive Impairment	English	Liu Jiao	China	2021	MCI	Participants were randomized into Qigong, brisk walking, or a healthy education control group for 6 months. The exercise groups participated in sessions 3 days/week, 60 min/day.	Qigong group ($n = 20$) Control group ($n = 20$)	24w	MOCA
6	Mental and Physical Activities Delay Cognitive Decline in Older Persons with Dementi	English	Jing Tao;	Hong Kong China	2014	Early to early-middle stages of dementia	Mahjong. Taiji group. Control group	Mahjong ($n = 36$) Taiji group ($n = 39$) Control group ($n = 35$)	24w	MOCA
7	Effects of Tai Chi on cognition and instrumental activities of daily living in community dwelling older people with mild cognitive impairment	English	Siu, Mei Yi	Hong Kong China	2017	MCI	The intervention group received 16 weeks of Yang-style Tai Chi training, two sessions per week, each lasting 1 h	Taiji group ($n = 80$) Control group ($n = 80$)	16w	MMSE
8	Effects of Tai Chi combined with tDCS on cognitive function in patients with MCI: a randomized controlled trial	English	Ying Xu	USA and China	2023	MCI	Taiji and tDCS.Tai Ji. ontrol	Taiji and tDCS ($n = 44$) Tai Ji ($n = 49$) ontrol group ($n = 44$)	24w	MOCA
9	Effects of Tai Chi Chuan on Cognitive Function in Adults 60 Years or Older With Type 2 Diabetes and Mild Cognitive Impairment in China: A Randomized Clinical Trial	English	Yannan Chen	USA and China	2023	MCI	Yang style tai Ji and walking training, both for 60 min/session, 3 times/wk. for 24 weeks	Taiji group ($n = 110$) Control group ($n = 110$)	36w	MOCA

(Continued)

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TABLE 1 (Continued)

No	Title	Language	Author	Country	Time	Patient	Intervention	Number	Course	Outcome
10	Effects of mind–body exercise baduanjin on cognition in community-dwelling older people with mild cognitive impairment: a randomized controlled trial	English	Xia Rui	China	2022	MCI	Baduanjin exercise group received 24 weeks of Baduanjin exercise training, 60 min sessions, 3 days per week; Brisk walking group received 24 weeks of brisk walking, 60 min per session, 3 sessions per week.	Qigong group ($n = 70$) Control group ($n = 65$)	24w	MOCA
11	Effects of exergaming based Tai Chi on Cognition and dual task gait in older adults with mild cognitive Impairment a randomized control trial	English	Chen Liang Liu	China	2022	MCI	EXER-TC and TC groups received 36 training sessions (three 50-min sessions per week) for 12 weeks	EXER-taiji ($n = 16$) Taiji group ($n = 17$) Control group ($n = 19$)	12 W	MOCA
12	The effects of a multimodal intervention on outcomes of persons with early-stage dementia	English	Sandy C. Burgener	USA	2008	Early to early-middle stages of dementia	40-week intervention, including Taiji exercises, and support group participation	Taiji group ($n = 24$) Control group ($n = 19$)	40w	MMSE
13	Clinical study of acupuncture combined with Tai Chi in the treatment of mild cognitive impairment caused by cerebral small vessel disease	Chinese	Ze Yu Shen	China	2021	MCI	Acupuncture combined with Yang style tai Ji intervention; the control group used only Yang style tai Ji intervention.	A + Taiji ($n = 31$); Control group ($n = 31$)	8w.	MOCA
14	A study on the evaluation of the clinical efficacy of Baduanjin in patients with mild cognitive dysfunction	Chinese	Qian Yang	China	2019	MCI	Ba duan jin qigong 5 times a week, 40 min each session, for 24 weeks. The control group received no intervention	Qigong group ($n = 32$) Control group ($n = 32$)	24w	MOCA
15	The effect of Naoling decoction combined with Tai Chi on the rehabilitation of patients with Alzheimer's disease	Chinese	Ri Zhen Li	China	2013	Early-stage Alzheimer's disease	he treatment group received Naoling Decoction combined with Yang style tai Ji exercise, while the control group received conventional treatment	Naoling +Ytaiji ($n = 32$) Control group ($n = 30$)	12w	MMSE
16	Study on the Rehabilitation Effects of Six-Character Formula of Health Qigong on Mild Cognitive Impairment in the Elderly	Chinese	Xin Tuan Zheng	China	2013	MCI	"Six Healing Sounds" fitness Qigong exercise, practiced twice daily for 30 min each session, 5 days a week for 6 months	Qigong group ($n = 45$) Control group ($n = 43$)	24w	MOCA
17	The Impact of Virtual Reality-Based Baduanjin Exercise on Mild Cognitive Impairment in Elderly Patients in Nursing Homes	Chinese	Sun Zhi Chen	China	2021	MCI	VR-based qigong 50 min per session, three times a week for 24 weeks	VR qigong ($n = 29$) Control group ($n = 28$)	24w	MOCA
18	Study on the Intervention Effect of Continuous Health Qigong Exercise on Mild Cognitive Impairment in the Elderly	Chinese	Jun Cai	China	2018	MCI	6 months of fitness Qigong exercises including Yi Jin Jing, Ba Duan Jin, Wu Qin Xi, Liu Zi Jue	Qigong group ($n = 28$), Control group ($n = 30$)	24w	MOCA, MMSE
19	Clinical Observation of the Efficacy of Eight-Style Tai Chi on Mild Cognitive Impairment Caused by Lacunar Infarction	Chinese	Mei Ling Huang	China	2021	MCI	Yang style tai Ji group practiced Eight Style Taijiquan for 30 min	Taiji group ($n = 33$) Control group ($n = 33$)	24w	MOCA

(Continued)

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TABLE 1 (Continued)

No	Title	Language	Author	Country	Time	Patient	Intervention	Number	Course	Outcome
20	Clinical Study of Baduanjin Combined with Transcranial Direct Current Stimulation in Treating Mild Cognitive Impairment After Stroke	Chinese	Jin Ping Feng	China	2022	MCI	The control group received transcranial direct current stimulation, while the observation group Baduanjin exercise	T + qigong ($n = 47$) Control group ($n = 47$)	8w	MOCA,MMSE
21	The Impact of Baduanjin on the Cognitive Levels of Patients with Mild Cognitive Impairment	Chinese	Tao Liu	China	2018	MCI	Baduanjin exercise intervention for 6 months	Qigong group ($n = 30$) Control group ($n = 30$)	24w	MOCA
22	Experimental Study on Tai ji Soft Ball Exercise in the Treatment of Senile Dementia	Chinese	Yong Zhou	China	2016	Early to early-middle stages of dementia	Taijiball(softball) exercise under professional guidance, compared to jogging in the control group	Taijiball group ($n = 18$) Control group ($n = 18$)	32w	MMSE
23	Study on the Impact and Mechanism of Health Qigong Yangfei Prescription on Cognitive Function in Patients with Stable Chronic Obstructive Pulmonary Disease	Chinese	Min Zhuang	China	2023	Severity levels GOLD 1–3 (FEV1 ≥ 30%)	Yangfeifang Qigong exercise, 5 days a week, 2 sessions per day, 35 min per session for 12 weeks	Qigong group ($n = 18$) Control group ($n = 18$)	12w	MOCA
24	59.Study on the Impact of Health Qigong 12 Duanjin on Patients with Mild Cognitive Impairment	Chinese	Heng jia Liu	China	2020	MCI	Twelve Dan jin qigong Exercises performed 5 times per week, 40 min per session, over 24 weeks	Qigong group ($n = 30$) Control group ($n = 30$)	24w	MOCA

raised concerns about publication bias and were rated as high risk. All other studies were assessed as low risk. Figure 2 summarizes the overall risk of bias and provides individual assessments for each study (Figure 2).

Meta-analysis

The first outcome measure was MOCA linkages between interventions. MOCA: 16 studies (Tuan and Juan, 2013; Jun and Zhongxing, 2018; tao et al., 2018; Jing et al., 2019; Hengjia et al., 2020; Liu et al., 2021; Meiling, 2021; Yu, 2021; Zhicheng et al., 2021; Jinping, 2022; Liu et al., 2022; Yu et al., 2022; Chen et al., 2023; Min and Xiaodan, 2023; Xia et al., 2023; Xu et al., 2023) used MOCA as an outcome indicator and four studies (Yu, 2021; Jinping, 2022; Liu et al., 2022; Xu et al., 2023) used a combination of traditional Chinese exercises and medical means, among which the direct comparison between Qigong and control group was the most, followed by the direct comparison between Taiji (Tai Chi) and control group, and the combination of Taiji and other interventions was the most. The figure shows a closed loop (Supplementary Figure 1).

Synthesized results

As regards MOCA indicators, the network meta-analysis results showed that compared with the control group, the three interventions (Aandtaiji, Qigong, and Taiji) showed significant advantages ($p < 0.05$) (Figure 3). The top three interventions for MOCA indicators were Aandtaiji (Acupuncture combined with Tai Chi) [RR = 4.11, 95% CI (1.102, 7.46), $p < 0.05$], Qigong [RR = 2.35, 95% CI (1.26, 3.36), $p < 0.05$], and Taiji [RR = 2.14, 95% CI (0.79, 3.72), $p < 0.05$], all showing significant effects (Supplementary Table 2). However, although Taiji-tDCS (Tai Chi combined with tDCS) [RR = 0.24, 95% CI (−2.36, 2.99), $p < 0.05$] was included in the analysis, it did not show a statistically significant effect compared to Aandtaiji.

SUCRA ranking for the top three is in the order Aandtaiji (0.927), Qigong (0.671), and Taiji (0.615) (Table 2).

MOCA subgroup

Linkages between interventions: This section provides an explanation of the relationships between different interventions in the network meta-analysis. To compare which exercises had the greatest impact on cognitive function, traditional Chinese exercises (such as Tai Chi) were classified into MOCA subgroups based on their names (Supplementary Figure 2).

For instance, BDJqigong and Ytaiji (Yang style Tai Chi) were directly compared with control groups in the previous studies. Other interventions combined Tai Chi or Qigong with additional treatments, such as YFFqigong and SEDJqigong, which had not been included in prior meta-analyses of traditional Chinese exercises and cognitive dysfunction. The figure illustrates a closed loop, indicating interconnected comparisons among interventions (Figure 4).

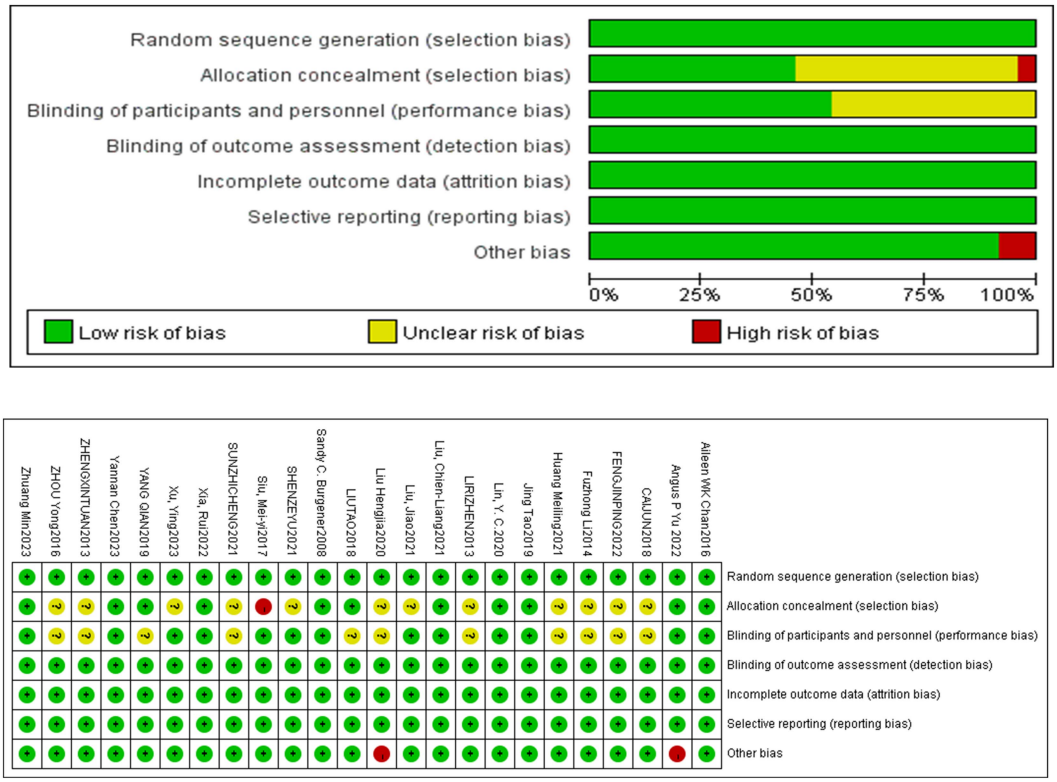

FIGURE 2
Summary of risk of bias for all the included studies. Method: this figure presents a risk of bias assessment based on the Cochrane Collaboration's framework. Bias categories include random sequence generation, allocation concealment, blinding, and other potential biases. Green: Low risk of bias. Yellow: Unclear risk of bias. Red: High risk of bias. Results: The bar chart summarizes the proportion of studies with low, unclear, or high risk of bias. Most categories show a low risk, with some uncertainty in allocation concealment and a small portion of high risk in "other bias." A table below shows individual study assessments, with color-coded dots indicating the bias level.

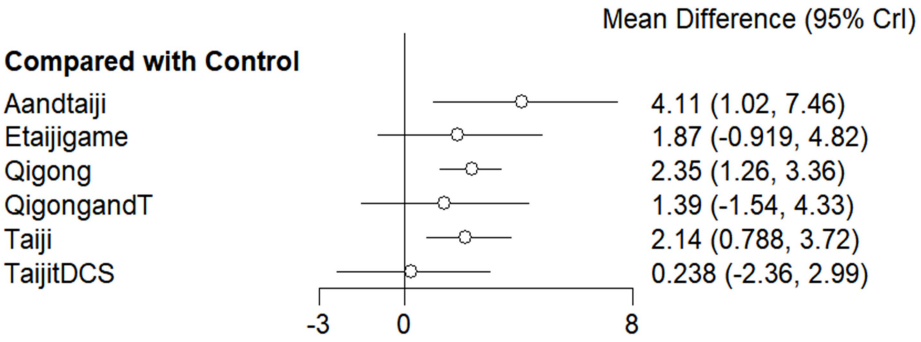

FIGURE 3
Comparison of MOCA index intervention and control groups (Forest Plot). 1: Qigong; 2: Qigong and Transcranial Direct Current Stimulation (tDCS); 3: Exergaming-based Tai Ji (body movement-controlled computer Tai Ji game); 4: Tai Ji; 5: Acupuncture and Tai Ji (Aandtaiji); 6: Tai Ji combined with tDCS (TaijitDcs). Method: This forest plot shows the mean differences between various interventions and the control group, with 95% credible intervals (CrI). Circles represent point estimates, and horizontal lines indicate credible intervals. Results: Significant positive effects were observed for interventions like Acupuncture and Tai Ji (Aandtaiji), followed by Qigong. Other interventions, such as Exergaming and Qigong with tDCS, showed unclear effects.

Synthesized results

The results of MOCA subgroup network meta-analysis showed that compared with the control group, four interventions—SEDJqigong [RR = 4.29, 95% CI (1.87, 6.60), $p < 0.05$], Acupuncture combined with Yang style of Tai Chi [RR = 4.28, 95% CI (0.75, 8.26), $p < 0.05$], YTaiji [RR = 2.31, 95% CI (0.87, 4.18), $p < 0.05$], and BDJqigong (RR = 1.90, 95% CI (0.04, 3.80), $p < 0.05$)—bestowed significant advantages (Figure 4; Supplementary Table 3).

TABLE 2 Ranking table of interventions.

SUCRA					
Group	Intervention	MOCA	NO	MMSE	NO
MOCA. MMSE	Etaijigame	0.541	/	/	/
	Qigong	0.671	2	0.3139417	/
	QigongandT	0.438	/	0.40127	/
	Taiji	0.615	3	0.375725	/
	TaijitDCS	0.197	/	/	/
	Naoandtaiji	/	/	0.703	2
	Taijiandqigong	/	/	0.670	3
	Taijiball	/	/	0.992	1
	Aandtaiji	0.927	1	/	/
MOCA Subgroup MMSE Subgroup	BDJqigong	0.467	/	/	/
	BDJqigongandT	0.375	/	0.428	/
	YWLBqigong	0.449	/	0.324	/
	Eytaijigame	0.582	3	/	/
	LZJqigong	0.563	/	0.391	/
	SEDJqigong	0.871	1	/	/
	YFFqigong	0.494	/	/	/
	Ytaiji	0.560	/	0.392	/
	YtaijitDs	0.192	/	/	/
	Naoandytaiji	/	/	0.708	2
	Taijiandqigong	/	/	0.676	3
	Taijiball	/	/	0.983	1
	Aandytaiji	0.850	2	/	/

1. Qigong: Qi gong; 2. QigongandT: Qigong and Transcranial Direct Current Stimulation (tDCS) therapy; 3. Etaijigame: Exergaming-Based Tai Chi, a body movement-controlled computer Tai Chi game; 4. Taiji: Tai Chi or Tai ji; 5. Aandtaiji: Acupuncture and Tai ji; 6. TaijitDcs: Tai Chi combined with Transcranial Direct Current Stimulation (tDCS); 7. BDJqigong: Baduanjin Qigong; 8. BDJqigongandT: Baduanjin Qigong and Transcranial Direct Current Stimulation (tDCS) therapy; 9. LZJqigong: Liuzijue Qigong; 10. SEDJqigong: 12 Duanjin Qigong; 11. YFFqigong: Yifei Fang Qigong; 12. YWLBqigong: Yijinjing Qigong, Wuqinxi Qigong, Liuzijue Qigong, and Baduanjin Qigong; 13. EYtaijigame: Body movement-controlled computer Yang style Tai ji game; 14. Ytaiji: Yang style of Tai ji; 15. AandYtaiji: Acupuncture combined with Yang style Tai ji; 16. YtaijitDcs: Yang style Tai ji combined with Transcranial Direct Current Stimulation (tDCS); 17. Naoandtaiji: Nao Ling Tang and Tai ji; 18. Taijiandqigong: Tai ji and Qigong, organized by combining Yang-style and Wu-style Tai ji with Ba Duan Jin Qigong, Wu Qin Xi Qigong, and Liu Zi Jue Qigong; 19. Taijiball: Tai ji soft ball exercise; 20. NaoandYtaiji: Nao Ling Tang and Yang style of Tai ji. 21. SUCRA: Surface Under the Cumulative Ranking Curve.

The top three SUCRA rankings were as follows: SEDJqigong (0.850), Aandyaiji (0.871), Eytaijigame (It is the body movement—controlled computer Yang style Tai Chi game) (0.581).

The second index MMSE

Linkages between interventions: MMSE: 11 studies (Burgener et al., 2008; Rizhen et al., 2013; Tuan and Juan, 2013; Cheng et al., 2014; Li et al., 2014; Yong et al., 2016; Jun and Zhongxing, 2018; Siu and Lee, 2018; Lin et al., 2019; Jinping, 2022) took MMSE as the outcome index, among which the direct comparison between Taiji and the control group was the most, followed by the direct comparison between Qigong and the control group. Of these 11 studies, two included interventions (Rizhen et al., 2013; Jinping, 2022) that combined traditional Chinese exercises with other interventions. In addition, this study included Taijiball intervention measures that had never been included in traditional Chinese exercises and cognitive dysfunction in the previous meta-analysis. The figure does not show a closed loop (Supplementary Figure 3).

Synthesized results

MMSE

The results of network meta-analysis showed that compared with the control group, Taijiball [RR = 8.74, 95% CI (5.94, 11.53), $p < 0.05$] had a significant advantage (Figure 5; Supplementary Table 4) The top three SUCRA rankings were as follows: Taijiball (0.992), Nao Ling Tang, and Tai Chi (Naoandtaiji) (0.703), and Taijiandqigong (Tai Chi Qigong is organized by combining Yang-style and Wu-style Tai Chi with Ba Duan Jin Qigong, Wu Qin Xi Qigong, and Liu Zi Jue Qigong) (0.670) (Table 2).

MMSE subgroups

The link between the interventions: There were studies that used a most direct comparison between Ytaiji and the control group, followed by the intervention combined with Qigong and other interventions combined with Ytaiji and the control group. The figure does not show a closed loop (Figure 6; Supplementary Table 5).

Synthesized results

MMSE subgroups

Compared with the control group, there was still only one intervention, Taijiball [RR = 8.75, 95% CI (4.81, 12.68), $p < 0.05$] (Figure 6).

The top three in the SUCRA ranking are: Taijiball (0.983), Naoandytaiji (Nao Ling Tang and Yang style of Tai Chi) (0.708), Taijiandqigong (0.676) (Table 2).

Among them, the traditional Chinese exercises (such as Tai Chi and Qigong) ranked first: Taijiball (0.983). The intervention method combining traditional Chinese exercises (such as Tai Chi and qigong) with other means ranked first: Naoandytaiji (0.708). In MMSE subgroup, traditional Chinese exercises were superior to the intervention method of traditional Chinese exercises combined with other means.

Meta-regression

Given the variability in the intervention durations (course) across different modalities, a meta-regression analysis was performed to assess the impact of intervention duration on MOCA and MMSE outcomes. This analysis aimed to quantify the extent to which intervention length influenced the respective cognitive performance measures. The results show that, compared with control group, Qigong [RR = 2.35, 95% CI (1.26, 3.36), $p < 0.05$], and

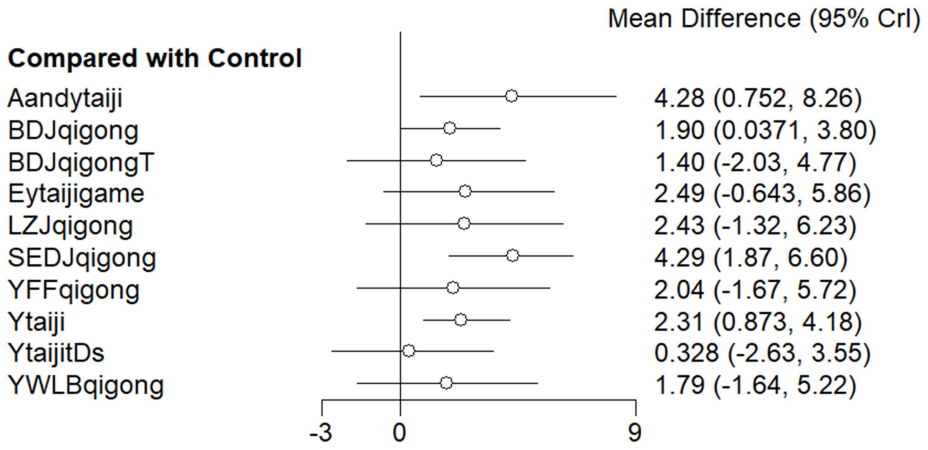

FIGURE 4
Comparison of MOCA subgroups intervention and control groups (Forest Plot). 1: Baduanjin Qigong + tDCS (BDJqigongandT); 2: Baduanjin Qigong (BDJqigong); 3: Liuzijue Qigong (LZJqigong); 4: Twelve Duanjin Qigong (SEDJqigong); 5: Yifei Fang Qigong (YFFqigong); 6: Yijinjing Qigong + Wuqinxi Qigong + Liuzijue Qigong + Baduanjin Qigong (YWLBqigong); 7: Yang-style Tai Ji game (EYtaijigame); 8: Yang-style Tai Ji (Ytaiji); 9: Acupuncture and Yang-style Tai Ji (AandYtaiji); 10: Yang-style Tai Ji combined with tDCS (YtaijitDcs). Method: The forest plot displays the mean differences between subgroup interventions and the control group, with 95% CrI. Results: Acupuncture with Yang-style Tai Ji (AandYtaiji) and Twelve Duanjin Qigong (SEDJqigong) showed significant improvements, while other interventions, such as Baduanjin Qigong, had smaller, non-significant effects.

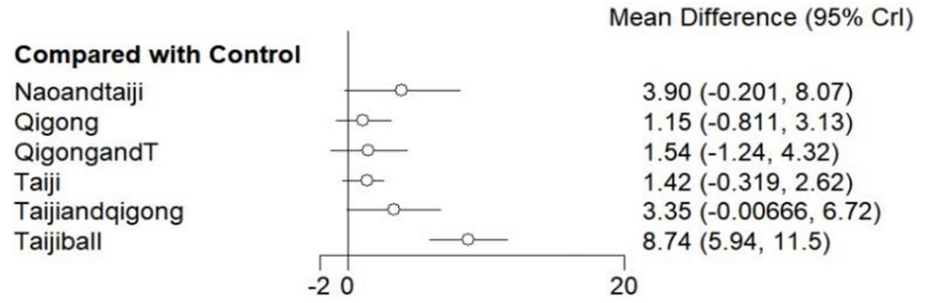

FIGURE 5
Comparison of MOCA subgroups intervention and control groups (Forest Plot). 1: Baduanjin Qigong + tDCS (BDJqigongandT); 2: Baduanjin Qigong (BDJqigong); 3: Liuzijue Qigong (LZJqigong); 4: Twelve Duanjin Qigong (SEDJqigong); 5: Yifei Fang Qigong (YFFqigong); 6: Yijinjing Qigong + Wuqinxi Qigong + Liuzijue Qigong + Baduanjin Qigong (YWLBqigong); 7: Yang-style Tai Ji game (EYtaijigame); 8: Yang-style Tai Ji (Ytaiji); 9: Acupuncture and Yang-style Tai Ji (AandYtaiji); 10: Yang-style Tai Ji combined with tDCS (YtaijitDcs). Method: The forest plot displays the mean differences between subgroup interventions and the control group, with 95% CrI. Results: Acupuncture with Yang-style Tai Ji (AandYtaiji) and Twelve Duanjin Qigong (SEDJqigong) showed significant improvements, while other interventions, such as Baduanjin Qigong, had smaller, non-significant effects.

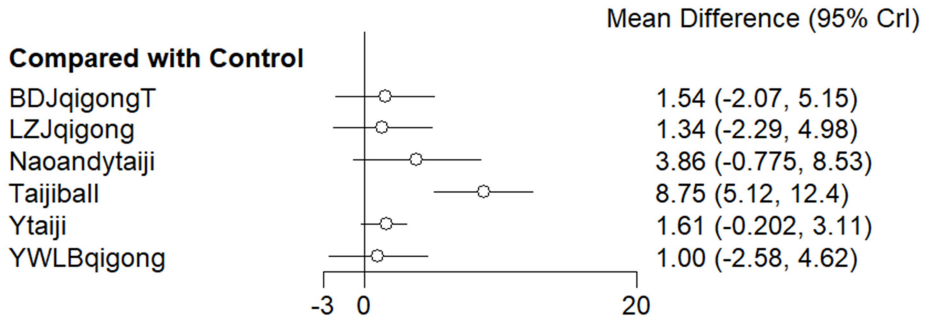

FIGURE 6
Comparison of MMSE subgroups intervention and control groups (Forest Plot). 1: Liuzijue Qigong (LZJqigong); 2: Nao Ling Tang and Yang-style Tai Ji (NaoanYtaiji); 3: Tai Ji and Qigong (combining Yang-style and Wu-style Tai Ji with Baduanjin, Wuqinxi, and Liuzijue Qigong); 4: Tai Ji soft ball exercise (Taijiball); 5: Yijinjing Qigong previous meta-analyses have limitations. Wuqinxi Qigong + Liuzijue Qigong + Baduanjin Qigong (YWLBqigong); 6: Yang-style Tai Ji (Ytaiji); 7: Baduanjin Qigong + tDCS (BDJQigongandT). Method: Mean difference analysis comparing various traditional exercises and a control group, with 95% CrI. Results: Tai Ji soft ball exercise (Taijiball) showed the greatest effect, while other interventions, such as Baduanjin Qigong with tDCS and Liuzijue Qigong, had smaller, non-significant effects.

Taiji [RR = 2.14, 95% CI (0.79, 3.72), $p < 0.05$], intervention time was correlated with MOCA index, the results were statistically significant, and the intervention time of other intervention measures had no significant correlation with MOCA index. From the MOCA subgroup analysis, the intervention time of Ytaiji [RR = 2.38, 95% CI (0.68, 4.48), $p < 0.05$] was related to the MOCA index, and the results were statistically significant. The intervention time of the rest of the interventions for the effects of MOCA indicators showed no significant correlation, and the results displayed no statistical significance. There was no significant correlation between the intervention time of different interventions and the MMSE indicators, and the results were not statistically significant (Table 2).

Publication bias

Publication bias was assessed for the two indexes. As shown in the figure, there is little possibility of bias in the data (Figure 7).

Discussion

Summary of the main findings

A meta-analysis of 24 studies involving 1808 patients, including 13 RCTs on traditional Chinese exercises alone or combined with other treatments, showed Aandytaiji ranked first for MOCA scores overall, followed closely by SEDJqigong, though the latter had a small sample size and potential risk of bias. Taijiball showed the most significant improvement in MMSE scores. The meta-regression results indicated longer durations of Qigong and Tai Chi interventions yielded better outcomes (Supplementary Table 6).

Interpretation of the results

First, this study confirms the efficacy of traditional Chinese exercises, alone or combined with other treatments, in treating cognitive impairment. The meta-analysis results are mixed. Lyu et al. (2021) found Tai Chi had no significant effect on cognitive

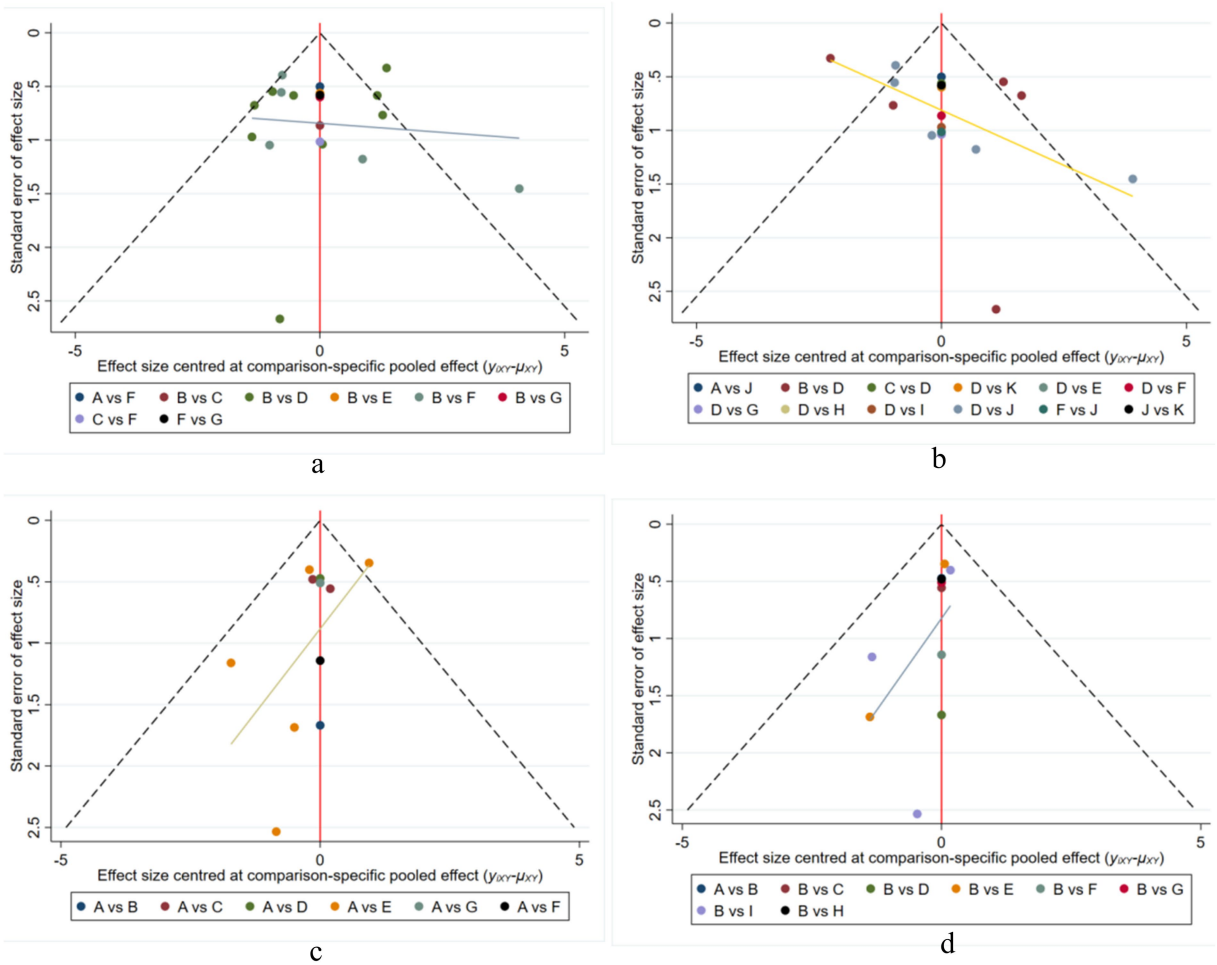

FIGURE 7
Funnel plots. **(a)** Funnel plot for MOCA indicators; **(b)** Funnel plot for MOCA subgroup indicators; **(c)** Funnel plot for MMSE indicators; **(d)** Funnel plot for MMSE subgroups. Method: Funnel plots display the effect sizes and standard errors of the included studies. Results: Some asymmetry was observed, indicating potential publication bias in certain comparisons.

dysfunction, while Zhou et al. (2022) reported significant improvements.

Secondly, several traditional Chinese exercises commonly used in research were not included in prior meta-analyses (Su et al., 2022; Zhou et al., 2022). This study is the first to examine the impact of traditional Chinese exercises, such as Tai Chi, on cognitive dysfunction within the context of a current meta-analysis. SEDJqigong (Jing et al., 2019; Hengjia et al., 2020), YFF qigong (Min and Xiaodan, 2023), and Taijiball (Yong et al., 2016) were among the interventions studied. Although SEDJqigong achieved the highest score in the MOCA subgroup analysis, its small sample size and potential risk of bias indicate that Aandytaiji remains the top-ranked intervention for MOCA overall. SEDJqigong, also known as Wenba Duan Jin (sitting Ba Duan Jin) (Lijiang, 2018), is a systemic exercise beneficial for both able-bodied individuals and those with lower limb disabilities (Lijiang, 2018; Tao, 2018). It involves cognitive functions such as memory, visuospatial ability, and executive ability and has a broader effect on cognitive function (Liu J. et al., 2024). In comparison, Aandytaiji enhances cognitive function and blood circulation, particularly in areas critical for cognition. Its combination of acupuncture and Tai Chi addresses ischemia, making it highly effective for early-stage dementia, further reinforcing its top ranking in the MOCA analysis (Romero-García et al., 2024; Subbarao et al., 2024). Taijiball ranked first in improving MMSE scores, and the limitations of previous meta-analyses were addressed in this analysis. In previous meta-analyses, Taijiball was not included as an intervention, limiting the assessment of traditional Chinese exercises on cognitive function, particularly MMSE scores. This study addresses that limitation by incorporating Taijiball, offering a more comprehensive perspective and explaining its strong performance in MMSE scores, providing new evidence of its contribution to cognitive function. Taijiball integrates soft, steady movements through the coordination of racket, ball, and body, providing a holistic workout (Wang et al., 2021). Continuous stimulation of acupuncture points on the hands during Taijiball practice activates the cerebral cortex, mitigating memory loss in the elderly. This supports Taijiball's brain health benefits from a TCM perspective (Sun et al., 2021).

Additionally, previous randomized controlled trials typically compared traditional Chinese exercises with comprehensive interventions. A few studies included these combined interventions in meta-analyses. This study found that combined interventions improved MOCA scores more effectively than traditional exercises alone, while traditional exercises alone were more effective in improving MMSE scores. For MOCA scores, the combined intervention of acupuncture and Tai Chi ranked first. Pang et al. (2022) found that the frontal and temporal lobes are crucial for cognitive function. Acupuncture at Baihui and Zhisan (Shentingxue and Benshen), combined with Tai Chi, improved blood supply to these lobes, addressing ischemia and hypoperfusion (Yang et al., 2021). Tai Chi, based on Yin-Yang theory, may delay cognitive decline in elderly individuals with MCI and improve cognitive function in early-stage dementia (Wei et al., 2022).

For MOCA indicators, Aandytaiji ranks the highest. For MMSE indicators, Taijiball is highly effective, though its limited inclusion in the literature may introduce bias. Further research is needed to assess its full impact.

Although Tai Chi was included in most studies, its SUCRA ranking was not the highest. Various forms of Qigong were employed in prior studies, but RCTs focused mainly on Yang's Tai Chi. There are many types of Tai Chi, each with unique characteristics. The limited number of studies on Chen's Tai Chi and other forms may explain the suboptimal outcomes. More research is needed to address this gap (Joshi et al., 2024).

These findings support the positive role of traditional Chinese exercises, alone or combined with other treatments, in treating cognitive impairment. Comparing specific exercises can positively impact clinical treatment strategies and reduce medication costs for cognitive impairment patients.

Discussion on heterogeneity

Variations in exercise protocols: This study examined different traditional Chinese exercises, such as Tai Chi, Qigong, and Taijiball, which differ significantly in practice. Tai Chi focuses on balance and gentle movements, while Qigong emphasizes breath regulation. These differences in duration, intensity, and frequency can lead to varying cognitive effects, increasing heterogeneity across studies (Cheng et al., 2024; Liu P. et al., 2024).

Participant characteristics: Participants vary by age, gender, and baseline cognitive impairment. Younger or healthier individuals may benefit more from interventions, while older adults or those with comorbidities like hypertension or diabetes may show weaker responses, contributing to variability in outcomes (Alford et al., 2024; Ibañez et al., 2024; Pramanik et al., 2024; Yin et al., 2024; Zhang L. et al., 2024).

Differences in study settings: Geographic and cultural factors also impact results. For example, participants in China may have higher adherence to Tai Chi due to cultural familiarity, while those in Western countries may be less engaged. Disparities in healthcare resources further affect intervention outcomes (Jimenez et al., 2024).

Study design and methodology: Variations in study design, including intervention duration, follow-up periods, and assessment methods, contribute to heterogeneity. Studies with shorter follow-ups may miss long-term effects, while longer studies may capture more significant cognitive changes (Wei et al., 2024; Ziccardi et al., 2024). Additionally, reliance on self-reported assessments versus clinical evaluations adds to variability.

Limitations

This study included 24 articles, but several limitations could affect the reliability of the results. First, allocation concealment is critical for preventing selection bias, and a lack of transparency in this regard may reduce internal validity (Sharpe et al., 2024). Additionally, blinding was uncertain in some studies, introducing potential performance and detection biases, which could lead to an overestimation of the treatment effects (Choy et al., 2024). Second, small sample sizes in two studies reduced statistical power, increasing the risk of random error and possibly exaggerating treatment effects. Publication bias is also a concern, as positive results are more likely to be published, while negative or null findings may be underreported (Zhang et al., 2013). These limitations, particularly small sample sizes, lack of blinding, and potential publication bias, could result in

overestimated effects and increased heterogeneity. Future research should focus on larger sample sizes, stricter blinding, and minimizing bias to improve the reliability and generalizability of the findings (Lin, 2018; Kulkarni et al., 2024; Tamrakar et al., 2024).

Clinical implications and future directions

The findings of this study align with previous research while offering new insights. Aandtaiji and Taijiball showed strong performance in both MOCA and MMSE scores, suggesting their potential to improve cognitive function by regulating central nervous system activity (You and Ogawa, 2020). These results support traditional Chinese exercises, alone or combined with medical interventions, as effective strategies for enhancing brain function through energy balance, increased oxygenation, and neural activation (Gharpure et al., 2024; He et al., 2024). These findings have important implications for clinical practice. Incorporating traditional Chinese exercises into treatment plans can reduce medication dependency and improve outcomes for patients with cognitive impairment. As a low-cost, easily implemented intervention, traditional Chinese exercises are particularly suitable for managing long-term cognitive decline. They offer great potential in resource-limited settings, helping to ease the financial burden on healthcare systems and families while providing sustained cognitive benefits (Flores-Sandoval et al., 2024; Laakso et al., 2024).

Conclusion

Research shows that traditional Chinese exercises, whether used alone or in combination with other treatments, can enhance cognitive abilities in patients with cognitive impairment. Combined treatments outperform traditional exercises alone in improving MOCA scores, whereas traditional exercises alone are more effective in enhancing MMSE scores. Additionally, longer practice durations of Tai Chi and Qigong lead to better results. Currently, despite the extensive research on Tai Chi as an intervention for cognitive impairment, the studies have primarily focused on a single form of Tai Chi, necessitating further in-depth research. This study is the first to include SEDJqigong and Taijiball, and more clinical trials are anticipated. These findings provide new evidence for the clinical treatment of cognitive impairment.

Data availability statement

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

Author contributions

JQ: Writing – original draft, Writing – review & editing. SK: Writing – original draft, Writing – review & editing.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2024.1475406/full#supplementary-material

SUPPLEMENTARY FIGURE 1
MOCA index intervention and control group network relationship graph. 1: Qigong; 2: Qigong and tDCS; 3: Exergaming-based Tai Ji (Etaijigame); 4: Tai Ji; 5: Acupuncture and Tai Ji (Aandtaiji); 6: Tai Ji combined with tDCS (TaijitDcs). Method: This network plot visualizes comparisons between interventions and the control group. Node size represents the sample size, and edge thickness reflects the number of studies. Results: The control group and Tai Ji had the most data, represented by larger nodes and thicker lines.

SUPPLEMENTARY FIGURE 2
MOCA subgroup intervention and control group network relationship graph. 1: Baduanjin Qigong + tDCS (BDJqigongandT); 2: Baduanjin Qigong (BDJqigong); 3: Liuzijue Qigong (LZJqigong); 4: Twelve Duanjin Qigong (SEDJqigong); 5: Yifei Fang Qigong (YFFqigong); 6: Yijinjing Qigong + Wuqinxi Qigong + Liuzijue Qigong + Baduanjin Qigong (YWLBqigong); 7: Yang-style Tai Ji game (EYtaijigame); 8: Yang-style Tai Ji (Ytaiji); 9: Acupuncture combined with Yang-style Tai Ji (AandYtaiji); 10: Yang-style Tai Ji combined with tDCS (YtaijitDcs). Method: A network plot displaying comparisons between subgroup interventions and the control group, with node size representing the sample size and edge thickness reflecting the number of comparisons. Results: Tai Ji and Qigong subgroups had the most comparisons with the control group.

SUPPLEMENTARY FIGURE 3
MMSE index intervention and control group network relationship graph. 1: Nao Ling Tang and Tai Ji (Naoantaiji); 2: Qigong and tDCS (QigongandT); 3: Exergaming-based Tai Ji (Etaijigame); 4: Tai Ji and Qigong (combining Yang-style and Wu-style Tai Ji with Baduanjin, Wuqinxi, and Liuzijue Qigong); 5: Tai Ji soft ball exercise (Taijiball). Method: Nodes represent interventions, and edges show direct comparisons between interventions and the control group. Results: The control group was most frequently compared with interventions such as Tai Ji and Qigong, indicated by larger nodes and thicker lines.

SUPPLEMENTARY FIGURE 4
MMSE subgroup intervention and control group network relationship graph. 1: Liuzijue Qigong (LZJqigong); 2: Nao Ling Tang and Yang-style Tai Ji (NaoanYtaiji); 3: Tai Ji and Qigong (combining Yang-style and Wu-style Tai Ji with Baduanjin, Wuqinxi, and Liuzijue Qigong); 4: Tai Ji soft ball exercise (Taijiball); 5: Yijinjing Qigong + Wuqinxi Qigong + Liuzijue Qigong + Baduanjin Qigong (YWLBqigong); 6: Yang-style Tai Ji (Ytaiji); 7: Baduanjin Qigong + tDCS (BDJQigongandT). Method: A network plot showing the relationship between various interventions and the control group. Results: The most frequent comparisons involved the control group and interventions such as Tai Ji and Qigong.

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Association between cardiometabolic index and biological aging in the US population: evidence from NHANES 2015–2020

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Purpose: It is crucial to identify biomarkers that influence the aging process and associated health risks, given the growing severity of the global population aging issue. The objectives of our research were to evaluate cardiac metabolic index (CMI) as a novel biomarker for identifying individuals at increased risk of accelerated biological aging and to assess its use in guiding preventive strategies for aging-related health risks.

Methods: The National Health and Nutrition Examination Survey (NHANES) provided cross-sectional data on participants with complete information on CMI, phenotypic age (PA), and other variables. Analyses of variance and weighted χ^2 tests were conducted to assess differences between groups. The relationship between CMI and biological aging was investigated using a weighted multivariate logistic regression model, restricted cubic spline (RCS) regression analysis, subgroup analysis, and interaction testing.

Results: A positive correlation between CMI and biological aging was observed in 6,272 participants. RCS regression analysis confirmed the non-linear relationship, identifying significant inflection point at 1.10. In the crude or adjusted models, the OR (95% CI), for the highest group versus the reference were 3.608 (3.108, 4.188), 3.397 (2.920, 3.952), and 1.550 (1.299, 1.850), respectively, when categorizing CMI into different groups. Subgroup analyses and interaction tests indicate that the association between CMI and biological aging remained consistent across different subgroups. Gender, race, education level, marital status, poverty income ratio (PIR), drinking status and diabetes had an interaction with CMI in relation to biological aging.

Conclusion: An elevated CMI is linked to increased risk for biological aging. This relationship may inform more effective prevention and treatment strategies for biological aging in the future. CMI be integrated into routine health screenings or aging assessments by healthcare professionals.

KEYWORDS

cardiometabolic index, biological aging, phenotypic age, NHANES, chronological age

1 Introduction

With one-fifth of the world's population predicted to be 65 or older by 2030, population aging is a global problem (Rudnicka et al., 2020). A steady decrease of physiological function is a hallmark of aging. It is believed to result from a build-up of molecular alterations or "hallmarks" that impair tissues' and organs' ability to function and recovery (Chakravarti et al., 2021; López-Otín et al., 2023). This, in turn, is thought to cause chronic morbidities, such as metabolic, cardiovascular, neoplastic, and neurodegenerative disorders, as well as geriatric symptoms like frailty and immobility (Abbasi et al., 2023; Wagner et al., 2023; Zhou et al., 2023; Iskusnykh et al., 2024; Montégut et al., 2024). An innate biological process that is adaptable and responsive to therapeutic interventions coexists with aging. Using of various genetic, nutritional, and pharmaceutical interventions, scientists have made impressive strides in the last few decades in extending the lifespan (Mkrtchyan et al., 2020; Sourada and Kuglík, 2020; Wang et al., 2022). Therefore, it is crucial to identify biomarkers that influence the aging process and associated health risks, given the growing severity of the global population aging issue. To uncover new insights into the management and delay of the aging process, this study intends to investigate possible associations between PA, a crucial marker of biological aging, and CMI.

PA is a crucial idea connected to biological aging (Liu et al., 2018; Kuo et al., 2021). Generally, chronological age (CA) and clinical biomarkers, and blood cell parameters are utilized to evaluate PA. Given that PA provides a more accurate representation of how the body ages than CA, studies have indicated that PA is a good predictor of death, chronic morbidities, and a decline in physical function (Kuo et al., 2022). Genetic predispositions and poor lifestyle choices, like heavy smoking, excessive alcohol use, chronic illnesses, and cancer, all contribute to an increased PA. On the other hand, living a healthy lifestyle that includes eating fruits and vegetables and engaging in moderate exercise might reduce PA (Noren Hooten et al., 2022; Li et al., 2024a; Wu et al., 2024).

CMI was introduced as a novel metric by Wakabayashi and Daimon (2015) to evaluate visceral obesity using blood lipid markers and the weight-to-height ratio (WHtR). WHtR, a measure of abdominal obesity that makes more sense than just measuring waist circumference (WC). It has been shown that WC or body mass index (BMI) as cardiovascular disease risk factors are less reliable discriminators than WHtR. Because BMI measurements do not distinguish between trunk and visceral obesity, whereas anatomical fat distribution is considered important because it produces different metabolic effects (Chen R. et al., 2022; Tao et al., 2024). However, CMI simultaneously takes into account triglyceride (TG) and high-density lipoprotein cholesterol (HDL-C), which are crucial indicators of cardiovascular risk and obesity (Liu C. et al., 2022; Baratta et al., 2023; Nussbaumerova and Rosolova, 2023). Survies indicate that the CMI is connected to cardiovascular illnesses, metabolic syndrome, and other conditions, implying the importance of it for linked disease screening (Lazzer et al., 2023; Miao et al., 2023; Sun et al., 2023; Ye et al., 2024). According to recent studies, people with high CMI may have more systemic inflammation (Carvalho et al., 2024; Xu B. et al., 2024). Conversely, regular exercise is linked to a large reduction in CMI (Xue et al., 2024). Moreover, elevated CMI is significantly correlated with insulin resistance (Feng et al., 2024; Song et al., 2024; Wu and Xu, 2024). However, physical activity, insulin resistance and inflammation are intimately associated with aging (Kurauti et al., 2021; Abbasi et al., 2023; Butt et al., 2024; Singh et al., 2024). Additionally, aging is significantly impacted by BMI (Etzel et al., 2022; Lundgren et al., 2022).

To our knowledge, no previous research has examined the relationship between biological aging and CMI. Thus, the objectives of our research were to assess the correlation between biological aging and CMI, to offer guidance on the prevention and management of aging.

2 Materials and methods

2.1 Data source

The database employed in this analysis, a longitudinal cohort study, was provided by the NHANES database, a nationally representative database that collects significant data on the health of the American public. By using a multistage, stratified random sampling approach, NHANES guarantees that a national sample is represented. A total of 34,785 participants' data were discovered after we screened and analyzed data from 2015 to 2020. The National Center for Health Statistics' Research Ethics Review Board thoroughly examined and approved the study involving human subjects, and each participant gave signed agreements indicating their informed consent.

2.2 Study participants

Using the following exclusion criteria, the analytical sample was reduced to 6,272 subjects: (1) individuals under the age of 20 years; (2) individuals lacking a complete CMI value; (3) individuals lacking a phenotypic age value; (4) individuals lacking records of necessary covariates, such as gender, age, race, education level, marital status, PIR, smoking, drinking, physical activity, BMI, the history of diabetes, hypertension, heart failure, stroke, and cancer. Figure 1 illustrates the inclusion and exclusion standards.

2.3 Assessment of CMI

As previously mentioned, anthropometric and biochemical data, such as height, WC, TG and HDL-C were used to compute CMI. The units used were milligrams per deciliter (mg/dl) for HDL-C and TG, and centimeters (cm) for height and WC. The CMI was calculated using the following formula (Liu et al., 2021):

$$\mathrm{CMI} = \frac{\mathrm{TG}}{\mathrm{HDL-C}} \times \frac{\mathrm{WC}}{\mathrm{height}}$$

For the purposes of our study, CMI was regarded as a continuous exposure variable, and all recruited participants were stratified into quartiles with cut-off values for subsequent analyses: Q1 group (CMI $\leq$ 0.59), Q2 group (0.60 $\leq$ CMI $\leq$ 1.06), Q3 group (1.07 $\leq$ CMI $\leq$ 1.92), and Q4 group (CMI $\geq$ 1.93).

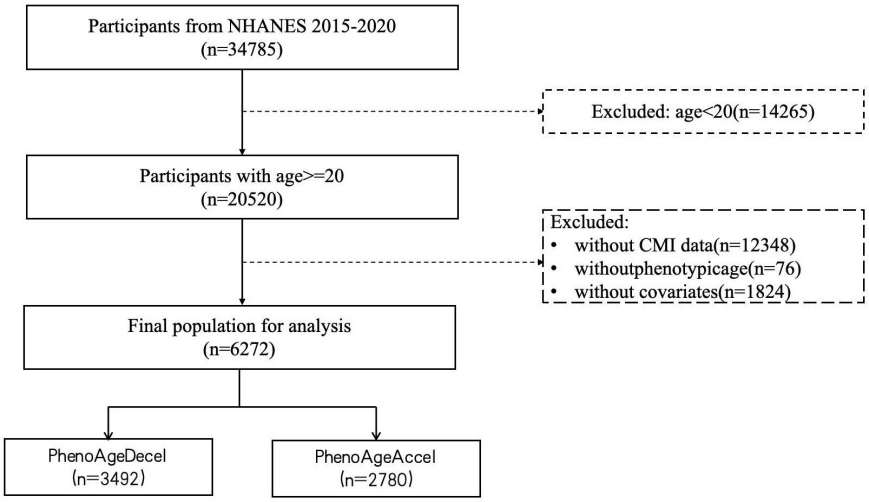

FIGURE 1
The flow chart of participant selection.

2.4 Assessment of PA

CA and nine biomarkers—albumin, creatinine, glucose, C-reactive protein (CRP), lymphocyte percentage, mean cell volume, erythrocyte distribution width, alkaline phosphatase, and white blood cell count—were used to calculate the PA. This is a metric for the expected age in a population that is correlated with the predicted risk of death for an individual. This indicator is widely used in the literature to identify risk factors for morbidity and mortality, to assess the effectiveness of treatments, and to elucidate the aging process (Levine et al., 2018; Chen L. et al., 2022). PA was determined using the formula (Liu W. et al., 2024):

$$\text{Phenotypic age} = 141.50 + \frac{\text{Ln}[-0.00553 \times \text{Ln}(\exp(\frac{-1.51714 \times \exp(\text{xb})}{0.0076927}))]}{0.09165}$$

$$\begin{aligned}\text{xb} = {} & -19.907 - 0.0336 \times \text{Albumin} + 0.0095 \times \text{Creatinine} \\ & + 0.1953 \times \text{Glucose} + 0.0954 \times \text{LnCRP} - 0.00120 \times \\ & \text{Lymphocyte Percent} + 0.0268 \times \text{Mean Cell Volume} \\ & + 0.3306 \times \text{Red Cell Distribution Width} + 0.00188 \\ & \times \text{Alkaline Phosphatase} + 0.0554 \times \text{White Blood Cell} \\ & \textit{Count} + 0.0804 \times \text{Chronological age}\end{aligned}$$

2.5 Assessment of biological aging

The residual of PA, which was corrected for CA using linear regression, was used to compute phenotypic accelerated age. Individuals classified as having phenotypic accelerated aging (PhenoAgeAccel) if their accelerated age was greater than 0, and as having phenotypic decelerated aging (PhenoAgeDecel) if their accelerated age was less than 015.

2.6 Assessment of covariates

The current study collected critical demographic data, such as age, gender, race (Mexican American, non-Hispanic white, non-Hispanic black, other races), education (below high school, high school or equivalent, high school above), marital status (married or living with a partner, living alone), PIR [PIR: $<$ 1.3 (low), 1.3 $\leq$ to $\leq$ 3.5 (medium), $>$ 3.5 (high)], BMI [BMI: $<$ 25 (normal), 25 $\leq$ to $\leq$ 30 (overweight), $>$ 30 (obesity)], smoking status was split into three categories: former smokers (those who had smoked at least 100 cigarettes in their lifetime and were currently giving up smoking); never smokers (those who had less than 100 cigarettes in their lifetime); and current smokers (those who had at least 100 cigarettes in their lifetime and were currently smoking), fewer than 12 alcohol-based drinks in the previous year (yes, no), physical activity was split into two categories: activity partners (those who had a minimum of 150 min per week of moderate-intensity or 75 min per week of vigorous-intensity physical activity), while others were classified as inactivity partners, the history of hypertension, diabetes, stroke, heart failure, cancer also were extracted from the database (Liu H. et al., 2022; Liu H. et al., 2024).

2.7 Statistical analysis

R software (version 4.2.2) was used for all statistical studies. Sampling weights were utilized in all analyses to interpret the complex NHANES survey design, in accordance with the NHANES analytical standards. Mean $\pm$ standard deviation (SD) was used to express continuous variables. Frequencies and percentages were used to express the data for categorical variables. For categorical variables, a χ^2 test was performed to compare the baseline characteristics between groups, whereas analysis of variance was employed for continuous data. The relationship between biological aging and CMI level was examined using multivariable logistic regression models. OR (Odds Ratio) values and 95% confidence

interval (95% CI) were obtained from logistic regression models, which were calculated to measure the strength of association between each independent variable and the outcome. Age, gender, ethnicity, PIR, education level, marital status, BMI, smoking, alcohol status, and history of hypertension, diabetes, heart failure, stroke, and cancer were all taken into account while adjusting the multivariable logistic regression models. Three criteria were used to choose confounding variables: clinical relevance, a *P*-value in univariate analysis of less than 0.05, and the availability of enough event data to build a strong regression model. To address concerns about over-adjustment for models, we conducted sensitivity analyses to assess the robustness of Model II and examined the consistency of our main findings across different model specifications. This approach confirmed that the addition of these covariates did not significantly impact the stability or interpretability of the key associations, supporting the robustness of Model II. The nonlinear correlations between CMI and biological aging (4 nodes, with the 25th percentile serving as a reference point) were evaluated using the RCS approach. For all analyses, a significance threshold < 0.05 was considered statistically significant.

3 Results

3.1 Baseline characteristics

In total, 6,272 participants were taken into account for this investigation. The CA was 50.28 ± 17.22 years, PA was 50.84 ± 20.03 years, and 50.4% of the individuals were male. PhenoAgeDecel and PhenoAgeAccel participants showed different characteristics. Overall, older participants, males, non-Hispanic Black individuals, lower education levels, living alone, lower PIR, higher BMI, higher likelihood of smoking, greater probability of not drinking, more likely to have hypertension, diabetes, heart failure, stroke, or cancer, and those with higher CMI levels were more likely to experience PhenoAgeAccel ($p < 0.05$). The baseline features of participants were summarized in Table 1.

3.2 Association of CMI levels and biological aging

The relationship between CMI level and biological aging was examined using weighted multivariable logistic regression models. The participants were categorized into quartiles of CMI for stratification purposes. The OR (95% CIs) for the highest group versus the reference (the lowest group) were 3.608 (3.108, 4.188), 3.397 (2.920, 3.952), and 1.550 (1.299, 1.850) for the unadjusted model, model I (adjusting for gender, year), and model II (adjusting for gender, age, race, education level, marital status, PIR, smoke, alcohol, physical activity, BMI, diagnosis of hypertension, diabetes, heart failure, stroke, and cancer), respectively, when categorizing CMI into different groups. Both the unadjusted and adjusted models showed a significant rise in the incidence of biological aging as the CMI increased. *P*-values for the trend were $P < 0.001$ (Table 2). Furthermore, we examined the dose response connection between the CMI and biological aging using limited Cubic Splines. The associations between CMI and biological aging with inflection points at 1.10 was discovered after multivariable adjustment. *P*-values for non-linear were $P < 0.001$ (Figure 2).

3.3 Stratified analyses

The following variables were analyzed using stratified analyses: gender, age, race, education level, marital status, PIR, smoking, drinking status, physical activity, BMI, and diagnoses of hypertension, diabetes, heart failure, stroke and cancer. As shown in Table 3, except for those with borderline diabetes and heart failure, a higher CMI level was linked to an increased risk of biological aging in most subgroups. Notably, gender, race, education level, marital status, PIR, drinking status and diabetes had an interaction with CMI in relation to biological aging. The correlation between CMI and biological aging was more significant in female (OR: 1.51; 95% CI: 1.41–1.62), other race (OR: 1.51; 95% CI: 1.39–1.64), high education (OR: 1.39; 95% CI: 1.31–1.47), living alone (OR: 1.41; 95% CI: 1.32–1.52), high PIR (OR: 1.37; 95% CI: 1.28–1.48), non-drinkers (OR: 1.40; 95% CI: 1.31–1.50), and diabetes groups (OR: 1.53; 95% CI: 1.34–1.76).

4 Discussion

According to our research, there is a positive correlation between biological aging and CMI. Furthermore, the link persisted even after controlling for other variables, suggesting that CMI was a detrimental element in the biological aging process. A non-linear relationship was identified through dose-response analysis. The inflection points was 1.10 according to threshold effect analysis. This finding can inform more accurate and effective prevention and treatment strategies for biological aging.

CMI is a novel anthropometric measure that shows a strong relationship to metabolic syndrome (Wakabayashi, 2022; Tamini et al., 2024). Numerous studies have shown that CMI is associated with various systemic diseases, highlighting its correlation with worse prognoses. Our results were in alignment with the previous research, which has demonstrated a positive association between biological aging and CMI. Metabolic syndrome is known as a group of risk factors for diabetes and cardiovascular diseases with a pathophysiology closely related to aging (Roddy, 2021; Li et al., 2024b; Oya et al., 2024). Nevertheless, no previous research has examined the relationships between CMI and biological aging. Numerous other anthropometric and metabolic markers, including BMI, triglyceride glucose (TyG) index, WHtR, and visceral adiposity index (VAI), have all been shown to be positively correlated with biological aging. According to a meta-analysis, the epigenetic age of the heavier twins in a BMI-discordant monozygotic twin pair (ΔBMI > 3 kg/m^2) was 5.2 months older than that of their lighter cotwin (Lundgren et al., 2022). A higher BMI z-score was substantially linked to a faster speed of aging as measured by DunedinPoAm ($b = 0.0017$ adjusting for all covariates). In the relationship between obesity and aging has grown as higher BMI across the lifespan has been linked to early onset of age-related illnesses and mortality (Etzel et al., 2022). In middle-aged and older populations, Qiu et al. (2024)

TABLE 1 Baseline characteristics of the study participants.

	Total (n = 6,272)	PhenoAge deceleration (n = 3,492)	PhenoAge acceleration (n = 2,780)	P-value
Chronological age, mean ± SD	50.28 ± 17.22	48.70 ± 17.01	52.26 ± 17.29	< 0.001
Phenotypic age, mean ± SD	50.84 ± 20.03	44.04 ± 17.32	59.39 ± 19.93	< 0.001
Gender, *n* (%)				< 0.001
Male	3,162 (50.4)	1,662 (47.6)	1,500 (54.0)	
Female	3,110 (49.6)	1,830 (52.4)	1,280 (46.0)	
Race, *n* (%)				< 0.001
Mexican American	886 (14.1)	520 (14.9)	366 (13.2)	
No-Hispanic White	2,335 (37.2)	1,336 (38.3)	999 (35.9)	
No-Hispanic Black	1,409 (22.5)	582 (16.7)	827 (29.7)	
Other Race/Ethnicity	1,642 (26.2)	1,054 (30.1)	588 (21.2)	
Education level, *n* (%)				< 0.001
Less than high school	1,131 (18.0)	583 (16.7)	548 (19.7)	
High school grade or equivalent	1,477 (23.5)	721 (20.6)	756 (27.2)	
College or above	3,664 (58.5)	2,188 (62.7)	1,476 (53.1)	
Marital status, *n* (%)				< 0.001
Married or living with a partner	3,769 (60.1)	2,186 (62.6)	1,583 (56.9)	
Living alone	2,503 (39.9)	1,306 (37.4)	1,197 (43.1)	
PIR, *n* (%)				< 0.001
Low	1,721 (27.4)	832 (23.8)	889 (32.0)	
Medium	2,558 (40.8)	1,351 (38.7)	1,207 (43.4)	
High	1,993 (31.8)	1,309 (37.5)	684 (24.6)	
Smoker status, *n* (%)				< 0.001
Former	2,018 (32.2)	1,040 (29.8)	978 (35.2)	
Never	3,358 (53.5)	2,109 (60.4)	1,249 (44.9)	
Current	896 (14.3)	343 (9.8)	553 (19.9)	
Alcohol status, *n* (%)				< 0.001
Non-drinkers	2,745 (43.8)	1,409 (40.3)	1,336 (48.1)	
Drinkers	3,527 (56.2)	2,083 (59.7)	1,444 (51.9)	
Physical activity, *n* (%)				< 0.001
Inactivity	3,310 (52.8)	1,753 (50.2)	1,557 (56.0)	
Activity	2,962 (47.2)	1,739 (49.8)	1,223 (44.0)	
BMI, *n* (%)				< 0.001
Normal	1,628 (26.0)	1,213 (34.7)	415 (14.9)	
Overweight	1,997 (31.8)	1,263 (36.2)	734 (26.4)	
Obese	2,647 (42.2)	1,016 (29.1)	1,631 (58.7)	
Hypertension, *n* (%)				< 0.001
No	3,926 (62.6)	2,494 (71.4)	1,432 (51.5)	
Yes	2,346 (37.4)	998 (28.6)	1,348 (48.5)	
Diabetes, *n* (%)				< 0.001
No	5,117 (81.6)	3,180 (91.1)	1,937 (69.7)	
Borderline	168 (2.7)	71 (2.0)	97 (3.5)	
Yes	987 (15.7)	241 (6.9)	746 (26.8)	

(Continued)

TABLE 1 (Continued)

	Total (n = 6,272)	PhenoAge deceleration (n = 3,492)	PhenoAge acceleration (n = 2,780)	P-value
Heart failure, *n* (%)				< 0.001
No	6,046 (96.4)	3,442 (98.6)	2,604 (93.7)	
Yes	226 (3.6)	50 (1.4)	176 (6.3)	
Stroke, *n* (%)				< 0.001
No	6,002 (95.7)	3,400 (97.4)	2,602 (93.6)	
Yes	270 (4.3)	92 (2.6)	178 (6.4)	
Cancer, *n* (%)				0.002
No	5,642 (90.0)	3,178 (91.0)	2,464 (88.6)	
Yes	630 (10.0)	314 (9.0)	316 (11.4)	
CMI, mean ± SD	1.56 ± 1.91	1.27 ± 1.33	1.93 ± 2.39	< 0.001

PIR, poverty income ratio; BMI, body mass index; CMI, cardiometabolic index.

TABLE 2 Association between CMI and PhenoAgeAccel in multiple logistic regression analyses model.

CMI categorical	Crude model		Model I		Model II	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Q1 (≤ 0.59)	Ref		Ref		Ref	
Q2 (0.60–1.06)	1.804 (1.554, 2.094)	< 0.001	1.736 (1.493, 2.018)	< 0.001	1.197 (1.014, 1.413)	0.034
Q3 (1.07–1.92)	2.601 (2.243, 3.017)	< 0.001	2.480 (2.135, 2.880)	< 0.001	1.359 (1.145, 1.612)	< 0.001
Q4 (≥ 1.93)	3.608 (3.108, 4.188)	< 0.001	3.397 (2.920, 3.952)	< 0.001	1.550 (1.299, 1.850)	< 0.001
P for trend	< 0.001		< 0.001		< 0.001	

CMI, cardiometabolic index; OR, odds ratio; CI, confidence interval; Ref, reference; Crude model adjust for: None; Model I adjust for: Gender; Age; Model II adjust for: Gender; Age; Race; Education level; Marital status; Poverty income ratio; Smoke; Alcohol; Physical activity; Body mass index; Hypertension; Diabetes; Heart failure; Stroke; Cancer.

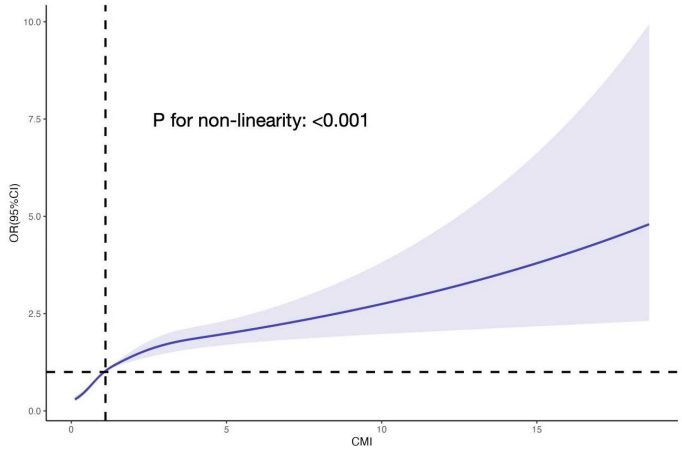

FIGURE 2
The RCS curve of the association between CMI and PhenoAgeAccel odds ratio among all the study participants. The associations between CMI and biological aging with inflection point at 1.10 was discovered after multivariable adjustment. P-values for non-linear were $P < 0.001$. RCS, restricted cubic spline; CMI, cardiometabolic index; OR, odds ratio.

clarified a non-linear connection between the TyG index and the α-Klotho protein (the serum anti-aging protein). When the TyG indices were less than 9.7, no discernible association was seen. Nonetheless, for every unit rise in TyG index over 9.738 there was a corresponding increase in klotho levels of 106.44 pg/ml (Qiu et al., 2024). Additionally, every 0.1 unit rise in WHtR was inversely correlated with the Successful Aging Index (SAI), lowering SAI by nearly 0.5 units (Koloverou et al., 2020). Every additional unit increase in VAI was correlated with a 0.312-year increase in PhenoAgeAccel. Among cancer patients, this positive correlation was more statistically significant. Furthermore, a segmented correlation was observed between VAI and PhenoAgeAccel, with a turning point identified at 10.543 (Xu C. et al., 2024). Additionally, a saturation effect was demonstrated

TABLE 3 Subgroup analysis by CMI.

Subgroup	No. of PhenoAge acceleration	OR (95% CI)	*P*-value	*P* for interaction
Gender				< 0.001
Male	1,500	1.22 (1.16, 1.28)	< 0.001	
Female	1,280	1.51 (1.41, 1.62)	< 0.001	
Age, year				0.266
≤ 40	790	1.36 (1.27, 1.46)	< 0.001	
> 40	1,990	1.29 (1.23, 1.36)	< 0.001	
Race				0.0283
Mexican American	366	1.19 (1.11, 1.30)	< 0.001	
No-Hispanic White	999	1.47 (1.37, 1.58)	< 0.001	
No-Hispanic Black	827	1.46 (1.28, 1.68)	< 0.001	
Other	588	1.51 (1.39, 1.64)	< 0.001	
Education level				< 0.001
Less than high school	548	1.19 (1.10, 1.28)	< 0.001	
High school grade or equivalent	756	1.30 (1.19, 1.42)	< 0.001	
College or above	1,476	1.39 (1.31, 1.47)	< 0.001	
Marital status				0.0426
Married or living with a partner	1,583	1.29 (1.23, 1.36)	< 0.001	
Living alone	1,197	1.41 (1.32, 1.52)	< 0.001	
PIR				0.0101
Low	889	1.21 (1.13, 1.30)	< 0.001	
Medium	1,207	1.35 (1.27, 1.44)	< 0.001	
High	684	1.37 (1.28, 1.48)	< 0.001	
Smoker status				0.624
Former	978	1.31 (1.23, 1.40)	< 0.001	
Never	1,249	1.31 (1.24, 1.39)	< 0.001	
Current	553	1.30 (1.16, 1.47)	< 0.001	
Alcohol status				0.0165
Drinkers	1,444	1.27 (1.21, 1.33)	< 0.001	
Non-drinkers	1,336	1.40 (1.31, 1.50)	< 0.001	
Physical activity				0.127
Inactivity	1,557	1.28 (1.22, 1.35)	< 0.001	
activity	1,223	1.36 (1.29, 1.45)	< 0.001	
BMI				0.655
Normal	415	1.33 (1.16, 1.52)	< 0.001	
Overweight	734	1.17 (1.09, 1.25)	< 0.001	
Obese	1,631	1.14 (1.08, 1.20)	< 0.001	
Hypertension				0.191
Yes	1,348	1.34 (1.25, 1.44)	< 0.001	
No	1,432	1.27 (1.21, 1.33)	< 0.001	
Diabetes				< 0.001
Yes	746	1.53 (1.34, 1.76)	< 0.001	
No	1,937	1.22 (1.17, 1.27)	< 0.001	

(Continued)

TABLE 3 (Continued)

Subgroup	No. of PhenoAge acceleration	OR (95% CI)	*P*-value	*P* for interaction
Borderline	97	1.36 (0.998, 1.93)	0.0639	
Heart failure				0.105
Yes	176	1.12 (0.934, 1.39)	0.267	
No	2,604	1.32 (1.27, 1.38)	< 0.001	
Stroke				0.445
Yes	178	1.45 (1.16, 1.89)	0.00245	
No	2,602	1.32 (1.27, 1.38)	< 0.001	
Cancer				0.253
Yes	316	1.42 (1.25, 1.64)	< 0.001	
No	2,464	1.31 (1.26, 1.37)	< 0.001	

PIR, poverty income ratio; BMI, body mass index; CMI, cardiometabolic index.

by a nonlinear association between the serum anti-aging protein klotho concentrations and the VAI score. It showed no discernible link when VAI was larger than 3.21, but they were negatively connected when VAI was less than 3.21 (Cui et al., 2023). In the current study, we introduced CMI as a novel predictor of biological aging. To date, this is the first study to evaluate the prognostic value of CMI as a metabolism-related index that is easy to obtain in the context of biological aging. However, additional research is necessary to validate the use of CMI in public health assessments of various specialized populations.

Although CMI is highly related to biological aging as elucidated by our study, the underlying biological mechanisms driving these associations are not fully deciphered. Chronic inflammation and reactive oxygen species (ROS) are thought to be significant factors in the progression of biological aging, which may explain the positive association between CMI and biological aging. The activation of the cyclic GMP-AMP synthase (cGAS)/stimulator of interferon genes (STING) pathway by mitochondria-derived cytosolic DNA (mt-DNA) has been found to produce inflammation factors. Previous studies highlight the crucial role that cytosolic mtDNA-induced cGAS-STING activation plays in the pathophysiology of obesity (Elzinga et al., 2023; Kim et al., 2023; Ma et al., 2023). Microglias exhibit cGAS activity in response to cytosolic DNA released from disrupted mitochondria, indicating a method by which cGAS-STING signaling is activated in the aging brain. Single-nucleus RNA-sequencing analysis of microglia in a cGAS gain-of-function mouse model demonstrates that engagement of cGAS in microglia is sufficient to direct aging-associated transcriptional states leading to bystander cell inflammation (Paul et al., 2021; Gulen et al., 2023; Jiménez-Loygorri et al., 2024). Furthermore, the positive energy balance typical of obesity worsens the excess deposition of ectopic fat with aging. Increased inflammatory cell infiltration and altered chemokine expression, including increased TNF-α and IL-6, are seen in visceral adipose tissue (Colleluori and Villareal, 2021). The increased adipose tissue inflammation with obesity and aging establishes the typical low-grade chronic inflammation observed in older adults (Villareal, 2023). These demonstrate the role of the inflammation in the aging and obesity. ROS as a physiologically significant cause of ribotoxic stress response activation and translational abnormalities (Lennicke and Cochemé, 2021). A significant fraction of the metabolic stress signals responsible for undesirable metabolic maladaptation in obesity and aging stem from damaged ribosomes (Shields et al., 2021; Hajam et al., 2022). ROS-induced ribosome impairment underlies ZAKα-mediated metabolic decline in obesity and aging (Snieckute et al., 2023). Excess calories raise the production of ROS, which harms the mitochondria, endoplasmic reticulum, and nucleus. ROS-induced DNA damage upregulates the cell cycle arrest-related proteins p16 and p21, which causes chromatin rearrangement, cellular senescence, and the release of proinflammatory mediators (Tam et al., 2020). As mentioned, the persistence of DNA damage is a common biological process linking aging and obesity. It is hypothesized that excess leptin synthesis, inflammation, and ROS cause adipose tissue to accumulate DNA damage, which then accumulates mutations in DNA repair genes. Senescence is further induced by the inadequate ability of DNA repair proteins to repair damaged DNA. Therefore, obesity speeds up the aging process by adding to the damage to DNA that comes with aging (Kasper et al., 2022; Kudabayeva et al., 2022; Chowdhury et al., 2023). More investigation is necessary because the precise molecular pathways are not fully understood.

There are various useful implications for this study. It has been discovered that a higher CMI significantly speeds up biological aging. Because the NHANES dataset, on which this study was based, used a fully random sampling procedure, our findings are guaranteed to be representative of the total population. People with high CMI may require additional interventions, such as nutrition, physical activity, and potentially medication-assisted dyslipidemia treatment, to slow down the aging process.

5 Study limitations

Firstly, despite adjusting for several confounders, unmeasured or residual confounding cannot be fully excluded. Secondly, treatment factors such oral antidiabetic drugs that could affect CMI were not taken into account. Thirdly, it should be mentioned that participant questionnaires were used to diagnose the study's cases of

hypertension, diabetes, heart failure, cancer, and stroke. This could introduce recollection bias and compromise the study's ability to make accurate diagnoses. Finally, a number of blood biomarkers were used to determine PA. However, these biomarkers may not correctly reflect other measures of biological aging, such as DNA methylation, telomere length.

6 Conclusion

After adjusting for potential confounders, our research demonstrated a positive correlation between CMI and biological aging. CMI be integrated into routine health screenings or aging assessments by healthcare professionals. Further cohort studies or randomized controlled trials are desperately needed to validate this result to provide more effective prevention and treatment strategies for biological aging in the future.

Data availability statement

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

Ethics statement

The studies involving humans were approved by the National Center for Health Statistics' Research Ethics Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

MS: Conceptualization, Data curation, Formal analysis, Investigation, Writing – original draft. SB: Supervision, Validation, Writing – review and editing.

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Conflict of interest

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

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Threshold effects of sleep duration and cognitive function in older adults with BMI ≥ 25 kg/m²

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Background: It has been demonstrated that older adults' cognitive capacities can be improved with sleep duration. However, the relationship between overweight, obesity, and cognitive decline remains a subject of debate. The impact of sleep duration on cognitive performance in seniors with a body mass index (BMI) ≥ 25 kg/m² is largely unknown. This makes it an intriguing subject to explore further.

Methods: This study used data from the National Health and Nutrition Examination Survey (NHANES) (2011–2014) with 2,243 participants. Weighted multivariate linear regression and smooth curve fitting were employed to investigate linear and non-linear relationships. A two-part linear regression model was used to determine the threshold effects. Additionally, subgroup analysis and interaction tests were conducted.

Results: Results showed that a negative association was found between sleep duration and scores in the fully adjusted model in the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) test, the Animal Fluency test (AFT), and the Digit Symbol Substitution test (DSST). A two-piecewise linear regression model was then applied to explore the threshold effect of sleep duration on cognitive performance. When sleep duration was less than 5 and 6 h per day, sleep duration was positively correlated with CERAD test scores [ß (95% CI): 2.11 (1.17, 3.05), $p < 0.0001$], AFT scores [β (95% CI): 0.25 (−0.17, 0.67), $p = 0.2376$], and DSST scores [ß (95% CI): 0.49 (−0.57, 1.56), $p = 0.3654$]. However, there was a threshold effect where sleep duration reached the three inflection points.

Conclusion: In overweight and obese older adults, there is a clear inverted U-shaped relationship between sleep duration and cognitive function, with consistent results across different subgroups. Sleep durations of around 5–6 h may help prevent cognitive decline in older adults with a BMI ≥ 25 kg/m².

KEYWORDS

cognitive function, overweight and obesity, sleep duration, threshold effects, NHANES

1 Introduction

We are living in an aging world, where a substantial number of people are likely to experience age-related cognitive decline, now one of the leading causes of disability worldwide (Alzheimer's disease facts and figures, 2015; Prince et al., 2015). Globally, dementia currently impacts over 50 million individuals, with projections indicating a threefold increase in prevalence by 2050, primarily driven by an aging population (Nichols et al., 2022). In general, cognitive decline is a significant public health concern that can result in dementia or mild

cognitive impairment (Alzheimer's disease facts and figures, 2024; Tolar et al., 2020).

According to earlier research, obesity and being overweight contribute to midlife cognitive decline and dementia, which accounts for one-third of all dementia cases globally (Pedditzi et al., 2016). Some studies have found that obesity and being overweight have been connected to alterations in volumetric cortical and subcortical function (Beyer et al., 2019). These modifications are linked to decreased cognitive function and adjustments to the white matter microstructure (Samara et al., 2019). Working memory (Alarcón et al., 2016), verbal memory, processing speed, fluid intelligence (Spyridaki et al., 2014), and executive function are among the cognitive domains that are impacted (Morys et al., 2021). However, recent studies suggest that being overweight and obese may be beneficial for older adults in late life (Norton et al., 2014). An increasing number of meta-analyses support the concept of the "obesity paradox" (Kim et al., 2020; Talaei et al., 2020), suggesting that obesity and being overweight may have a protective effect against cognitive decline in middle-aged and older adults (Pedditzi et al., 2016). Therefore, the impact of obesity and being overweight on the risk of cognitive impairment or dementia remains a subject of debate (Gustafson, 2015).

Over the past few decades, the prevalence of obesity has risen significantly (Global BMIMC et al., 2016; Lu et al., 2014; Ngandu et al., 2015). Sleep deprivation and narcolepsy have become increasingly prevalent in older adults (Cheng et al., 2021). Sleep deprivation exerts substantial effects on both brain structure and function (Cheng et al., 2021). Numerous studies have demonstrated that poor sleep is associated with an increased risk of dementia (He et al., 2024; Liu et al., 2016; Lee et al., 2024). However, a study from China found that sleep duration has an inverted U-shaped relationship with cognitive scores, with both short and long sleep durations associated with lower cognitive scores (Li et al., 2022). Moreover, regarding nighttime sleep duration, an optimal range of approximately 7–8 h has been associated with a reduced risk of cognitive impairment. Both insufficient and excessive nighttime sleep significantly increases the risk of cognitive decline (Xu et al., 2020).

Limited research has investigated the association between sleep duration and cognitive function in overweight and obese older adults. This cross-sectional study aims to explore the relationship between sleep duration and cognitive function in older adults who are overweight or obese. Using threshold effect analysis, it identifies the optimal nighttime sleep duration for achieving peak cognitive function in this population, intending to provide lifestyle recommendations for dementia prevention among older adults who are overweight or obese in the United States.

2 Materials and methods

2.1 Study population

This cross-sectional study utilized data from NHANES, a national survey conducted by the National Center for Health Statistics (NCHS) to assess Americans' health and nutritional conditions. NHANES employed a sophisticated, multistage probability sampling design to obtain a nationally representative sample of the non-institutionalized US population. Participants provided information about demographics, socioeconomic status, and health status through a household interview, whereas mobile examination centers (MECs) handled laboratory and physical assessments.

The NCHS Research Ethics Review Board authorized all NHANES study methods, and all participants provided informed consent. Detailed information about the study design and data can be obtained at www.cdc.gov/nchs/NHANES/.

The study population was recruited from NHANES 2011–2014, and all participants with complete CERAD test, AFT, DSST, BMI, and sleep duration data were included in this study. According to the World Health Organization (WHO), overweight is defined as a BMI between 25 and 29.9 kg/m^2, and obesity is defined as a BMI of 30 kg/m^2 or higher. Therefore, in this study, we defined overweight and obesity in the study population as a BMI ≥ 25 kg/m^2. The World Health Organization also classifies those 60 years of age and older as older adults (Beard et al., 2016). Consequently, individuals aged 60 and above were classified as older adults in our research. A total of 19,931 participants were enrolled. After excluding participants with age < 60 years (n = 16,299), missing cognitive assessment (n = 484), BMI (n = 61), and sleep duration (n = 7) data, and excluding BMI < 25 kg/m^2 (n = 837), a final total of 2,243 eligible participants were enrolled in this study (Figure 1).

2.2 Explanatory variable: sleep duration

Participants' sleep duration was assessed with the question, "How much sleep (do you/does SP) usually get at night on weekdays or workdays?" Sleep duration ranged from 2 to 11 h, and if participants reported more than 12 h, it was recorded as 12 h, representing total nighttime sleep. Nighttime sleep plays a vital role in brain neurorepair, memory consolidation, metabolic waste

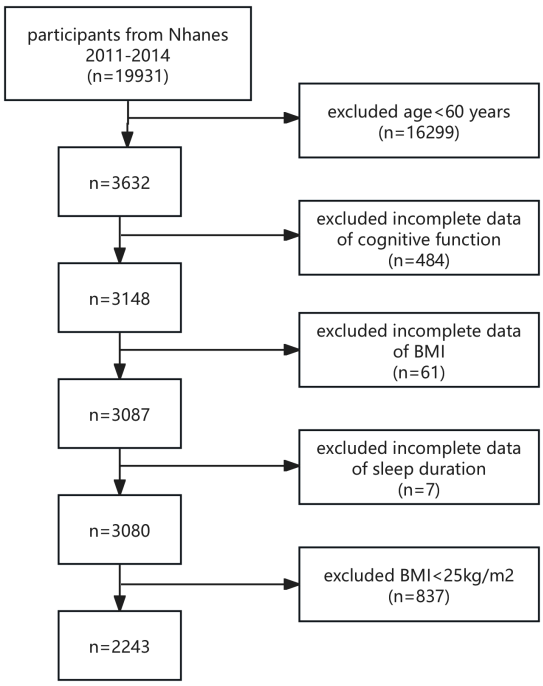

FIGURE 1
Flowchart of the sample selection from NHANES 2011–2014.

clearance, and cognitive function maintenance. This includes synchronization with the circadian rhythm, which regulates different sleep stages like slow-wave and rapid-eye-movement sleep, crucial for brain health. Nighttime sleep also supports cognitive functions by influencing neurotransmitter balance (e.g., dopamine, norepinephrine) and hormones (e.g., growth hormone, cortisol). Furthermore, it minimizes external disruptions, ensuring higher sleep quality (Bubbico et al., 2019; You et al., 2019; Gabelle et al., 2017). In this study, sleep duration was considered a continuous variable.

2.3 Outcome variable: cognitive function

The CERAD test evaluates immediate and delayed recall of newly learned verbal information (Fillenbaum et al., 2008). The CERAD test comprises three consecutive learning trials followed by a delayed recall. Participants are asked to read aloud a list of 10 unrelated words in each learning trial. Afterward, they immediately recall as many words as possible. The delayed recall occurs approximately 10 min after the learning trials. Each trial has a maximum score of 10 points, with a total possible score of 40 points, combining the results of the three learning trials and the delayed recall.

The AFT assesses verbal category fluency, which is a measure of executive function, along with other cognitive abilities such as semantic memory and processing speed (Clark et al., 2009). In this task, participants are required to generate as many animal names as possible within a one-minute timeframe, with one point awarded for each correct response.

The DSST is a comprehensive assessment of cognitive functioning involving processing speed, visual scanning, sustained attention, and short-term memory (Casagrande et al., 2021). The test is administered on paper, with a key at the top showing nine numbers paired with unique symbols. Participants are given 2 min to match and copy the corresponding symbols into the 133 boxes that are aligned with the numbers.

2.4 Assessment of covariates of interest

According to factors identified in previous research that are associated with sleep duration or cognitive function, this study controlled for several covariates of interest, including sex (male/female), age (years), marriage (married/divorced/widowed/living alone), race (Mexican American/other Hispanic/non-Hispanic white/non-Hispanic black/other race), the income-poverty ratio of family (<1/≥1), education level (less than middle school/less than high school/high school or GED/ college or AA degree/college or higher), smoking status (≥ 100-lifetime cigarettes/ <100-lifetime cigarettes), alcohol intake (≥12 drinks per year/ <12 drinks per year), hypertension (yes/no), hyperlipidemia (yes/no), and diabetes mellitus (yes/no/borderline).

2.5 Statistical analysis

In descriptive analyses, continuous variables are summarized by mean and standard error (SE). To examine the association between sleep duration and cognitive test scores in overweight and obese older adults, multivariable regression models were used, accounting for the NHANES complex sampling design (sampling weights). Three different model analyses were performed. The crude model was unadjusted for any covariates, Model 1 adjusted for sex, age, and race, and Model 2 adjusted for sex, age, race, marital status, education level, income-poverty ratio, hypertension, hyperlipidemia, diabetes, smoke status, and alcohol intake status. Generalized additive models (GAM) and smoothed curves were also used to address potential non-linear relationships between sleep duration and cognitive test scores. If a non-linear association was observed, a piecewise linear regression model (segmented regression) was used to fit each interval and calculate the threshold effect. A likelihood ratio test comparing a linear model (non-segmented) with the piecewise linear regression model was conducted to determine the presence of a threshold effect. The inflection point (K) connecting the two segments was determined using the maximum likelihood model and a two-step recursive method. Subgroup analysis was performed using stratified multivariable logistic regression models, with stratification factors including sex (male/female), age (≤69/70–79/>79 years), smoke status (≥100 lifetime cigarettes/<100 lifetime cigarettes), alcohol intake (≥12 drinks per year/<12 drinks per year), hypertension (yes/no), hyperlipidemia (yes/no), and diabetes mellitus (yes/no/borderline). These stratification factors were also treated as potential effect modifiers, and interaction terms were added using likelihood ratio tests to assess heterogeneity in associations across different subgroups. All statistical analyses were performed using the R software (version 4.2) and the EmpowerStats add-in (version 4.2). The threshold for statistical significance was set at a two-tailed p-value of 0.05.

3 Results

3.1 Baseline characteristics

The study population comprised 2,243 individuals aged 60 years or older (including 60 years) with a BMI above the normal range, drawn from NHANES (2011–2014). Of these, 1,095 (48.82%) were male and 1,148 (51.18%) were female. The mean age of the 2,243 participants was 69.35 years, the mean sleep duration was 7.04 h, and the mean values of the three tests related to cognitive function (CERAD test, AFT, and DDST) were 24.38, 16.51, and 45.88, respectively.

Analysis of sleep duration as a continuous variable across different demographic, lifestyle, and health categories revealed significant differences in sleep duration based on age, race, hypertension status, overweight or obesity status, and different CERAD test score ranges. These findings were statistically significant ($p < 0.05$) (Table 1).

3.2 Association between sleep duration and cognitive function in overweight and obese older adults

This study found that in the demographic model (Model 1), each additional hour of sleep was associated with a decrease of 0.22 in CERAD test scores ($\beta = -0.22$, 95% CI: −0.40, −0.04), a decrease of

TABLE 1 Mean ± Standard error (SE) in sleep duration (hours/day) by level of demographic variables, lifestyle variables influencing sleep duration, and classification of cognitive function scores.

Sleep duration (hours/day)	*N*	Mean ± SE	*p*-value
Sex			0.515
Male	1,095	7.06 ± 1.46	
Female	1,148	7.02 ± 1.51	
Age (years)			**<0.001***
<=69	1,212	6.87 ± 1.47	
>69, <=79	688	7.12 ± 1.45	
>79	343	7.46 ± 1.51	
BMI (kg/m^2)			**0.010***
> = 25, <30	1,071	7.12 ± 1.39	
> = 30	1,172	6.96 ± 1.57	
Race			**<0.001***
Mexican American	240	7.00 ± 1.46	
Other Hispanic	246	6.80 ± 1.44	
Non-Hispanic White	1,041	7.32 ± 1.38	
Non-Hispanic Black	577	6.70 ± 1.59	
Other Race–Including Multi-Racial	139	6.81 ± 1.59	
Education level			0.182
Less than 9th grade	286	6.85 ± 1.60	
9-11th grade (Includes 12th grade with no diploma)	335	7.11 ± 1.55	
High school graduate/GED or equivalent	524	7.06 ± 1.56	
Some college or AA degree	639	7.00 ± 1.44	
College graduate or above	459	7.12 ± 1.33	
Income-poverty ratio			0.761
<1	365	7.02 ± 1.73	
> = 1	1,697	7.04 ± 1.42	
Alcohol intake			0.153
Alcohol intake > = 12 drinks /year	1,458	7.07 ± 1.47	
Alcohol intake <12 drinks /year	732	6.95 ± 1.50	
Smoke status			0.564
Smoke > = 100 cigarettes /life	1,130	7.07 ± 1.49	
Smoke <100 cigarettes /life	1,113	7.00 ± 1.48	
Diabetes mellitus			0.077
Yes	617	6.96 ± 1.61	
No	1,515	7.08 ± 1.44	
Borderline	111	6.82 ± 1.42	
Hyperlipidemia			0.359
Yes	1,310	7.07 ± 1.45	
No	933	7.00 ± 1.54	
Hypertension			**0.002***
Yes	1,518	7.05 ± 1.49	
No	725	7.01 ± 1.46	
Score of the CERAD test			**0.007***
<10	65	7.60 ± 2.07	

(Continued)

TABLE 1 (Continued)

Sleep duration (hours/day)	*N*	Mean ± SE	*p*-value
10–19	436	7.11 ± 1.67	
20–29	1,195	7.02 ± 1.44	
>29	547	6.95 ± 1.33	
Score of the AFT			0.236
<10	198	7.23 ± 1.80	
10–19	1,418	7.01 ± 1.50	
20–29	545	7.00 ± 1.33	
>29	46	6.91 ± 1.17	
Score of the DSST			0.161
<10	24	6.75 ± 1.67	
10–19	104	7.29 ± 1.58	
20–29	270	7.09 ± 1.54	
>29	1732	7.00 ± 1.43	

BMI, body mass index; CERAD, the Consortium to Establish a Registry for Alzheimer's Disease; AFT, the Animal Fluency test; DSST, the Digit Symbol Substitution test. Significant values ($P < 0.05$) are in bold.

TABLE 2 Association between sleep duration and cognitive function in multiple regression model.

	Crude	Model 1	Model 2
Score of the CERAD test	−0.30(−0.49, −0.11) **0.0021***	−0.22 (−0.40, −0.04) **0.0183***	−0.25 (−0.43, −0.07) **0.0063***
Score of the AFT	−0.10 (−0.25, 0.06) 0.2306	−0.16 (−0.30, −0.01) **0.0353***	−0.17 (−0.32, −0.02) **0.0231***
Score of the DSST	−0.37 (−0.87, 0.13) 0.1493	−0.60 (−1.04, −0.17)**0.0067***	−0.78 (−1.16, −0.40) **<0.0001***

Crude: Unadjusted. Model 1: Adjusted for sex, race, and age. Model 2: Adjusted for sex, race, age, marital status, income-poverty ratio, education level, smoke status, alcohol intake, hypertension, hyperlipidemia, and diabetes mellitus. Significant values ($p < 0.05$) are in bold.

0.16 in AFT scores ($\beta = -0.16$, 95% CI: −0.30, −0.01), and a decrease of 0.60 in DSST scores ($\beta = -0.60$, 95% CI: −1.04, −0.17).

In the fully adjusted model (Model 2), sleep duration remained negatively associated with CERAD test, AFT, and DSST scores. Each additional hour of sleep was associated with a decrease of 0.25 in CERAD test scores ($\beta = -0.25$, 95% CI: −0.43, −0.07), a decrease of 0.17 in AFT scores (β = −0.17, 95% CI: −0.32, −0.02), and a decrease of 0.78 in DSST scores (β = −0.78, 95% CI: −1.16, −0.40). All results were statistically significant ($p < 0.05$) (Table 2).

3.3 Subgroup analysis

Our study indicates a negative correlation between cognitive function and sleep duration. Based on previously identified confounding factors, we further assessed the relationship between sleep duration and cognitive function in both predefined and exploratory subgroups. Stratified analyses and interaction tests were performed as shown in Table 3 and Figure 2 (Association between sleep duration and different cognitive function scores stratified by age, sex, alcohol intake, smoke status, diabetes mellitus. Adjusted for all presented covariates. (A) CERAD test; (B) AFT; (C) DSST.* $p < 0.05$).

The results demonstrated that there were no significant interactions between any of the stratifying variables and the relationship between sleep duration and cognitive function. Specifically, the negative association between sleep duration and cognitive test scores in overweight and obese older adults was consistent across all stratified groups (all *p*-values for interaction >0.05).

3.4 Non-linear correlation between sleep duration and cognitive function in older adults with BMI $\geq$ 25 kg/m^2

The solid red line represents the smooth curve fit between variables. The dotted line represents the 95% confidence interval for the fit. The dose–response relationship between sleep duration with the score of the CERAD test (A), the score of the Animal Fluency test (B), and the score of the Digit Symbol Substitution test (C) in obese elders (Figure 3).

3.5 Threshold effect analysis

After fully adjusting for covariates, we applied a threshold effect model and identified the inflection points (K) for the CERAD test, AFT, and DSST at 5, 6, and 6 h of sleep, respectively. To the left of the inflection point for CERAD test, a positive association between sleep duration and CERAD test was detected ($\beta = 2.11$, 95% CI: 1.17, 3.05). However, to the right of this point, sleep duration was negatively associated with CERAD test ($\beta = -0.51$, 95% CI: −0.71, −0.30), with a log-likelihood ratio (LLR) of <0.001.

TABLE 3 Effect size of sleep duration (hours/day) on cognitive function in prespecified and exploratory subgroups.

Sleep duration (hours/day)	Score of the CERAD test	Score of the AFT	Score of the DSST
Age (years)			
<=69	−0.10 (−0.34, 0.14) 0.4193	−0.24 (−0.45, −0.03) **0.0231***	−0.82 (−1.35, −0.30) **0.0022***
>69, <=79	−0.41 (−0.75, −0.06) **0.0205***	−0.10 (−0.38, 0.18) 0.4825	−0.30 (−1.02, 0.41) 0.4015
>79	−0.53 (−1.02, −0.05) 0.0319	−0.11 (−0.43, 0.22) 0.5169	−1.68 (−2.61, −0.75) **0.0005***
P for interaction	0.1825	0.6198	0.0750
Sex			
Male	−0.34 (−0.60, −0.07) **0.0137***	−0.12 (−0.35, 0.11) 0.3062	−0.59 (−1.13, −0.06) **0.0303***
Female	−0.18 (−0.43, 0.07) 0.1590	−0.20 (−0.40, −0.00) **0.0460***	−0.94 (−1.48, −0.40) **0.0007***
P for interaction	0.2789	0.5509	0.2839
Alcohol intake			
Alcohol Intake > = 12 drinks /year	−0.33 (−0.54, −0.12) **0.0023***	−0.20 (−0.39, −0.02) **0.0337***	−1.02 (−1.48, −0.57) **<0.0001***
Alcohol Intake <12 drinks /year	−0.13 (−0.47, 0.21) 0.4433	−0.12 (−0.37, 0.12) 0.3293	−0.38 (−1.07, 0.30) 0.2729
P for interaction	0.2887	0.6594	0.1479
Smoke status			
Smoke > = 100 cigarettes /life	−0.34 (−0.59, −0.10) **0.0059***	−0.13 (−0.35, 0.09) 0.2472	−0.76 (−1.30, −0.22) **0.0058***
Smoke <100 cigarettes /life	−0.20 (−0.47, 0.07) 0.1513	−0.20 (−0.40, 0.01) 0.0610	−0.76 (−1.30, −0.22) 0.0058
P for interaction	0.4267	0.6535	0.9940
Diabetes mellitus			
Yes	−0.22 (−0.55, 0.11) 0.1865	−0.07 (−0.32, 0.19) 0.6155	−0.70 (−1.37, −0.02) 0.0437
No	−0.27 (−0.49, −0.04) 0.0222	−0.25 (−0.44, −0.05) 0.0124	−0.89 (−1.38, −0.41) 0.0003
Borderline	−0.16 (−1.07, 0.75) 0.7323	0.65 (−0.05, 1.35) 0.0722	−0.81 (−2.47, 0.85) 0.3419
P for interaction	0.9817	0.0640	0.9183

All presented covariates were fully adjusted (as Model 2). Significant values ($p < 0.05$) are in bold.

With regard to AFT, no statistically significant association was observed between sleep duration and the inflection point ($\beta = 0.25$, 95% CI: −0.17, 0.67). However, a robust inverse correlation was observed on the right side of the inflection point ($\beta = -0.32$, 95% CI: −0.52, −0.12), with an LLR of 0.0019.

Similarly, no significant association was identified between DSST and sleep duration on the left side of the inflection point ($\beta = 0.49$, 95% CI: −0.57, 1.56). In contrast, a clear negative association was observed on the right side ($\beta = -1.21$, 95% CI: −1.71, −0.70), with an LLR of 0.012 (Table 4).

4 Discussion

In this population-based study, a negative correlation was observed between sleep duration and cognitive function in overweight and obese older adults. Furthermore, the relationship between sleep duration and cognitive function was found to be non-linear. Our study's results indicate a threshold effect between sleep duration and cognitive function in overweight and obese older adults. Specifically, cognitive test scores demonstrated a significant improvement with increasing sleep duration up to a certain point, after which a decline was observed. In particular, a decline in cognitive scores was observed following 5 h of sleep for the CERAD test total score, 6 h for the animal fluency test, and 6 h for the digit symbol substitution test.

The findings of our study indicate an inverted U-shaped relationship between sleep duration and cognitive function in overweight and obese older adults, which is consistent with the results of previous clinical studies conducted in aging populations (Li et al., 2022; Keil et al., 2023; Fjell et al., 2023). Using cohort data from the China Health and Retirement Longitudinal Study revealed that moderate sleep duration, rather than prolonged sleep, was associated with higher cognitive function. A further study based on the UK Biobank dataset provided evidence that both excessive and limited sleep are important risk factors of cognitive impairment in older adults, which aligns with the findings presented here (Yu et al., 2023).

Moreover, a population-based study has corroborated the finding that the optimal duration of sleep for cognitive function is approximately 5–7.5 h, with sleep extending up to 8 h being associated with a decline in cognitive performance (Coulthard and Blackman, 2021). A meta-analysis of nine cohort studies also identified a U-shaped dose–response relationship between sleep duration and the risk of cognitive impairment, with the lowest risk observed at 7–8 h of sleep (Xu et al., 2020).

Our research focuses on globally significant issues such as population aging, overweight and obesity, and the prevention of dementia risk through lifestyle interventions. Earlier studies generally concluded that overweight and obesity has a negative impact on cognitive function. However, recent scholars have introduced the concept of the "obesity paradox" (Kim et al., 2020). In this study, after

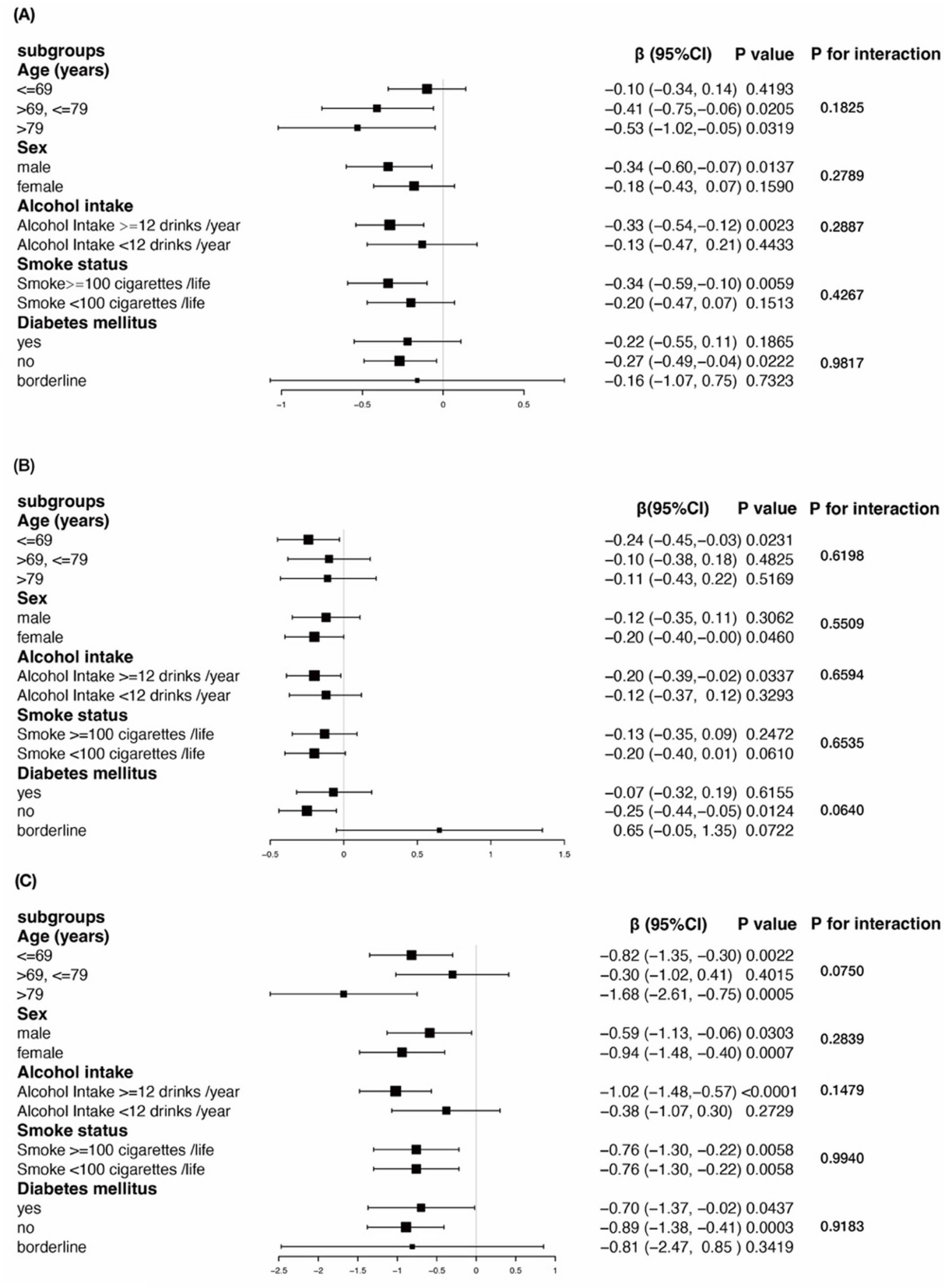

FIGURE 2
Subgroup analysis for the association between sleep duration and cognitive function in older adults with BMI ≥ 25 kg/m^2.

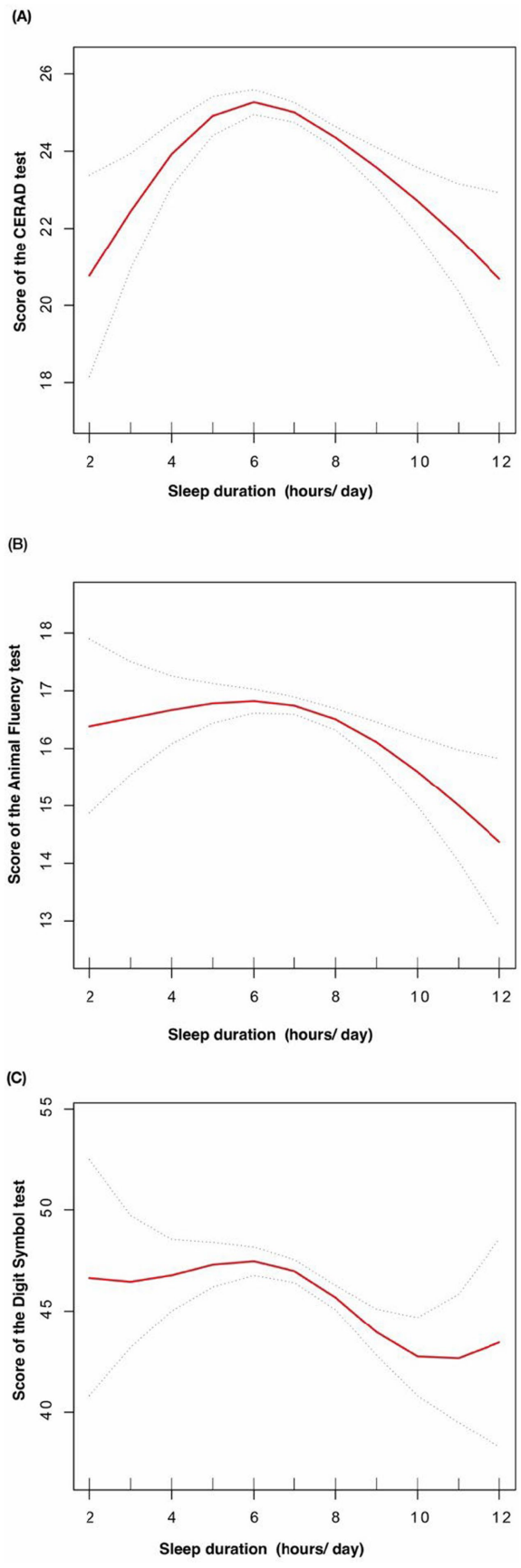

FIGURE 3
The dose-response relationship between sleep duration with cognitive function in obese elders.

adjusting for multiple covariates, we found that among overweight and obese older adults, the relationship between sleep duration and cognitive function follows a threshold effect. Specifically, the risk of cognitive decline is lowest when total nighttime sleep duration is around 5–6 h. This conclusion remains robust across different subgroups.

The study results show a reverse U-shaped relationship between sleep duration and cognitive function, which is consistent with other research findings. However, through threshold effect analysis, the optimal sleep duration, compared to 7–8 h, was shortened to 5–6 h, which is an interesting finding. This may be due to the potential protective effects of overweight and obesity on cognitive decline in middle-aged and older adults (Pedditzi et al., 2016), aligning with the concept of the "obesity paradox."

In addition, several potential mechanisms may explain the observed reverse U-shaped association: sleep is essential for restorative functions and maintaining homeostasis, and prolonged sleep may indicate circadian dysregulation, associated with sleep disorders and cognitive impairment (Devore et al., 2014). Moreover, increased levels of interleukin-6 (IL-6) and C-reactive protein (CRP) have been observed in long sleepers (Benington, 2000), suggesting a link between prolonged sleep, inflammation, and cognitive impairment. The prefrontal cortex, critical for executive function, may be particularly vulnerable to sleep disturbances (Cavaillès et al., 2023) and may be particularly vulnerable to sleep disorders (Thomas et al., 2000; Yaffe et al., 2016).

Short sleep duration may disrupt glymphatic clearance, leading to amyloid-β accumulation, associated with neurodegenerative processes in Alzheimer's disease (Xie et al., 2013). Insufficient sleep has also been associated with an increased risk of cardiovascular disease and related risk factors (Jike et al., 2018; Bock et al., 2022; Itani et al., 2017), and it may also lead to increased inflammation and HPA(Hypothalamic–Pituitary–Adrenal) axis activity (Minkel et al., 2014), which could be another pathway contributing to cognitive impairment, especially in older adults, all of which are linked to cognitive decline and dementia risk (Livingston et al., 2020; Yaffe et al., 2020). Cognitive decline may result from the degradation of neurons that promote wakefulness and sleep (Oh et al., 2019).

Our study holds its own strengths. First, the study utilized a large and representative sample based on the NHANES database. Second, three different models were employed to adjust for potential confounders, enhancing the reliability of our findings. And then, by conducting subgroup analyses, we examined the robustness of the association between sleep duration and cognitive function in overweight and obese older adults across different groups. Finally, our study provides insights into managing sleep duration in overweight and obese populations to maximize cognitive benefits.

However, the results of this study should be interpreted with caution for several limitations. Although the NHANES database is well-suited for cross-sectional studies, further research is needed to elucidate the mechanisms underlying the association between sleep duration and cognitive function in the overweight and obese older adults. While we accounted for several covariates in this study, it is not possible to exclude all potential confounders. Due to the limitation of the self-reported sleep questionnaires from 2011 to 2014, which only included total nighttime sleep duration without data on sleep quality or daytime sleep, this study has certain constraints. Future research

TABLE 4 Threshold effect analysis of sleep duration (hours/day) on cognitive function.

Outcome	Score of the CERAD test	Score of the AFT	Score of the DSST
Fitting by the standard linear Model	−0.25 (−0.43, −0.07) **0.0064***	−0.17 (−0.32, −0.02) **0.0231***	−0.78 (−1.16, −0.40) **<0.0001***
Fitting by the two-piecewise linear Model			
Inflection point (K)	5	6	6
<K-segment effect	2.11 (1.17, 3.05) < 0.0001*	0.25 (−0.17, 0.67) 0.2376	0.49 (−0.57, 1.56) 0.3654
>K-segment effect	−0.51 (−0.71, −0.30) **<0.0001***	−0.32 (−0.52, −0.12) **0.0019***	−1.21 (−1.71, −0.70) **<0.0001***
Log likelihood ratio	**<0.001***	**0.032***	**0.012***

Adjusted for sex, race, age, marital status, income-poverty ratio, education level, smoke status, alcohol intake, hypertension, hyperlipidemia, and diabetes mellitus. CERAD, the Consortium to Establish a Registry for Alzheimer's Disease; AFT, the Animal Fluency test; DSST, the Digit Symbol Substitution test. Significant values ($p < 0.05$) are in bold.

should further investigate the relationship between multidimensional aspects of sleep and cognitive abilities.

Data availability statement

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

Ethics statement

The Research Ethics Review Board (ERB) of the US National Center for Healthcare Statistics (NCHS) authorized the 2011-2014 NHANES (Protocol Number: protocol#2011-17 and continuation of protocol #2011-17). Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

KQ: Data curation, Formal analysis, Methodology, Writing – original draft. YL: Investigation, Writing – review & editing. CH: Formal analysis, Writing – review & editing. JG: Supervision, Writing – review & editing. YH: Conceptualization, Supervision, Validation, Writing – review & editing.

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Conflict of interest

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

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2024.1529639/full#supplementary-material

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Improving cognitive impairment through chronic consumption of natural compounds/extracts: a systematic review and meta-analysis of randomized controlled trials

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Introduction: This systematic review and meta-analysis aimed to compare the efficacy of extended supplementation (≥6 weeks) with natural compounds or extracts in improving cognitive function in patients with mild cognitive impairment (MCI) or Alzheimer's disease (AD).

Methods: A comprehensive literature search was conducted across Cochrane, PubMed, PsycARTICLES, Scopus, and Web of Science databases from inception to April 10, 2024. Eligible studies were randomized controlled trials evaluating cognitive outcomes in patients with MCI or AD using the Mini-Mental State Examination (MMSE) and the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog).

Results: From an initial pool of 6,687 articles, 45 were deemed relevant for qualitative analysis. Of these, 37 studies demonstrated improvements or positive trends in cognitive outcomes with natural compound or extract supplementation. A total of 35 studies met the criteria for meta-analysis. The meta-analysis, involving 4,974 participants, revealed significant improvements in ADAS-Cog scores (pooled standardized mean difference = −2.88, 95% confidence interval [CI]: −4.26 to −1.50; $t_{24} = -4.31$, $p < 0.01$) following supplementation. Additionally, a suggestive trend toward improvement in MMSE scores was observed in a subgroup analysis of 1,717 participants (pooled standardized mean difference = 0.76, 95% CI: 0.06 to 1.46, $t_{18} = 2.27$, $p = 0.04$).

Conclusion: These findings support the potential cognitive benefits of extended (≥6 weeks) supplementation with natural compounds or extracts in individuals with MCI or AD. Further research is warranted to confirm these results and elucidate the underlying mechanisms.

Systematic review registration: https://www.crd.york.ac.uk/PROSPERO/.

KEYWORDS

aging, Alzheimer's disease, cognitive dysfunction, meta-analysis, neurodegeneration

1 Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that significantly affects individuals worldwide. It is characterized by a gradual decline in cognitive abilities, manifesting as memory loss, personality changes, and difficulties with daily functioning (Katzman, 1993). Mild cognitive impairment (MCI), often considered a precursor to AD, represents a stage of cognitive decline that does not yet meet the diagnostic criteria for dementia (Morris, 1997). With the global population aging, the prevalence of both AD and MCI is projected to rise significantly (Deary et al., 2009), posing critical challenges to healthcare systems and society at large.

The current treatment options for AD and MCI remain limited (Long and Holtzman, 2019), driving growing interest in exploring natural compounds and extracts as potential therapeutic interventions (Andrade et al., 2019). Natural compounds derived from plants, fruits, and vegetables have demonstrated promising properties, including anti-inflammatory, anti-oxidant, and neuroprotective effects (Wang et al., 2022). Recent studies have focused on elucidating the mechanisms through which these compounds and extracts may enhance cognitive function and provide neuroprotection against degenerative processes (Andrade et al., 2019).

Examples of natural compounds extensively studied for their neuroprotective effects include alkaloids, polyphenols, and terpenoids (Jiang et al., 2017). Flavonoids such as quercetin (Dastmalchi et al., 2008; Khan et al., 2019) and catechins (Ide et al., 2018) exhibit anti-inflammatory and anti-oxidant properties that safeguard neurons from oxidative stress and inflammation. Polyphenols, including resveratrol (Lee et al., 2017; Sawda et al., 2017; Turner et al., 2015) and curcumin (Hamaguchi et al., 2010; Ono et al., 2004; Rainey-Smith et al., 2016), have shown potential in improving cognitive function and protecting against neurodegeneration. Similarly, terpenoids such as ginsenosides (Heo et al., 2012; Heo et al., 2016; Lee et al., 2008; Lee et al., 2022; Park H. et al., 2019; Sheng et al., 2015) have been reported to improve memory and cognitive function through neuroprotective mechanisms.

Randomized controlled trials (RCTs) have assessed the efficacy of natural compounds and extracts in improving cognitive function and slowing the progression of AD and MCI (Akhondzadeh et al., 2003a, 2003b; Akhondzadeh et al., 2010a; Akhondzadeh et al., 2010b; Heo et al., 2012; Lee et al., 2008; Muangpaisan et al., 2022; Noguchi-Shinohara et al., 2020; Tsolaki et al., 2016; Wang et al., 2018). Among the most extensively investigated natural extracts are *Ginkgo biloba* (DeKosky et al., 2008; Gauthier and Schlaefke, 2014; Herrschaft et al., 2012; Hofferberth, 1994; Ihl et al., 2011; Kanowski and Hoerr, 2003; Le Bars et al., 1997; Le Bars et al., 2000; Le Bars et al., 2002; Li et al., 2023; Lopez et al., 2019; Maurer et al., 1997; Mazza et al., 2006; Schneider et al., 2005; Shi et al., 2010; Snitz et al., 2009) and *Curcuma longa* (Baum et al., 2008; Obulesu and Rao, 2011; Ono et al., 2004; Rainey-Smith et al., 2016). Both have demonstrated potential in enhancing global cognitive function and protecting against cognitive decline.

This systematic review and meta-analysis aim to synthesize the current evidence from RCTs on the effects of natural compounds and extracts on cognitive function in individuals with AD or MCI. By evaluating their therapeutic potential, this study seeks to provide a comprehensive overview of the current state of knowledge and assess the feasibility of incorporating these natural agents into treatment strategies for AD and MCI.

2 Methods

2.1 Inclusion criteria

This study applied the population, intervention, comparator, outcome, and study design framework (PICOS) (Supplementary Table S1) to establish the inclusion criteria for relevant studies. Eligible studies met the following criteria: (1) study design: Randomized controlled trials including parallel or multi-arm trials; (2) participants: Patients diagnosed with AD or cognitive impairment according to established diagnostic criteria, such as the *Diagnostic and Statistical Manual of Mental Disorders (DSM)*, the *National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA)*, or the *International Classification of Diseases (ICD)*; (3) Intervention and control groups: An experimental group receiving natural compounds or extracts, compared with a control group receiving a placebo, equivalent, or standard treatment; (4) Outcome measures: Cognitive outcomes assessed via the Mini-Mental State Examination (MMSE) and/or the Alzheimer Disease Cooperative Study-Activities of Daily Living Scale (ADAS-cog). Exclusion criteria included studies that: (1) were derived from the same trial; (2) Lacked analyzable data; (3) Were not available in full-text format; (4) Were not published in English; (5) Combined multiple natural compounds or extracts in the intervention.

2.2 Data sources

The systematic review followed guidelines outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (version 6.3; Higgins et al., 2022) and the *Centre for Reviews and Dissemination* (University of York, 2009). The study adhered to the preferred reporting items for systematic reviews and meta-analysis framework (PRISMA) (Supplementary Table S2; Moher et al., 2009). The review protocol was registered in International prospective register of systematic reviews (PROSPERO) under registration number CRD42022369293. A systematic search was conducted across Cochrane, PubMed, PsycARTICLES, Scopus, and Web of Science databases from inception to April 10, 2024. The search strategy included the following terms: (Alzheimer's disease OR Alzheimer dementia) AND (natural OR compound OR flower OR plant OR extract* OR powder OR oil) AND (cognition OR cognitive function OR cognit*).

Abbreviations: ADL, Activities of Daily Living; ADAS-cog, Alzheimer Disease Cooperative Study-Activities of Daily Living Scale; AD, Alzheimer's disease; NINCDS-ADRDA, Alzheimer's Disease and Related Disorders Association; CSF, Cerebrospinal fluid; CDR, Clinical Dementia Rating; CGIC, Clinical Global Impression of Change; CIBIC+, Clinician's Interview-Based Impression of Change Plus; CIs, Confidence intervals; DSM, Diagnostic and Statistical Manual of Mental Disorders; DHA, Docosahexaenoic acid; EPA, Eicosapentaenoic acid; IADL, Instrumental Activities of Daily Living; MCI, Mild cognitive impairment; MMSE, Mini Mental State Examination; PRM, Prolonged-release melatonin; RCTs, Randomized controlled trials; SDs, Standard deviations; SMD, Standardized mean difference.

2.3 Study selection

Two independent reviewers screened articles for eligibility using EndNote X9 for reference management. First, titles and abstract were screened for relevance. Full texts of potentially eligible studies were then reviewed. Reference lists from included studies and relevant systematic reviews were also hand-searched to identify additional eligible articles.

2.4 Risk of bias and quality assessment

The risk of bias was assessed using the Cochrane Risk of Bias tool (RoB2), which evaluates aspects such as randomization, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting (Sterne et al., 2019). Studies were categorized as having low risk, some concerns, or high risk of bias. When applicable, funnel plots and Egger's test (Egger et al., 1997) were employed to evaluate potential publication bias.

2.5 Data collection

A standardized form was used to extract the following data: Publication information (authors, title, year); Study characteristics (design and number of participants); Participant characteristics (drug type, dosage, and duration of intervention); Cognitive outcomes (mean values and standard deviations for MMSE and ADAS-cog scores). When data were presented as means with 95% confidence intervals (CIs) or as medians with interquartile ranges, these were converted into means and standard deviations (SDs) using methods from the *Cochrane Handbook* (Chapter 6.5.2; Higgins et al., 2022) or Wan et al.'s formulas (Wan et al., 2014).

2.6 Data synthesis

Pooled data were analyzed using R (version 4.3.3) with the "meta" package. For long-term studies (≥ 6 weeks), endpoint and baseline data were used to calculate mean differences for intervention and control groups. Results were presented in forest plots as weighted mean differences or standardized mean differences (SMDs) with 95% CIs and two-sided p values. Subgroup analyses were conducted to explore variations in study designs and characteristics.

Global cognitive outcomes were evaluated using: (a) MMSE, scores range from 0 to 30, with higher scores indicating better cognition; and (b) ADAS-cog, scores range from 0 to 70, with higher scores indicating greater cognitive impairment. Effect sizes were calculated as Hedges' g, classified as very small (< 0.2), small (0.2–0.5), moderate (0.5–0.8), and large (> 0.8; Hedges, 2009). The Hartung-Knapp-Sidik-Jonkman random-effects model was used to account for heterogeneity in treatment effects (Inthout et al., 2014).

Statistical heterogeneity was assessed using the chi-squared (χ^2) test and I^2 statistic. I^2 value ≥50% indicated moderate heterogeneity, while values between 75 and 100% suggested substantial heterogeneity (Higgins et al., 2003). Sensitivity analyses were performed by systematically excluding studies to identify potential outliers influencing the overall effect size. Statistical significance was set at $p < 0.05$ for all analyses.

3 Results

3.1 Literature search

The study selection process is illustrated in Figure 1, adhering to PRISMA guidelines (Moher et al., 2009). A comprehensive search across five databases yielded 6,687 articles, supplemented by 55 additional articles identified through manual searches of reference lists from relevant studies. After the removal of duplicates, 5,491 articles remained. Of these, 5,393 were excluded for not being human intervention studies, randomized controlled trials or for only having abstract-level information available. Following the screening of titles and abstracts, 98 articles evaluating cognitive function were shortlisted for full-text review. Subsequently, 53 articles were excluded due to not meeting inclusion criteria. Ultimately, 45 trials were included in the qualitative review, of which 35 provided sufficient data for meta-analysis.

3.2 Qualitative analysis and study characteristics

The systematic review incorporated 45 studies, with a detailed summary provided in Table 1. These studies addressed various dimensions, including study quality, sample size, participant characteristics (e.g., health status, diagnostic criteria), intervention types, dosages, durations, cognitive assessment measures, and key outcome metrics.

The total sample size across the included studies was 8,532 participants, with a mean age of 72 years. Among these studies, 31 focused on older adults clinically diagnosed with mild to moderate Alzheimer's disease (AD) based on established diagnostic criteria such as NINCDS-ADRDA, DSM-III, or DSM-IV (e.g., Akhondzadeh et al., 2003a, 2003b; Akhondzadeh et al., 2010a; Akhondzadeh et al., 2010b; Fernando et al., 2023; Freund-Levi et al., 2008; Herrschaft et al., 2012; Hofferberth, 1994; Ihl et al., 2011; Le Bars et al., 1997; Le Bars et al., 2002; Maurer et al., 1997; Mazza et al., 2006; Muangpaisan et al., 2022; Noguchi-Shinohara et al., 2020; Quinn et al., 2010; Rafii et al., 2011; Rasi Marzabadi et al., 2022; Schneider et al., 2005; Thal et al., 1999; Turner et al., 2015; van et al., 2000; Wade et al., 2014; Wang et al., 2018; Xu et al., 2012). Two studies investigated vascular dementia (Erkinjuntti et al., 2002; Xu et al., 2012), and two other examined AD with comorbid neuropsychiatric symptoms (Herrschaft et al., 2012; Ihl et al., 2011). Additional studies addressed participants with multi-infarct dementia (Le Bars et al., 1997; Le Bars et al., 2002) or concurrent use of acetylcholinesterase inhibitors (AChEIs) (Freund-Levi et al., 2008). Twelve studies specifically targeted older adults with MCI (e.g., Boespflug et al., 2018; Calapai et al., 2017; Chatzikostopoulos et al., 2024; Kaddoumi et al., 2022; Lee et al., 2017; Lee et al., 2013; Lee et al., 2020; Noguchi-Shinohara et al., 2023; Park H. et al., 2019; Shin et al., 2009; Tsolaki et al., 2016; Tsolaki et al., 2020; You et al., 2021), and one study focused on amnestic and multi-domain MCI (Tsolaki et al., 2016). Two studies exclusively addressed participants with moderate-to-severe AD (Farlow et al., 2019; Farokhnia et al., 2014).

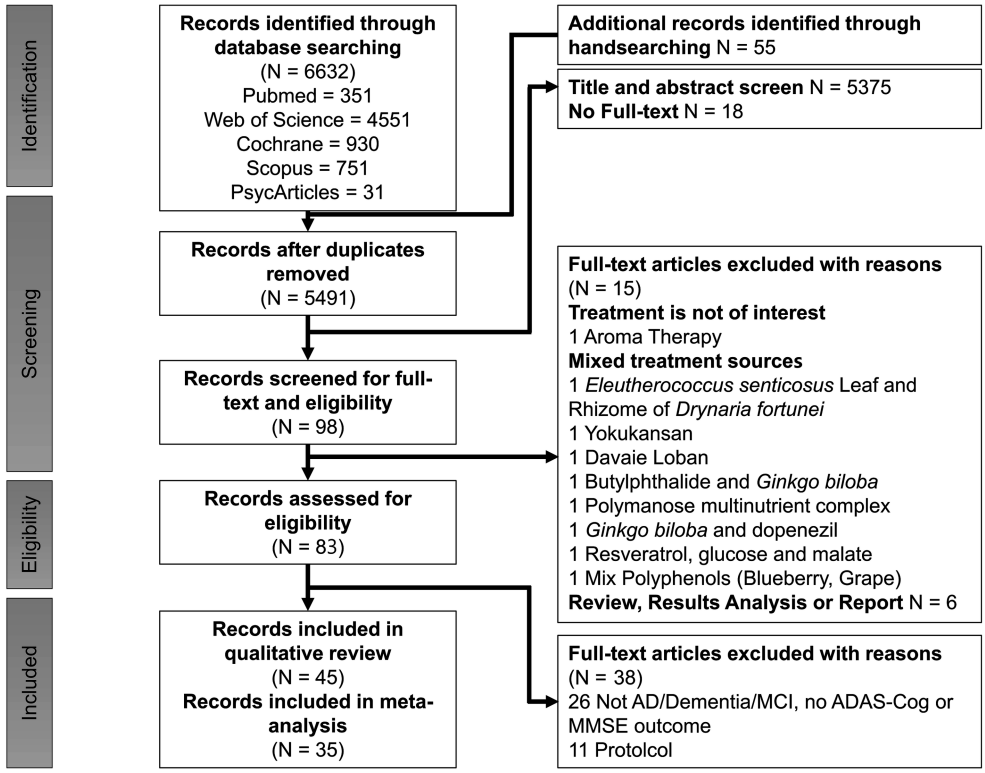

FIGURE 1
PRISMA flow diagram for study selection.

The interventions in the reviewed studies had an average duration of 27 weeks, ranging from 6 to 96 weeks, and predominantly utilized natural extracts. These extracts included *Cocos nucifera* (*N* = 1; Fernando et al., 2023), *Cosmos caudatus* (*N* = 1; You et al., 2021), *Crocus sativus* L. (*N* = 5; Akhondzadeh et al., 2010a, Akhondzadeh et al., 2010b; Farokhnia et al., 2014; Rasi Marzabadi et al., 2022; Tsolaki et al., 2016), *Ganoderma lucidum* (*N* = 1; Wang et al., 2018), *Garcinia mangostana* L. (*N* = 1; Muangpaisan et al., 2022), *Ginkgo biloba* (*N* = 8; Herrschaft et al., 2012; Hofferberth, 1994; Ihl et al., 2011; Le Bars et al., 1997; Le Bars et al., 2002; Maurer et al., 1997; Mazza et al., 2006; Schneider et al., 2005), *Melissa officinalis* (*N* = 3; Akhondzadeh et al., 2003a; Noguchi-Shinohara et al., 2023; Noguchi-Shinohara et al., 2020), *Olea europaea* L. (*N* = 2; Kaddoumi et al., 2022; Tsolaki et al., 2020), *Panax ginseng* (*N* = 1; Park H. et al., 2019), *Polygala tenuifolia* Willdenow (*N* = 1; Shin et al., 2009), *Punica granatum* (*N* = 1; Chatzikostopoulos et al., 2024), *Salicornia europaea* L. (*N* = 1; Lee et al., 2020), *Salvia officinalis* (*N* = 1; Akhondzadeh et al., 2003b), *Vitis vinifera* (*N* = 2; Calapai et al., 2017; Lee et al., 2017), *Vaccinium ashei*, and *Vaccinium corymbosum* L. (*N* = 1; Boespflug et al., 2018). These supplements were administered orally, primarily in the form of capsule powders, capsule liquids, or liquid solutions, as detailed in Table 1. The concentration of the natural extracts varied significantly across studies. Specifically, *Cocus nucifera* was administered at a dosage of 30 mL per day, *Cosmos caudatus* at 500 mg/day, and *Crocus sativus* L. at 30 mg/day. *Ganoderma lucidum* was provided at 1 g/day, while *Garcinia mangostana* L. dosage ranged from 220 to 560 mg/day depending on body weight. For *Ginkgo biloba*, the standardized *Ginkgo biloba* extract (EGb) 761 was administered in dosages ranging from 80 mg/day to 240 mg/day, typically at 120 or 240 mg/day. *Punica granatum* was given as 5 drops of seed oil daily. The administration of *Melissa officinalis* varied among studies: Noguchi-Shinohara et al. (2023), Noguchi-Shinohara et al. (2020) provided capsule powder containing at least 500 mg of rosmarinic acid per capsule, whereas Akhondzadeh et al. (2003a) offered a liquid solution with a concentration sufficient to provide at least 500 μg of citral per milliliter. The administration protocols for *Olea europaea* L. also differed between studies. Kaddoumi et al. (2022) supplemented participants with 30 mL/day of extra-virgin oil compared to refined olive oil at the same dosage. In contrast, Tsolaki et al. (2020) supplemented participants with high phenolic early extra-virgin olive oil or moderate phenolic oil at 50 mL/day, comparing these interventions to a Mediterranean diet. *Panax ginseng* was supplied in powder from at a dosage of 3 g/day, *Polygala tenuifolia* Willdenow (root extract powder designated as BT-11) at 300 mg/day, and *Salicornia europaea* at 600 mg/day. *Salvia officinalis* was administered as a liquid solution. *Vitis vinifera* was provided as powders at dosages of 250 mg/day (Calapai et al., 2017) and 72 g/day (Lee et al., 2017). Lastly, a combination of *Vaccinium ashei Reade* and *Vaccinium corymbosum* L. was administered in a 1:1 ratio at a daily dose of 25 g (Boespflug et al., 2018).

In addition to these natural extracts, fifteen studies supplemented participants with other natural compounds, including Bryostatin (*N* = 1; Farlow et al., 2019), Docosahexaenoic acid (DHA) (*N* = 3; Freund-Levi et al., 2008; Lee et al., 2013; Quinn et al., 2010), Huperzine A (*N* = 2; Rafii et al., 2011; Xu et al., 2012), Melatonin (*N* = 1; Wade et al., 2014), Physostigmine (*N* = 2; Thal et al., 1999; van et al., 2000),

TABLE 1 Summary of interventions assessing the effects of natural compounds/extracts on cognition.

References	Country	Study design	Sample (Number of subjects, mean age (years), male (%), health status)	Intervention type, dose, and duration	Cognitive tasks	Outcome
Wade et al. (2014)	UK/USA	RCT, double-blind	*N = 80;* 75; male 50%; Mild–Moderate AD[a]	Add-on prolonged-release melatonin 2 mg or placebo, 24 weeks	ADAS-cog, MMSE, IADL, PSQI, CGI, NPI, WHO-5, SDI	Safe and well tolerated; Improvement of IADL, MMSE, PSQI; No significant improvement of ADAS-Cog
Kaddoumi et al. (2022)	USA	RCT, double-blind	*N = 25;* 66; male 30%; MCI (WMS-IV)	Extra-virgin olive oil 30 mL/day, refined olive oil 30 mL/day, 26 weeks	MMSE, CDR	Improvement of CDR. Enhances brain connectivity and reduces BBB permeability.
Hofferberth (1994)	Germany	RCT, double-blind	*N = 40;* 63; male 50%; Dementia/AD[a]	*Ginkgo biloba* 80 mg or placebo daily, 12 weeks	SKT, SCAG, Saccade Test	Safe and well tolerated; Improvement of SKT and Saccade Test
van et al. (2000)	USA	RCT, double-blind	*N = 176;* 72; male 45%; Mild–Moderate AD: (NINCDS-ADRDA)	Physostigmine 24 or 30 mg/day or placebo, 12 weeks	MMSE, ADAS-cog, CGIC, IADL, CIBIC+	Improvement of ADAS-cog, and CIBIC+. No significant improvement of MMSE, CGIC, and IADL. Adverse events: nausea and vomiting 47.0% of all physostigmine-treated subjects
Boespflug et al. (2018)	USA	RCT, double-blind	*N = 16;* 78; male 54%; MCI (NINCDS-ADRDA)	25 g 50% *Vaccinium ashei* Reade, 50% *Vaccinium corymbosum* L. or placebo, 16 weeks	MoCA, VLT, GAS, GAI	Improvement of blood oxygen level-dependence; no clear indication of working memory enhancement
Calapai et al. (2017)	Italy	RCT, double-blind	*N = 111;* 66; male 48%; MCI[a]	*Vitis vinifera* powder 250 mg/day or placebo, 12 weeks	MMSE, RBANS	Improvement of MMSE and RBANS
Wilcock et al. (2000)	Europe/Canada	RCT, double-blind	*N = 653;* 72; male 37%; Mild–Moderate AD (NINCDS-ADRDA)	Galantamine 24, 32 mg or placebo daily, 26 weeks	ADAS-cog	Improvement of ADAS-cog
Herrschaft et al. (2012)	Germany	RCT, double-blind	*N = 410;* 65; male 30%; Mild–Moderate AD with neuropsychiatric (NINCDS-ADRDA)	EGb 240 mg or placebo daily, 24 weeks	ADCS-ADL CGIC, SKT, NPI, DEMQOL-Proxy, VFT	Safe; Improvement of SKT and NPI
Quinn et al. (2010)	USA	RCT, double-blind	*N = 402;* 76; male 48%; Mild–Moderate AD[b]	Algal DHA 2 g/d or placebo, 78 weeks	ADAS-cog, MMSE, CDR, NPI, ADCS-ADL	No improvement of ADAS-cog and CDR
Lee et al. (2017)	USA	RCT, double-blind	*N = 10;* 72; male 50%; MCI[a]	*Vitis vinifera* 72 g/day or placebo, 26 weeks	ADAS-cog, MMSE, VLT, WCST, WAIS-III, WATR, CFT	No improvement in cognitive measures; Maintains cerebral metabolism; Delays decline in left prefrontal, cingulate, and left superior posterolateral temporal cortex
Maurer et al. (1997)	Germany	RCT, double-blind	*N = 20;* 68; male 50%; Mild–Moderate AD (DSM-III-R)	EGb 240 mg/day or placebo, 12 weeks	SKT, ADAS-cog, ADAS-noncog, CGI (item 2)	Improvement of cognitive functions
Rockwood et al. (2001)	UK/USA/Canada	RCT, double-blind	*N = 386;* 75; male 64%; Mild–Moderate AD (NINCDS-ADRDA)	Dose escalation of galantamine from 8 to 24–32 mg (individual case) or placebo daily, 12 weeks	ADAS-cog, CIBIC+, ADL	Improvement in cognitive measures
Park H. et al. (2019)	South Korea	RCT, double-blind	*N = 90;* 61; male 33.3%; MCI (Petersen criteria)	*Panax ginseng* powder 3 g/day or placebo, 24 weeks	MMSE, IADL, LVT, RCFT	Safe; Improvement of RCFT and RCFT 20-min delayed recall

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TABLE 1 (Continued)

References	Country	Study design	Sample (Number of subjects, mean age (years), male (%), health status)	Intervention type, dose, and duration	Cognitive tasks	Outcome
Shin et al. (2009)	South Korea	RCT, double-blind	*N = 58;* 67; male 18%; MCI[a]	*Polygala tenuifolia* Willdenow extract (BT-11) 300 mg or placebo daily, 8 weeks	MMSE, CERAD	Improvement of CERAD
Lee et al. (2020)	South Korea	RCT, double-blind	*N = 53;* 60; male 23%; Subjective/MCI[a]	PhytoMeal (desalted *Salicornia europaea L.*)-ethanol extract 600 mg or placebo daily, 12 weeks	ADAS-cog	Safe; Improvement of frontal executive function in the patients with MCI.
Thal et al. (1999)	USA	RCT, double-blind	*N = 475;* 72; male 45%; Mild–Moderate AD (NINCDS-ADRDA)	Controlled release physostigmine 30 or 36 mg or placebo daily, 24 weeks	ADAS-cog, CIBIC, CGIC	Improvement of ADAS-cog and CIBIC+; No significant difference on CGIC; Adverse events: nausea, vomiting, diarrhea, anorexia, dyspepsia, and abdominal pain
Lee et al. (2013)	Malaysia	RCT, double-blind	*N = 36;* 66; male 20%; MCI[a]	DHA 1.3 g or 0.45 g eicosapentaenoic acid (EPA) placebo, 52 weeks	MMSE, CDT, GDS, RAVLT, VR, WMS-R	Safe and well tolerated; Improvement in short-term, working memory, immediate verbal memory, and delayed recall capability.
Rasi Marzabadi et al. (2022)	Iran	RCT, double-blind	*N = 60;* 75; male 22%; Mild–Moderate AD (NINCDS-ADRDA)	*Crocus sativus* L. 30 mg/day or donepezil 30 mg/day, 12 weeks	MMSE	No significant difference between two groups; Reduce inflammation and oxidative stress in treatment group
Schneider et al. (2005)	USA	RCT, double-blind	*N = 410;* 68; male 46%; Dementia (NINCDS-ADRDA)	*Ginkgo biloba* extract 120 mg or 240 mg, or placebo daily, 26 weeks.	ADAS-cog	Improvement in subgroup of patients with neuropsychiatric symptoms
Farokhnia et al. (2014)	Iran	RCT, double-blind	*N = 64;* 77; male 55%; Moderate–Severe AD (DSM-IV)	*Crocus sativus* L. 30 mg/day or memantine 20 mg/day, 52 weeks	MMSE, SCIRS, FAST	No significant difference between two groups
Raskind et al. (2000)	USA	RCT, double-blind	*N = 636;* 75; male 38%; Mild–Moderate AD (NINCDS-ADRDA)	Galantamine from 24, 32 mg or placebo daily, 26 weeks	ADAS-cog, CIBIC+	Improvement in cognitive measures
Mazza et al. (2006)	Italy	RCT, double-blind	*N = 76;* 68; male 46%; Mild–Moderate dementia (DSM-IV)	*Ginkgo biloba* 160 mg/day, donepezil 5 mg/day or placebo, 24 weeks	MMSE, SKT, CGI (item 2)	Improved cognitive function; No differences in the efficacy of EGb 761 and donepezil
Farlow et al. (2019)	USA	RCT, double-blind	*N = 141;* 71; male 49%; Moderate–Severe AD[a]	7 intravenous infusion (45 ± 5min) doses of Bryostatin 24 μg, 48 μg, first 2 doses (week 0, and 1), and 20 μg, 40 μg last 5 doses (week 3, 5, 7, 9, and 11), or placebo, 12 weeks	SIB	Safe; Improvement of SIB
Rafii et al. (2011)	USA	RCT, double-blind	*N = 210;* 72; male 45%; Mild–Moderate AD (NINCDS-ADRDA)	Huperzine A 200 μg or 400 μg or placebo daily, 16 weeks	ADAS-cog, MMSE, NPI	No improvement of ADAS-cog (200 μg); Improvement of ADAS-cog (400 μg)
Noguchi-Shinohara et al. (2020)	Japan	RCT, double-blind	*N = 23;* 72; male 52.17%; Mild AD (NIA-AA)	*Melissa officinalis* one capsule (500 mg rosmarinic acid) or placebo daily, 24 weeks	ADAS-cog, MMSE, CDR, DAD, NPI-Q	No improvement in cognitive measures; Improvement of NPI-Q
Noguchi-Shinohara et al. (2023)	Japan	RCT, double-blind	*N = 323;* 71; male 45%; Subjective/MCI (DSM-V)	*Melissa officinalis* one capsule (500 mg rosmarinic acid) or placebo daily, 96 weeks	ADAS-cog, MMSE, CDR-SB	No improvement in cognitive measures; May help prevent cognitive decline in older adults without hypertension

(Continued)

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TABLE 1 (Continued)

References	Country	Study design	Sample (Number of subjects, mean age (years), male (%), health status)	Intervention type, dose, and duration	Cognitive tasks	Outcome
Le Bars et al. (1997)	USA	RCT, double-blind	*N* = 327; 68; male 46%; AD and multi-infarct dementia (DSM-III-R)	EGb 120 mg/day or placebo, 52 weeks	ADAS-cog, GERRI, CGIC	Improvement of ADAS-cog and GERRI
Le Bars et al. (2002)	USA	RCT, double-blind	*N = 236;* 68; male 42%; AD and multi-infarct dementia (DSM-III-R)	EGb 120 mg/day or placebo, 52 weeks	ADAS-cog, GERRI	Improvement of ADAS-cog and GERRI
Tariot et al. (2000)	USA	RCT, double-blind	*N = 978;* 77; male 64%; Mild/Moderate AD (NINCDS-ADRDA)	Galantamine of 8, 16, 24 mg or placebo daily, 22 weeks	ADAS-cog, CIBIC+	Improvement in cognitive measures
Ihl et al. (2011)	Germany	RCT, double-blind	*N = 410;* 65; male 32%; Mild–Moderate AD with neuropsychiatric (NINCDS-ADRDA)	EGb 240 mg or placebo daily, 24 weeks	ADCS-ADL CGIC, SKT, NPI, DEMQOL-Proxy, Verbal Fluency Test	Improvement of SKT and NPI
Turner et al. (2015)	USA	RCT, double-blind	*N = 119;* 71; male 54%; Mild–Moderate AD (NINCDS-ADRDA)	500 mg (QAM), 1,000 mg (500 mg BID), 1,500 mg (1,000 mg QAM, 500 mg QPM), 2000 mg (1,000 mg BID) Resveratrol dose escalation every 13 weeks or placebo, 52 weeks.	MMSE, CDR, ADAS-cog, NPI	Safe and well tolerated; No significant difference in cognitive measures between groups
Akhondzadeh et al. (2003a)	Iran	RCT, double-blind	*N = 35;* 73; male 57% Mild–Moderate AD (NINCDS-ADRDA) criteria	*Melissa officinalis* (at least 500 mg citral/ml) extract 60 drops/day or placebo 60 drops/day; 16 weeks	ADAS-cog, CDR-SB	Safe; Improvement of ADAS-cog, CDR-SB
Akhondzadeh et al. (2003b)	Iran	RCT, double-blind,	*N = 30;* 72; male 61%; Mild–Moderate AD (NINCDS-ADRDA)	*Salvia officinalis* extract 60 drops / day or placebo drop 60 drops / day, 16 weeks	ADAS-cog, CDR-SB	Safe; Improvement of ADAS-cog, and CDR-SB
Akhondzadeh et al. (2010a)	Iran	RCT, double-blind	*N = 44;* 72; male 54%; Mild–Moderate AD (DSM-IV and NINCDS-ADRDA)	Capsule *Crocus sativus L.* (Saffron) 30 mg / day (15 mg twice per day) or capsule of placebo (two capsules per day); 16 weeks	ADAS-Cog, CDR-SB	Safe; Improvement of ADAS-cog, and CDR-SD
Akhondzadeh et al. (2010b)	Iran	RCT, double-blind	*N = 54;* 73; Mild–Moderate AD (DSM-IV and NINCDS-ADRDA)	*Crocus sativus* 30 mg or donepezil 10 mg daily, 22 weeks	ADAS-cog, CDR-SB	No significant difference in cognitive measures between groups; Adverse event: vomiting in donepezil group
Erkinjuntti et al. (2002)	Finland	RCT, double-blind	*N = 592;* 75; male 53%; Mild–Moderate vascular Dementia (NINCDS-ADRDA and NINDS-AIREN)	Galantamine 24 mg or placebo daily, 26 weeks	ADAS-cog, CIBIC+	Improvement in cognitive measures
Tsolaki et al. (2016)	Greece	RCT, single-blind	*N = 35;* 70; male 25%; amnesic and multi domain MCI (Petersen and Winblad criteria)	*Crocus sativus*, 52 weeks[c]	GDS, FRSSD, NPI, MoCA, MMSE	Improvement of MMSE
Tsolaki et al. (2020)	Greece	RCT, double-blind	*N = 50;* 69; male 30%; MCI (Petersen criteria)	Greek High Phenolic Early Harvest Extra Virgin Olive Oil 50 mL/day, Moderate Phenolic 50 mL/day, Mediterranean Diet, 52 weeks	MMSE, ADAS-cog	Improvement in cognitive function

(Continued)

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TABLE 1 (Continued)

References	Country	Study design	Sample (Number of subjects, mean age (years), male (%), health status)	Intervention type, dose, and duration	Cognitive tasks	Outcome
Muangpaisan et al. (2022)	Thailand	RCT, double-blind	*N = 102;* 77; male 31%; AD (DSM-IV-TR and NINCDS-ADRDA)	Mangosteen pericarp 4 to 8 mg/kg, 220 mg (≤ 55 kg), 24 weeks; 280 mg (> 55 kg), first 12 weeks, and 560 mg, last 12 weeks, or placebo daily, 24 weeks	ADAS-cog, ADCS-ADL, NPI-Q, CDR-SB	Safe and well tolerated; Improvement of ADAS-cog (low-dose); Reduced oxidative stress
Wang et al. (2018)	China	RCT[d]	*N = 42;* 75; male 30%; AD (NINCDS-ADRDA)	Spore Powder of *Ganoderma Lucidum* (SPGL); 4 capsules of 1,000 mg (250 mg/capsule) or placebo each time, 3 times daily, and 7 days weekly for a total of 6 weeks	ADAS-cog, WHOQOL-BREF, NPI	Safe and well tolerated; No improvement in cognitive measures
Freund-Levi et al. (2008)	Sweden	RCT, double-blind	*N = 204;* 74; male 55%; AD with AChEIs treatment (DSM-IV)	1.7 g DHA and 0.6 g EPA or placebo daily, 26 weeks	NPI, DAD, MADRS	Improvement of NPI in *APOE4* carriers and of MADRS in non-*APOE4* carriers
You et al. (2021)	Malaysia	RCT, double-blind	*N = 48;* range 60 to 75; MCI (Petersen criteria)	*Cosmos caudatus* 500 mg or placebo, daily, 12 weeks	MMSE	Improvement of MMSE
Xu et al. (2012)	China	RCT, double-blind	*N = 78;* 72; male 65%; Mild–Moderate vascular Dementia (DSM-IVR and NINDS-AIREN)	Huperzine A 0.1 mg (BID) or placebo (Vitamin C 100 mg BID), 12 weeks	MMSE, CDR, ADL	Improvement in cognitive measures
Chatzikostopoulos et al. (2024)	Greece	RCT[d]	*N = 80;* 69; male 44%; MCI (DSM-V)	5 drops of Pomegranate Seed Oil or Mediterranean Diet, 52 weeks	MMSE, MoCA, RAVLT, ROCFT, ADAS-cog, TMT B, FUCAS	Improvement of ADAS-cog, RAVLT and TMT B
Fernando et al. (2023)	Sri Lanka	RCT, double-blind	*N = 84;* 73; male 34%; Mild–Moderate AD (NINCDS/ADRDA)	30 mL Virgin Coconut oil or Canola oil (Control) daily, 24 weeks	MMSE, CLOX	No significant differences in cognitive scores. MMSE scores improved among *APOE* ε4 carriers.

ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADAS-noncog, Alzheimer's Disease Assessment Scale-Noncognitive Subscale; ADCS-ADL, Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory 23 - item Scale; CDR-SB, Clinical Dementia Rating Scale – Sums of Boxes; CDR, Clinical Dementia Rating, CDT, Clock Drawing Test; CERAD, Consortium to Establish a Registry for Alzheimer's Disease Assessment Packet; CFT, Category Fluency Test; CGI (item 2), Clinical Global Impression; CGIC, Clinical Global Impression of Change; CIBIC, Clinician Interview-Based Impression of Change with Caregiver Input; CLOX, Clock Drawing Task; DAD, Disability Assessment for Dementia; DEMQOL, Dementia Quality of Life; FAST, Functional Assessment Staging; FRSSD, Functional Rating Scale of Symptoms of Dementia; FUCAS, Functional Cognitive Assessment Scale; GAI, Geriatric Anxiety Inventory; GDS, Geriatric Depression Scale; GERRI, Geriatric Evaluation by Relative's Rating Instrument; IADL, Instrumental Activities of Daily Living; MADRS, Montgomery-Asberg Depression Rating Scale; MCI, Mild Cognitive Impairment; MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment; NIA-AA, National Institute on Aging - Alzheimer's Association Workgroup; NPI, Neuropsychiatric Inventory; PSQI, Pittsburgh Sleep Quality Index; RAVLT, Rey Auditory Verbal Learning Test; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; RCFT, Rey Complex Figure Test; SCAG, Sandoz Clinical Assessment - Geriatric; ROCFT, Rey-Osterrieth Complex Figure Test; SCIRS, Severe Cognitive Impairment Rating Scale; SDI, Sleep Disorders Inventory; SIB, Severe Impairment Battery; SKT, Syndrom Kurz test; TMT B, Trail Making Test Part B; VFT, Verbal Fluency Test; VLT, Verbal Learning Test; VR, visual reproduction; WAIS-III, Wechsler Adult Intelligence Scale - III; WATR, Wechsler Test of Adult Reading; WCST-64, Wisconsin Card Sorting Test - 64; WHO-5, World Health Organization 5 Well-Being Index; WHOQOL-BREF, World Health Organization Quality of Life questionnaire; WMS-IV, Memory Scale Fourth Edition; WMS-R, Wechsler Memory Scale – Revised.

[a] Diagnosed, hospitalized, nursing, or cognitive deficit and/or personality change present for at least 6 months, as observable by a physician and/or close contact of the patient, in combination with MMSE, SKT, or CERAD.

[b] Recruited through ADCS.

[c] Dosage not specified.

[d] Blind procedure not reported.

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Galantamine ($N = 5$; Erkinjuntti et al., 2002; Raskind et al., 2000; Rockwood et al., 2001; Tariot et al., 2000; Wilcock et al., 2000), and Resveratrol ($N = 1$; Turner et al., 2015). Bryostatin was intravenously infused seven times over a 12-week period, with dosages of either 24 μg twice and 20 μg five times or 48 μg twice and 40 μg five times, and the mean infusion time was 45 ± 5 min. For DHA supplementation, Quinn et al. (2010) used algae-derived DHA without eicosapentaenoic acid (EPA) at 2 g/day, whereas Lee et al. (2013) and Freund-Levi et al. (2008) utilized fish-derived DHA containing EPA, supplementing participants with 1.3 g DHA plus 0.45 g EPA/day and 1.7 g DHA pluls 0.6 g EPA/day, respectively.

Huperzine A was administered at dosages of 0.1 mg, 0.2 mg, or 0.4 mg/day. Galantamine dosages ranged from 8 mg to 32 mg/day, with 24 mg/day being the most frequently used dosage. Resveratrol was administered with an escalating dosage ranging from 500 mg to 2,000 mg/day.

All studies included in the analysis employed a RCT design. Among these, one study implemented a single-blind procedure (Tsolaki et al., 2016), and two studies did not report a blinding procedure (Chatzikostopoulos et al., 2024; Wang et al., 2018). The remaining studies were conducted with double-blinding. Most studies adhered to well-designed case–control methodologies in accordance with predefined inclusion criteria and provided comprehensive descriptions of their objectives, definitions, and methodologies.

While all studies aimed to investigate the effects of natural compounds or extracts on cognitive health, there were variations in the selection of control groups. Specifically, 37 studies utilized isoenergetic placebos as the control intervention, whereas four studies employed commonly prescribed drugs. For instance, Rasi Marzabadi et al. (2022), Akhondzadeh et al. (2010a), and Mazza et al. (2006) used donepezil as the control intervention to compare its effects with those of *Crocus sativus* or *Ginkgo biloba* extract. Farokhnia et al. (2014) used memantine as the control intervention to compare its effects with *Crocus sativus* L. One study on *Olea europaea L.* (Kaddoumi et al., 2022) used refined olive oil as the control to compare with extra-virgin olive oil, while other studies on *Olea europaea L.* and *Punica granatum* employed the Mediterranean diet as the control intervention (Chatzikostopoulos et al., 2024; Tsolaki et al., 2020). Additionally, Fernando et al. (2023) utilized canola oil as the control intervention to compare its effects with those of virgin coconut oil. These methodological considerations, including blinding procedures and the selection of appropriate control groups, were meticulously implemented to ensure the robustness and validity of the findings regarding the impact of natural compounds and extracts on cognitive health.

3.3 Study quality

The quality of the included RCTs was assessed using the Cochrane Risk of Bias tool. Of the 35 studies included in the meta-analysis, 25 exhibited a low risk of bias in randomization, 8 raised some concerns, and 1 was rated as high risk (Figure 2). Deviation from intended interventions showed low risk in 31 studies, while 4 raised concerns.

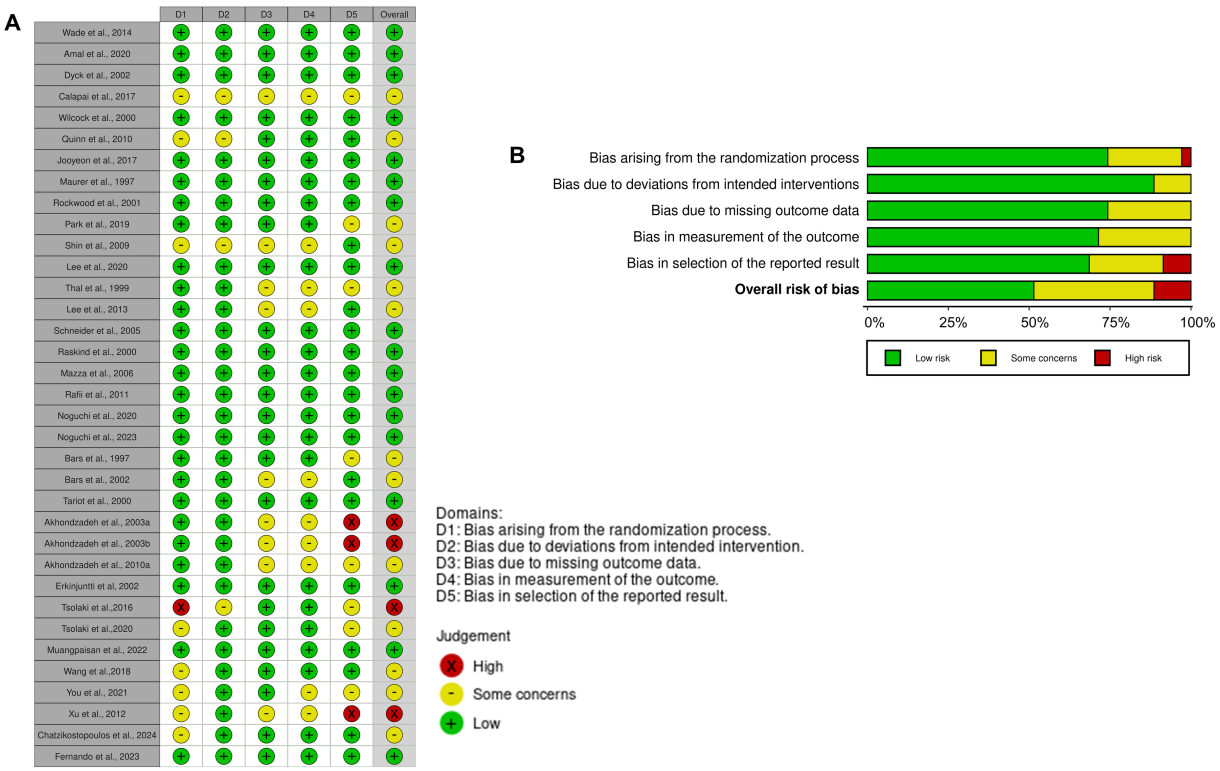

FIGURE 2
Risk of bias evaluation using Cochrane ROB2. Illustration **(A)** presents the outcomes of bias assessment as per the Cochrane framework, while Illustration **(B)** summarizes these findings. RoB2, *Revised Cochrane risk-of-bias tool for RCTs*.

Regarding missing outcome data, 27 studies were rated as low risk and 9 as having some concerns. Outcome measurement risk was low in 25 studies, with 10 raising concerns. Finally, selection bias for reported results was rated low in 24 studies, with 8 raising some concerns and 3 being high risk.

Overall, 18 studies were deemed to have low risk, 13 presented some concerns, and 4 demonstrated high risk of bias (Figure 2). These assessments provided a robust foundation for interpreting the results of the meta-analysis.

3.4 Key results from the studies encompassed in the systematic review

Table 1 displays all 45 studies included in the cognitive analysis. Of these, 34 studies reported trends toward cognitive improvement with supplement use, four studies found no significant differences between supplements and commonly prescribed drugs (donepezil, memantine), and seven studies observed no improvement in cognitive measures.

3.4.1 Primary findings from studies on natural extracts

Fernando et al. (2023) conducted a 24-week study involving patients with MCI who received 30 mL of virgin coconut oil (VCO) daily. While overall supplementation with VCO did not result in significant cognitive improvements, patients carrying the APOE ε4 allele exhibited enhanced MMSE scores compared to controls. The intervention was deemed safe, as lipid profiles and glycated hemoglobin levels remained stable. Similarly, administration of *Cosmos caudatus* for 12 weeks led to significant enhancements in cognitive and mood-related outcomes, including MMSE scores, tension, mood disturbance, and malondialdehyde levels. However, You et al. (2021) noted that the short duration and poor bioavailability of flavonoids might limit the biochemical effects of *Cosmos caudatus*.

Several studies on *Crocus sativus* L. (also known as saffron) reported cognitive benefits. Notably, one-year supplementation resulted in magnetic resonance imaging (MRI)-detected structural changes in the left inferior temporal gyrus, potentially linked to improved cognitive function. Electroencephalogram (EEG) assessments revealed shorter P300 latencies, indicating enhanced cognitive processing speed. In a trial by Akhondzadeh et al. (2010a), saffron supplementation for up to 16 weeks improved attention, memory, and visual-motor coordination in patients with mild-to-moderate AD, as evidenced by higher scores on the ADAS-Cog and clinical dementia rating sum of boxes (CDR-SB). Conversely, Farokhnia et al. (2014) compared *Crocus sativus* with memantine in moderate-to-severe AD patients over one year. Both treatments attenuated cognitive decline, with saffron effectively reducing behavioral and psychological symptoms of dementia. The intervention was well-tolerated, with only mild, self-limiting gastrointestinal symptoms, dizziness, and headaches reported. In contrast, supplementation with *Ganoderma lucidum* did not yield significant cognitive or quality of life improvements over a six-week period in a study involving 42 AD patients, likely due to the short intervention duration and small sample size. On the other hand, *Garcinia mangostana L.* supplementation for up to 24 weeks demonstrated significant improvements in ADAS-cog scores and reductions in the oxidative stress biomarker 4-hydroxynonenal in a low-dose group, with the intervention being well-tolerated (Muangpaisan et al., 2022).

Ginkgo biloba has been extensively studied, yielding mixed results. Schneider et al. (2005) found no significant difference in ADAS-cog scores between the treatment and placebo groups after 52 weeks in patients with mild-to-moderate AD. However, at the 26-week mark, clinician's interview-based impression of change plus (CIBIC+) scores improved significantly in the treatment group. Le Bars et al. (1997) reported improvements in ADAS-Cog score and the Geriatric evaluation by relative's rating instrument (GERRI) in *Ginkgo biloba*-treated subjects compared to placebo. Additionally, Herrschaft et al. (2012) demonstrated that *Ginkgo biloba* improved cognition, psychopathology, functional measures, and quality of life in patients with mild-to-moderate dementia, including AD and vascular dementia, over a 24-week period. The supplementation of *Ginkgo biloba* in older adults warrants caution due to its potential to increase bleeding risk when combined with anticoagulants or antiplatelet agents (Ke et al., 2021) and to disrupt blood glucose regulation in diabetic patients with AD (Kudolo, 2001). Consequently, caregivers contemplating the use of natural products or extracts are strongly advised to seek guidance from healthcare professionals. Furthermore, healthcare providers should thoroughly assess the potential adverse effects of such supplements before recommending them, particularly in the clinical management of individuals with MCI or AD who often present with complex comorbidities.

Melissa officinalis (also known as lemon balm) supplementation showed cognitive benefits in AD patients. A 16-week study administering 500 μg per day improved ADAS-cog and CDR-SB scores and reduced agitation in patients with mild-to-moderate AD. Longer trials (96 weeks) with 500 mg of rosmarinic acid per day suggested potential preventative effects on cognitive decline in non-hypertension subjects. Tsolaki et al. (2020) investigated high-phenolic and moderate-phenolic extra-virgin olive oil (EVOO) and reported significant improvements in most cognitive domains compared to a Mediterranean diet. Complementary studies have linked EVOO consumption to reduced blood–brain barrier permeability in brain regions associated with memory and cognitive performance (Kaddoumi et al., 2022).

In Korean subjects with MCI, six months of *Panax ginseng* supplementation improved visual memory (Park H. et al., 2019). *Polygala tenuifolia* extract enhanced word recognition and recall and improved the overall scores in a mental cognitive test battery in aging adults, showing effects comparable to placebo (Shin et al., 2009; Wang et al., 2019). *Punica granatum* seed oil supplementation over 52 weeks benefited cognitive functions, as indicated by ADAS-Cog and memory tests, with pre- to post-treatment improvements in processing and executive functions in the MCI group (Chatzikostopoulos et al., 2024).

Additional interventions included *Vitis vinifera*, which improved cognitive and mood scores over 12 weeks in elderly individuals (Calapai et al., 2017), and *Vaccinium* (blueberry) supplementation in MCI, which was associated with increased activation in brain regions involved in memory (Boespflug et al., 2018). A phase II study on Bryostatin reported no overall significant effect on severe impairment battery (SIB) scores; however, there were positive cognitive trends in completers at 20 μg (7 doses/12 weeks), although higher doses led to dropouts due to adverse events (Farlow et al., 2019).

DHA supplementation yielded varied outcomes. Quinn et al. (2010) did not observe a reduction in the rate of cognitive decline in AD patients, whereas Lee et al. (2013) found that fish-derived DHA containing EPA enhanced short-term and working memory in elderly subjects with MCI. Freund-Levi et al. (2008) reported that DHA supplementation in AD patients decreased agitation and depression independent of cognitive improvement. Collectively, these studies suggest that various natural supplements may offer symptomatic and cognitive benefit in both MCI and AD.

3.4.2 Major findings of studies on natural compounds

Recent trials have explored diverse pharmacological approaches to address cognitive decline in both AD and vascular dementia. Huperzine A has shown significant potential as a cognitive enhancer. A 16-week phase II trial in patients with mild-to-moderate AD demonstrated its safety and tolerability, with statistically significant cognitive improvements compared to placebo as measured by the MMSE and ADAS-cog (Rafii et al., 2011). Similarly, a 12-week study on vascular dementia patients revealed significant cognitive enhancements on the MMSE, Clinical Dementia Rating (CDR), and Activities of Daily Living (ADL) scales, with greater gains observed in the treatment group (Xu et al., 2012). Gastrointestinal symptoms, including nausea, vomiting, and diarrhea, were the most commonly reported adverse events, though they were generally mild and transient.

Prolonged-release melatonin (PRM) has also emerged as a promising add-on therapy for AD. Wade et al. (2014) found that PRM significantly improved cognitive performance, as evidenced by MMSE and Instrumental Activities of Daily Living (IADL) scores, and enhanced sleep quality based on the Pittsburgh Sleep Quality Index. These effects were particularly notable in patients with comorbid insomnia, who exhibited clinically meaningful improvements in cognition and sleep efficiency compared to placebo. PRM was well-tolerated, with an adverse event profile comparable to the placebo group (Wade et al., 2014).

Physostigmine has been evaluated for cognitive enhancement in mild-to-moderate AD with mixed outcomes. van et al. (2000) reported significant improvements in ADAS-cog and Clinician's Interview-Based Impression of Change Plus (CIBIC+) scores, but no benefits were observed in secondary outcomes such as the Clinical Global Impression of Change (CGIC). Additionally, gastrointestinal side effects, including nausea and vomiting, were prevalent, affecting 47% of participants and limiting its usability. Similarly, Thal et al. (1999) observed significant cognitive and behavioral improvements with controlled-release physostigmine but noted high dropout rates due to adverse gastrointestinal effects, such as nausea, diarrhea, and dyspepsia. Despite these limitations, both studies indicated an acceptable safety profile, with no cardiac rhythm disturbances or liver function abnormalities reported.

Galantamine, a cholinesterase inhibitor, has consistently demonstrated robust efficacy in improving cognitive and functional outcomes in AD across multiple studies. Rockwood et al. (2001) reported superior cognitive performance ADAS-cog and global response rates (CIBIC+) compared to placebo over three months, with fewer patients experiencing cognitive decline. Galantamine also enhanced both basic and instrumental ADL while maintaining a favorable tolerability profile, with gastrointestinal symptoms being the most frequent but generally mild. Long-term efficacy was confirmed in studies by Raskind et al. (2000) and Wilcock et al. (2000), which demonstrated sustained improvements in cognition, daily functioning, and clinician-rated impressions of change over six months. Notably, slow dose escalation strategies improved tolerability and reduced adverse events. These findings underscore the therapeutic potential of galantamine in managing AD symptoms.

Resveratrol, a naturally occurring polyphenol, has produced less definitive clinical outcomes. In a year-long trial involving AD patients, Turner et al. (2015) observed no statistically significant effects on AD biomarkers or cognitive function. However, trends toward reductions in cerebrospinal fluid (CSF) Aβ40 levels and increases in the Aβ40/Aβ42 ratio suggested potential effects on amyloid deposition. Resveratrol was generally well-tolerated, with no significant differences in adverse events between treatment and placebo groups. The study's limited sample size and duration, however, constrained the generalizability of its findings.

In summary, Huperzine A, PRM, physostigmine, and galantamine have demonstrated varying degrees of efficacy as cognitive enhancers in AD and vascular dementia, with galantamine emerging as a particularly promising option due to its sustained benefits and tolerability. While resveratrol holds theoretical potential, its clinical utility remains inconclusive, necessitating further investigation into its long-term effects and mechanisms of action.

3.5 Meta-analyses

The cognitive assessments employed in the included studies utilized a variety of tools, such as the ADAS-cog, MMSE, CDR-SB, Disability Assessment for Dementia, Functional Rating Scale of Symptoms of Dementia, and Geriatric Depression Scale (Table 1). However, not all of these measures were incorporated into the subsequent meta-analyses.

To assess the overall effect size, the meta-analysis also conducted subgroup analyses to examine the impact of distinct categories, including natural extracts, natural compounds, and specific compound classes such as terpenoids, phenols, and alkaloids (Figures 3–6). However, due to limited data availability, more granular subgroup analyses focusing on specific plant structural extracts (Supplementary Figures S1, S2) and hormonal compounds (Figures 5, 6) could not sufficiently explore variations arising from study designs and participant characteristics. Consequently, these findings must be interpreted with caution and in consideration of the underlying limitations.

As summarized in Table 1, 25 studies provided sufficient data for meta-analysis using the ADAS-cog, a widely recognized neuropsychological tool for evaluating cognitive severity in dementia (Akhondzadeh et al., 2003a, 2003b; Akhondzadeh et al., 2010a; Akhondzadeh et al., 2010b; Chatzikostopoulos et al., 2024; Erkinjuntti et al., 2002; Le Bars et al., 1997; Le Bars et al., 2002; Lee et al., 2017; Lee et al., 2020; Maurer et al., 1997; Muangpaisan et al., 2022; Noguchi-Shinohara et al., 2023; Noguchi-Shinohara et al., 2020; Quinn et al., 2010; Rafii et al., 2011; Raskind et al., 2000; Rockwood et al., 2001; Schneider et al., 2005; Tariot et al., 2000; Thal et al., 1999; Tsolaki et al., 2020; van et al., 2000; Wade et al., 2014; Wang et al., 2018; Wilcock et al., 2000). Additionally, 19 studies provided sufficient data for meta-analysis using the MMSE, a commonly used

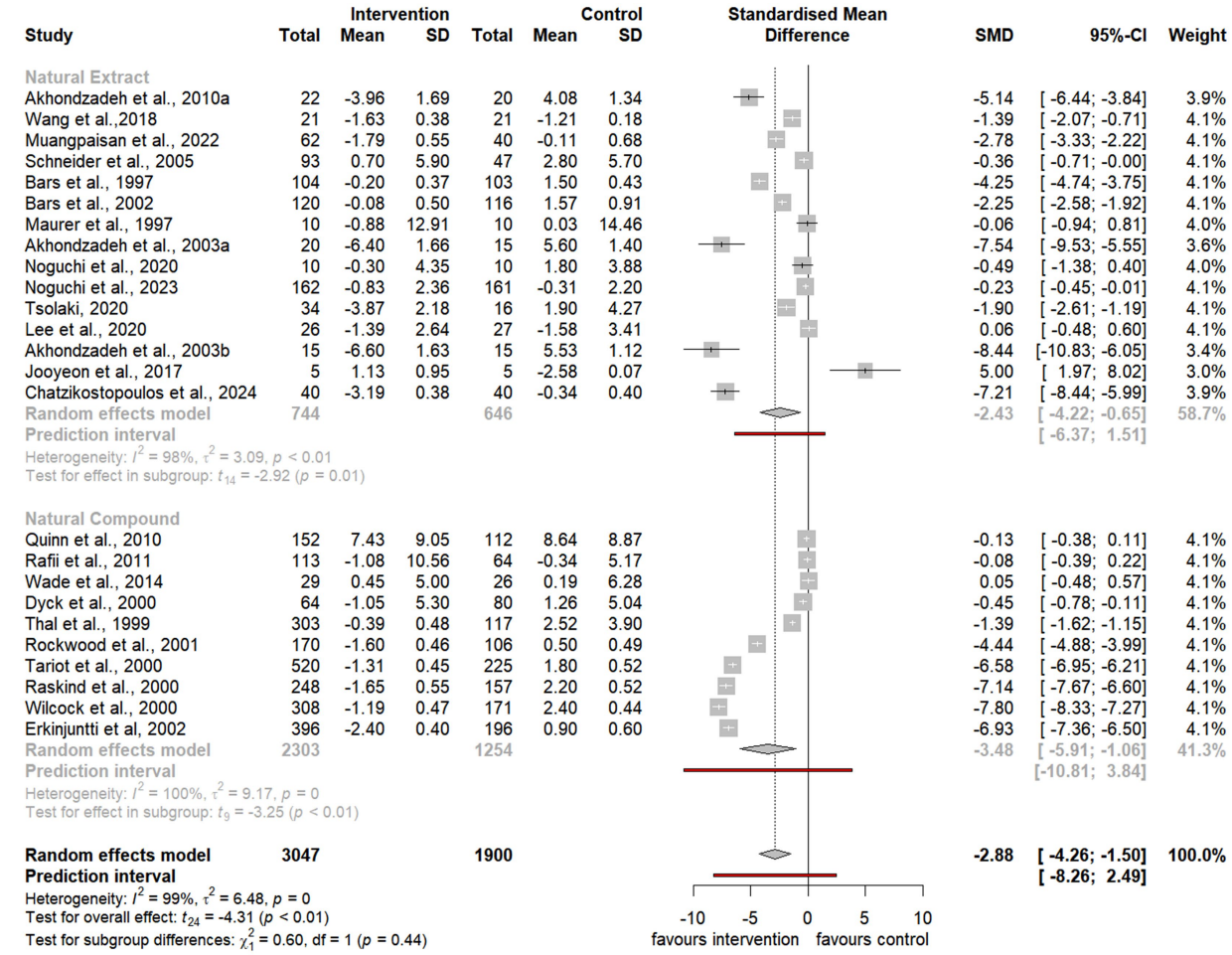

FIGURE 3
Forest plot for effect of natural compound/extract intervention studies assessing ADAS-cog classified by type of supplementation. ADAS-cog, *Alzheimer Disease Cooperative Study-Activities of Daily Living Scale*.

tool to evaluate cognitive impairment in clinical and research contexts (Calapai et al., 2017; Chatzikostopoulos et al., 2024; Fernando et al., 2023; Kaddoumi et al., 2022; Lee et al., 2017; Lee et al., 2013; Mazza et al., 2006; Noguchi-Shinohara et al., 2023; Noguchi-Shinohara et al., 2020; Park K. C. et al., 2019; Quinn et al., 2010; Rafii et al., 2011; Shin et al., 2009; Tsolaki et al., 2016; Tsolaki et al., 2020; van et al., 2000; Wade et al., 2014; Xu et al., 2012; You et al., 2021).

Notably, the meta-analysis identified a significant improvement in ADAS-cog scores among participants receiving natural extracts or compounds compared to controls (SMD = −2.88, 95% CI −4.26 to −1.50, $t_{24} = -4.31$, $p < 0.01$) (Figure 3). Similarly, MMSE scores showed significant improvement following interventions compared to controls (SMD = 0.76, 95% CI 0.06 to 1.46, $t_{18} = 2.27$, $p = 0.04$) (Figure 4).

Despite the observed heterogeneity, these findings suggest that natural extracts and compounds exert a significant and substantial effect on global cognitive function. However, the variability in effect sizes across individual studies indicates that these impacts may differ depending on the cognitive domain or compound characteristics.

To address the heterogeneity, additional subgroup and moderator analyses were conducted to investigate the influence of factors such as the type of natural extract, compound class (e.g., terpenoids, phenols, and alkaloids), and outcome measures on the observed cognitive improvements following intervention.

3.5.1 Subgroup analyses: effects of natural extracts and natural compounds

Subgroup analyses of natural extracts indicated a significant improvement in ADAS-cog scores following supplementation (SMD = −2.43, 95% CI −4.22 to −0.65, $t_{14} = -2.92$, $p = 0.01$) (Figure 3), although substantial heterogeneity was observed ($I^2 = 98\%$, $p < 0.01$). Additionally, there was a notable trend toward improvement in MMSE scores after supplementation (SMD = 0.65, 95% CI 0.04 to 1.26, $t_{12} = 2.31$, $p = 0.04$), also accompanied by significant heterogeneity ($I^2 = 91\%$, $p < 0.01$) (Figure 4).

Similarly, subgroup analyses of natural compounds demonstrated a significant improvement in ADAS-cog scores following supplementation, with a larger effect size (SMD = −3.48, 95% CI −5.91 to −1.06, $t_9 = -3.25$, $p < 0.01$) (Figure 3), albeit with considerable heterogeneity ($I^2 = 100\%$, $p = 0$). Furthermore, while there was a trend toward improvement in MMSE scores after supplementation, this was not statistically significant (SMD = 1.03, 95% CI −1.36 to 3.42, $t_5 = 1.11$, $p = 0.32$) and was accompanied by notable heterogeneity ($I^2 = 97\%$, $p < 0.01$) (Figure 4).

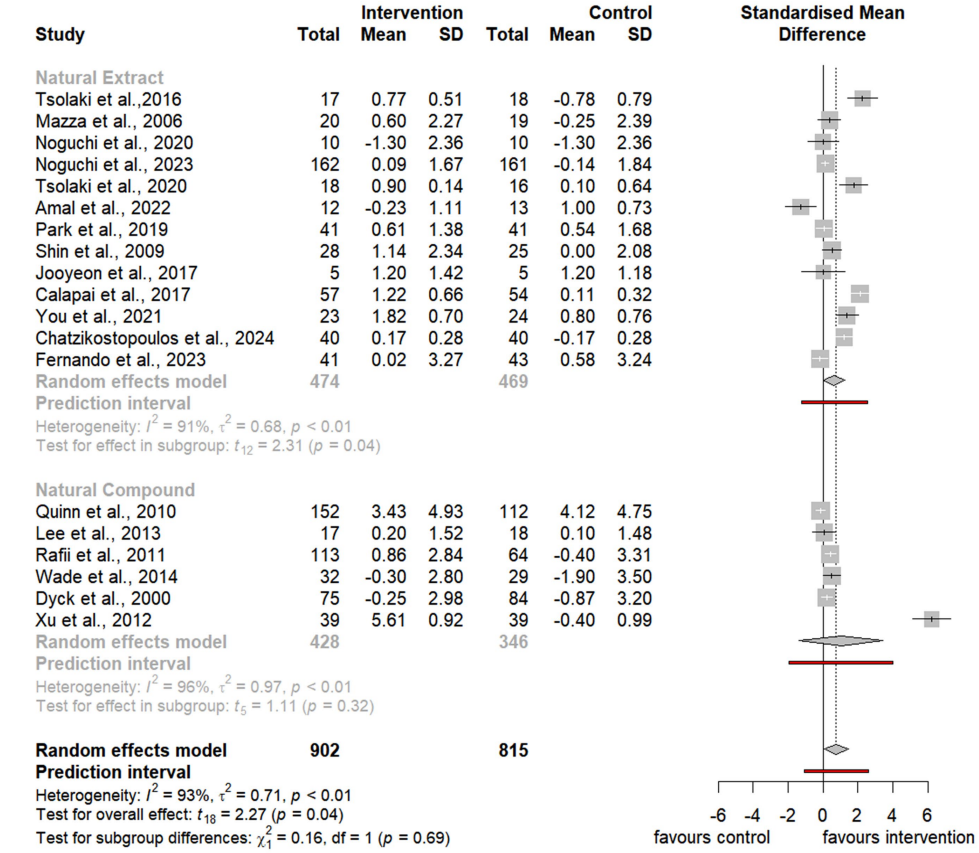

FIGURE 4
Forest plot for effect of natural compound/extract intervention studies assessing MMSE classified by type of supplementation. MMSE, *Mini Mental State Examination*.

3.5.2 Subgroup analyses: effects of terpenoids, phenols, and alkaloids

Subgroup analyses were conducted to evaluate the effects of terpenoids, phenols, and alkaloids. Natural extracts were classified based on the primary bioactive compound classes that have demonstrated efficacy in preclinical or clinical studies related to AD. However, it is essential to note that other bioactive compounds, beyond these primary classes, may also contribute to the observed health benefits. Therefore, the results of these subgroup analyses should be interpreted with caution and careful consideration.

Subgroup analyses focusing on terpenoids revealed a borderline significant improvement in ADAS-cog scores following supplementation (SMD = −2.20, 95% CI −4.34 to −0.06, t_5 = −2.65, p = 0.05) (Figure 5), although substantial heterogeneity was observed (I^2 = 98%, p < 0.01). Additionally, there was a trend toward improvement in MMSE scores after supplementation (SMD = 0.85, 95% CI −0.24 to 1.94, t_4 = 2.18, p = 0.10), also accompanied by significant heterogeneity (I^2 = 85%, p < 0.01) (Figure 6).

Similarly, subgroup analyses for alkaloids demonstrated a significant improvement in ADAS-cog scores following supplementation, with a larger effect size (SMD = −4.34, 95% CI −7.06 to −1.63, t_7 = −3.79, p < 0.01) (Figure 5). However, substantial heterogeneity was present (I^2 = 100%, p = 0). Furthermore, there was a trend toward improvement in MMSE scores, although it was not statistically significant (SMD = 2.14, 95% CI −6.19 to 10.46, t_2 = 1.10, p = 0.38), and notable heterogeneity was present (I^2 = 98%, p < 0.01) (Figure 6).

Last, subgroup analyses for phenols indicated a trend toward improvement in ADAS-cog scores following supplementation (SMD = −2.00, 95% CI −5.19 to 1.20, t_7 = −1.48, p = 0.18) (Figure 5). However, considerable heterogeneity was observed (I^2 = 96%, p < 0.01). Similarly, there was a trend toward improvement in MMSE scores, which was not statistically significant (SMD = 0.48, 95% CI −0.85 to 1.81, t_5 = 0.93, p = 0.39), with substantial heterogeneity (I^2 = 94%, p < 0.01) (Figure 6).

To evaluate potential publication bias, funnel plots (Supplementary Figures S3, S4) were generated to visually examine the distribution of effect sizes. The plots revealed a wide range of effect sizes. Further analysis using Egger's regression test indicated no significant publication bias (Supplementary Figures S5, S6). Specifically, funnel plots for studies assessing ADAS-cog scores displayed a symmetrical distribution (Supplementary Figure S3), and Egger's test confirmed the absence of publication bias (Supplementary Figure S5). For MMSE scores, the funnel plots showed an asymmetric distribution (Supplementary Figure S4), but Egger's regression test was non-significant (Supplementary Figure S6), suggesting no strong evidence of publication bias.

To address potential bias, the Trim-and-Fill method was applied. This adjustment did not significantly alter the findings, further

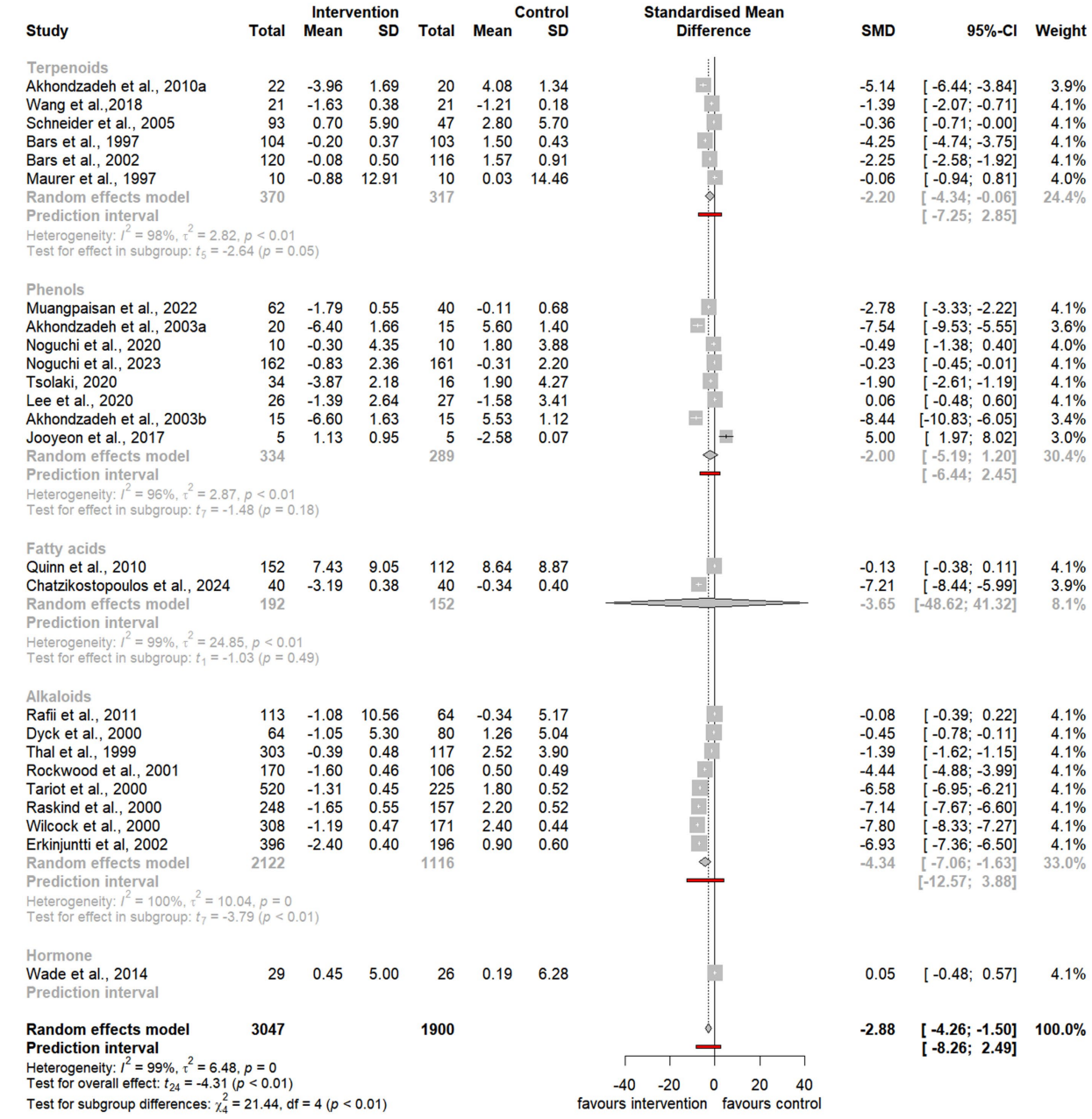

FIGURE 5
Forest plot for effect of natural compound/extract intervention studies assessing ADAS-cog classified by class of major compound(s). ADAS-cog, *Alzheimer Disease Cooperative Study-Activities of Daily Living Scale*.

supporting the robustness of the results despite the observed heterogeneity in the studies assessing ADAS-cog and MMSE outcomes.

4 Discussion

This systematic review comprehensively analyzed 43 studies evaluating the effects of various natural compounds and extracts, administered in forms such as powders and liquid capsules, as interventions for individuals with MCI or AD. Of these studies, 33 reported significant improvements in cognitive function, while 4 found no notable differences between the natural supplements and conventional pharmacological treatments. The accompanying meta-analysis revealed statistically significant improvements in ADAS-Cog scores in intervention groups compared to controls following supplementation with natural compounds or extracts. Furthermore, a borderline improvement was observed in MMSE scores.

These findings suggest that the analyzed natural compounds, particularly in powder form, may exhibit cognitive-protective properties, although they are unlikely to halt disease progression. The meta-analysis highlights the potential benefits of prolonged supplementation (≥6 weeks) with specific natural compounds or extracts for cognitive enhancement in individuals with MCI or AD. Notably, terpenoids and alkaloids demonstrated superior efficacy

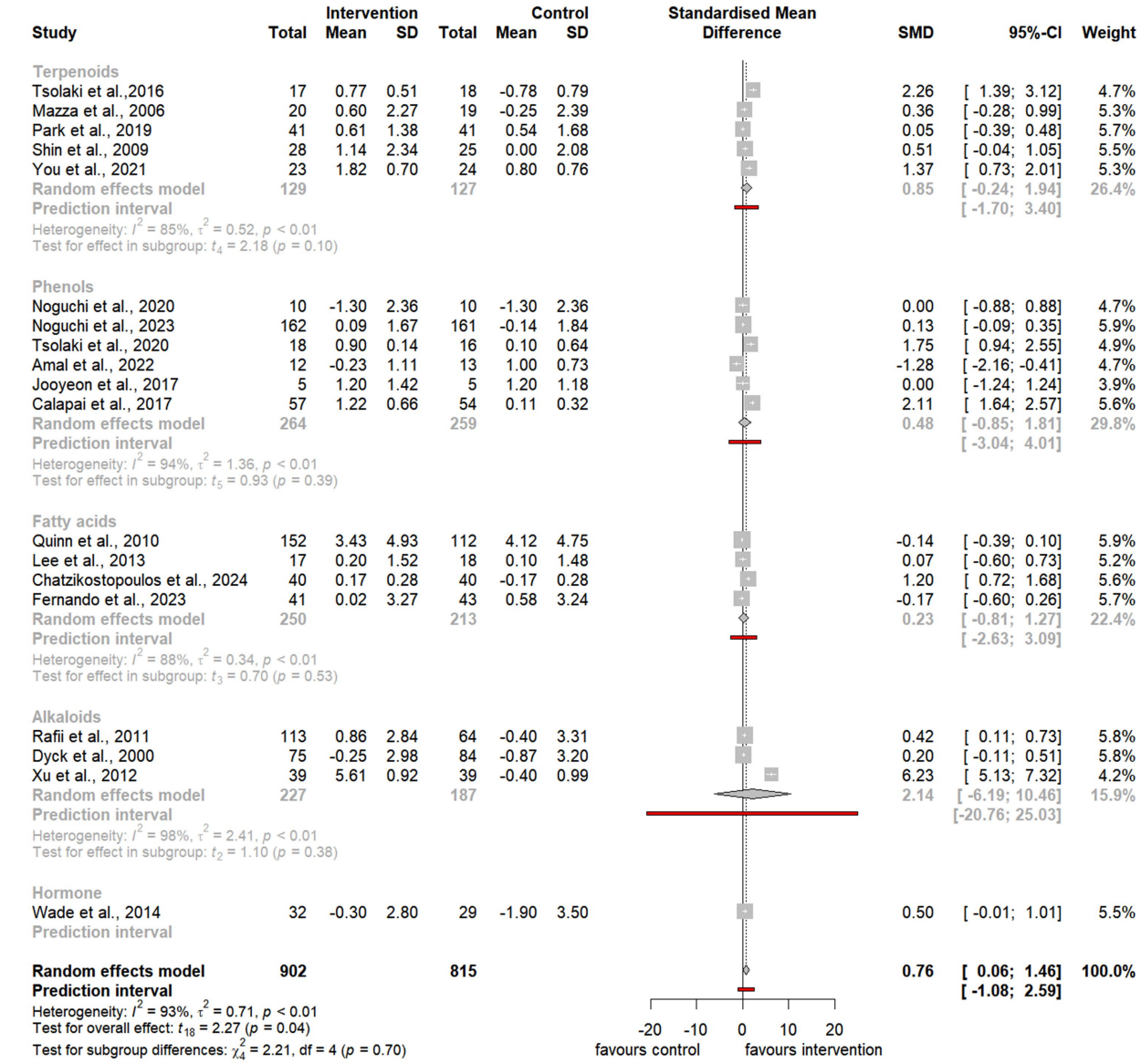

FIGURE 6
Forest plot for effect of natural compound/extract intervention studies assessing MMSE classified by class of major compound(s). MMSE, *Mini Mental State Examination*.

in improving global cognitive function compared to phenolic compounds.

4.1 Terpenoids

Terpenoids derived from a variety of natural sources, including *Ginkgo biloba*, *Crocus sativus* L. (saffron), ginseng, *Polygala tenuifolia* Willdenow (Polygala), *Ganoderma lucidum* (Reishi mushroom), and *Cosmos caudatus*, exhibit diverse neuroprotective properties and hold therapeutic potential for AD. In *Ginkgo biloba*, terpenoid components such as ginkgolides and bilobalide are recognized for their antioxidant and neuroprotective effects. Although some studies report modest cognitive benefits in AD patients, others find no significant effects. These inconsistencies may stem from variability in formulations, dosages, study designs, and patient-specific factors, including the stage of the disease (DeKosky et al., 2008; Herrschaft et al., 2012; Hofferberth, 1994; Ihl et al., 2011; Kanowski and Hoerr, 2003; Le Bars et al., 1997; Le Bars et al., 2002; Maurer et al., 1997; Mazza et al., 2006; Schneider et al., 2005; Shi et al., 2010; Snitz et al., 2009).

Saffron contains active compounds such as crocin, crocetin, and safranal, which demonstrate antioxidant, anti-inflammatory, and neuroprotective effects. Specifically, crocetin has been shown to modulate Aβ pathology, while safranal enhances cognitive function in preclinical AD models (Ahmad et al., 2023; Akhondzadeh et al., 2010a; Farokhnia et al., 2014; Finley and Gao, 2017; Pandey et al., 2020; Rasi Marzabadi et al., 2022; Tsolaki et al., 2016). Similarly, ginsenosides—the triterpene saponins found in ginseng—exhibit efficacy in improving cognitive function and mitigating AD-related pathologies through their antioxidant and anti-inflammatory

properties (Heo et al., 2012; Lee et al., 2008; Park H. et al., 2019; Wang et al., 2019). Tenuifolin, a triterpenoid saponin from *Polygala tenuifolia*, along with related compounds such as polygalasaponin F, has been associated with memory enhancement and neuroprotection by modulating neurotransmitter levels and reducing oxidative stress (Deng et al., 2020; Jia et al., 2004; Moratalla-López et al., 2019; Park H. et al., 2019). In *Ganoderma lucidum*, triterpenoids like ganoderic acids provide neuroprotective effects by attenuating neuroinflammation and oxidative stress, potentially leading to improved cognitive function in AD (Qi et al., 2021; Zheng et al., 2023). Overall, the diverse terpenoid compounds from these natural sources offer promising avenues for the development of therapeutic strategies targeting the multifaceted pathologies of AD.

4.2 Phenols

The bioactive constituents of *Cosmos caudatus* include flavonoids (e.g., quercetin and kaempferol), phenolic acids (e.g., caffeic acid), and carotenoids (e.g., β-carotene). These compounds exhibit antioxidant and neuroprotective properties, suggesting their potential in mitigating AD-related neurodegeneration, despite the limited specific research available (Wang et al., 2023). Phenolic compounds found in *Melissa officinalis* (lemon balm), *Olea europaea* (olive), *Garcinia mangostana* (mangosteen), *Salicornia europaea* (samphire), *Salvia officinalis* (sage), and *Vitis vinifera* (grape) further highlight their therapeutic potential. Rosmarinic acid in lemon balm has demonstrated both anti-inflammatory and neuroprotective effects (Petrisor et al., 2022). Compounds derived from olives, such as oleuropein, hydroxytyrosol, and oleocanthal, have shown efficacy in reducing oxidative stress and Aβ pathology while providing cognitive benefits in AD models (Abdallah et al., 2022; Abuznait et al., 2013; Nardiello et al., 2018). Xanthones from mangosteen, including α-mangostin and γ-mangostin, possess strong antioxidant and anti-inflammatory properties, and catechin flavonoids provide additional neuroprotection (Do and Cho, 2020; Pratiwi et al., 2022; Yang et al., 2021). *Salicornia europaea* contains phenolics and carotenoids, such as lutein, which may help reduce oxidative stress (Fitzner et al., 2021). Sage's phenolic compounds, including carnosic and ursolic acid, have been shown to improve cognitive function and memory while providing neuronal protection (Ghorbani and Esmaeilizadeh, 2017; Mirza et al., 2021; Yi-Bin et al., 2022). Compounds in grapes, particularly resveratrol, have been found to inhibit Aβ aggregation and neuroinflammation, along with providing additional antioxidant benefits through proanthocyanidins and flavonoids such as quercetin (Tabeshpour et al., 2018).

4.3 Alkaloids

Several alkaloids, including bryostatin, huperzine A, physostigmine, and galantamine, exhibit significant therapeutic potential. Bryostatin, a macrolide derived from *Bugula neritina*, modulates protein kinase C and has shown promise in treating neurodegenerative and oncological conditions (Farlow et al., 2019; Nelson et al., 2017; Zonder et al., 2001). Huperzine A, extracted from *Huperzia serrata*, enhances cognitive function by inhibiting acetylcholinesterase, a key enzyme involved in AD pathology (Friedli and Inestrosa, 2021; Liu et al., 2020; Rafii et al., 2011; Xu et al., 2012). Galantamine, an FDA-approved acetylcholinesterase inhibitor, alleviates AD symptoms by enhancing cholinergic signaling, thereby providing cognitive and functional benefits (Santos et al., 2020).

4.4 Other classes

Other bioactive compounds, such as omega-3 fatty acids (e.g., DHA) and melatonin, contribute significantly to neuroprotection in AD. DHA has been shown to reduce neuroinflammation, oxidative stress, and Aβ aggregation, while also supporting neuronal survival and synaptic plasticity (Freund-Levi et al., 2008; Khalid et al., 2022; Lee et al., 2013; Quinn et al., 2010; Thomas et al., 2015; Xiao et al., 2022; Yurko-Mauro et al., 2010). Melatonin, known for its role in regulating circadian rhythms and sleep, provides antioxidant and anti-inflammatory effects that mitigate AD pathology, including Aβ accumulation and tau hyperphosphorylation (Cardinali et al., 2014; Furio et al., 2007; Hardeland, 2018; Li et al., 2020; Lin et al., 2013; Wade et al., 2014; Xu et al., 2020).

These natural compounds present a multifaceted approach to combating AD by targeting oxidative stress, inflammation, and amyloid and tau pathologies. However, further research is required to optimize their clinical utility and establish standardized protocols for therapeutic application.

4.5 Strengths and limitations

The meta-analysis presented in this study emphasizes the need for further research to validate the potential cognitive benefits of natural compounds and extracts, despite the promising results identified in individual interventions. While previous systematic reviews have addressed natural compounds in preclinical and clinical trials (Ahmad et al., 2023; Andrade et al., 2019; Li et al., 2023), this study distinguishes itself by focusing exclusively on RCTs that evaluated global cognitive domains using widely accepted measures such as the ADAS-cog and MMSE. By employing meta-analyses and providing statistical evidence, this study contributes to a more comprehensive understanding of the effects of natural compounds and extracts. Furthermore, the study's selection criteria targeted RCTs that utilized a single species of natural extract or specific compound, excluding those involving multiple extracts, compounds, or formulations. This approach aligns closely with real-world practices typically employed by caregivers, making the findings highly relevant for daily clinical management of individuals with MCI or AD. It is essential for individuals considering any dietary supplement to consult healthcare professionals or AD specialists, who can provide personalized guidance based on individual circumstances and health status. Although short-term cognitive improvement was observed across all RCTs, the validation of long-term efficacy in individuals with cognitive impairment necessitates large-scale longitudinal trials. To the best of our knowledge, this study is the first systematic review and meta-analysis that compares the effects

of various forms of natural compounds and extracts on patients with MCI or AD using recognized assessment measures such as the MMSE and ADAS-cog. Despite the positive findings, several limitations must be acknowledged. This include the diversity in intervention types, variations, in duration and participant characteristics, and the moderate to high risk of bias in the quality of studies using the same cognitive tasks. Additionally, the vast scope of this topic inevitably meant that not all types or species of natural compounds and extracts could be included. Some natural compounds are still in the preclinical or early clinical phases, and certain studies employing non-RCT designs, such as pilot or cross-over studies, were excluded from this review. This exclusion does not imply a lack of potential benefit to cognitive health. Despite a rigorous search methodology, including additional hand-searching, it is possible that some relevant articles were inadvertently missed. Furthermore, each natural compound and extract originates from distinct sources and possesses unique mechanisms of action and biological effects, necessitating a cautious interpretation of the findings. Future research should address these limitations and aim to provide a more comprehensive understanding of the therapeutic potential of natural compounds and extracts in improving cognitive function.

5 Conclusion

This systematic review provides preliminary evidence suggesting the potential cognitive benefits of natural compounds and extracts, particularly as assessed by the ADAS-cog. Additionally, there is significant suggestive evidence indicating improvements in MMSE scores. Notably, this study represents the first systematic review and meta-analysis to comprehensively compare and categorize the effects of various forms of prolonged consumption of natural compounds, extracts, and isolated food supplements in individuals diagnosed with MCI or AD. The study does not offer robust evidence to endorse any individual natural compound or extract reviewed as a substitute for conventional medications in the prevention or treatment of mild cognitive impairment or Alzheimer's disease.

Data availability statement

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

Author contributions

LNH: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing. HSL: Data curation, Investigation, Validation, Writing – review & editing. SJL: Data curation, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – review & editing.

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Conflict of interest

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

Generative AI statement

The authors declare that no Gen AI was used in the creation of this manuscript.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2024.1531278/full#supplementary-material

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A synergistic effect of secondhand smoke with vitamin D deficiency on cognitive impairment in older adults: a cross sectional study

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Objectives: To investigate whether exposure to secondhand smoke (SHS) aggravates the detrimental effect of vitamin D deficiency (VDD) on cognitive performance in the elderly.

Methods: Based on National Health and Nutrition Examination Surveys (NHANES) 2011–2014, 1,446 non-smoking participants (≥ 60 years old) with detailed serum 25-hydroxyvitamin D [25(OH)D], concentration of cotinine and tests score of cognitive function were included. Cognitive impairment was defined as having a cognitive score in the lowest quartile. The possible synergistic effect of SHS with VDD on cognitive impairment was evaluated by using a multivariable logistic regression model.

Results: VDD was independently associated with risk of low the Digit Symbol Substitution Test (DSST) scores, increased by nearly 60% [< 34, adjusted odds ratio (aOR) = 1.62, 95% CI: 1.03 ~ 2.53]. Although it only had an association with cognitive impairment indicated by DSST and the Animal Fluency test (AFT) in the crude model, SHS exposure showed significant synergistic effects with VDD on DSST (aOR: 3.03, 95% CI: 1.57 ~ 5.83, $P_{interaction}$ = 0.001) and AFT (aOR: 2.40, 95% CI: 1.34 ~ 4.29, $P_{interaction}$ = 0.003), respectively, after adjusting for the possible confounders. In further stratified analysis, a more obvious synergistic effect of SHS with VDD on DSST (aOR: 4.73, 95%CI:1.77 ~ 12.68, $P_{interaction}$ = 0.002) and AFT (aOR: 5.30, 95%CI: 1.63 ~ 17.24, $P_{interaction}$ = 0.006) was found in obese and overweight subjects, respectively.

Conclusion: SHS exposure had synergistic effect with VDD on cognitive impairment among elderly and the interaction effect was more obvious in overweight and obese individuals.

KEYWORDS

25-hydroxyvitamin D, secondhand smoke, cognitive impairment, elderly, synergistic effect

1 Introduction

With increasing age of the global population, age-related cognitive decline and the correspondent strategy to cope with it has become an intensive interesting topic in scientific research. Studies based on population data indicate that about one-third of Alzheimer's disease (AD) cases worldwide could be attributed to factors that can potentially be modified, including nutrition and environmental harmful substance exposure (1, 2). Vitamin D deficiency (VDD), a worldwide concern, has been suggested to be associated with cognitive impairment, particularly among older people (3). A meta-analysis involving 7,688 subjects shown a significantly increased risk of cognitive impairment in VDD subjects (4). Similarly, serum Vitamin D(VD) levels were positively correlated with cognitive performance in the United States elderly (5, 6). Cohort studies have demonstrated that severe VDD is associated with about 2-fold increased risk of developing AD (7). Other than that, VD supplementation has been shown to improve cognitive impairment both in mild cognitive impairment (MCI) elderly (8) and AD patients (9) in randomized controlled trials, although some trials did not find the same effects (10).

There is an increasing amount of evidence indicating that the use of tobacco, both through active smoking and exposure to secondhand smoke (SHS), is linked to a decline in cognitive abilities (11, 12), as well as accelerates cognitive decline (13) and dementia (14). Despite a decrease in cigarette smoking rates in the United States, the prevalence of smoking among adults still stood at 19.0% in 2020 (15). As far as we know, older individuals who spend more time indoors are at a higher risk of being exposed to SHS, which has been reported to elevate the risk of cognitive decline including reduced processing speed and executive function (16). Mounting evidence support the correlation between VDD and cognitive impairment. Mechanistically, SHS in related to VDD and cognitive impairment. A few studies have shown that tobacco has an endocrine-disrupting effect and has linked it to dysfunctional VD endocrine systems accompanied with declined serum levels of VD metabolites (17–19). VD-parathyroid hormone (PTH) axis dysfunction due to tobacco smoke exposure may lead to disruption of VD metabolism and dysregulation of VD metabolism-related enzyme genes (20). However, till now, whether SHS is involved in the relationship between VDD and cognitive impairment has not been reported.

Taken together, we hypothesized that there could be a synergistic effect of SHS with VDD on cognitive decline in older individuals. Therefore, we examined how the simultaneous exposure to SHS and VDD affects cognitive function in people aged 60 and above, evaluating the potential interaction effects by using data from National Health and Nutrition Examination Surveys (NHANES) 2011–2014. Understanding this relationship could assist health authorities in making informed decisions about implementing health promotion strategies and interventions to prevent cognitive impairment in the elderly.

2 Methods

2.1 Study population

Data from NHANES 2011–2014 with cognitive tests in the elderly were utilized. NHANES is conducted by the Centers for Disease Control and Prevention's National Center for Health Statistics (NCHS) to assess the health and nutritional status of the United States civilian population via interviews and physical exams. Conducted every 2 years since 1999, participants represented the general population of the United States through a complex multi-stage sampling method. The first was the conduct of a questionnaire, followed by a physical examination and the collection of biological specimens of the participants. Participants with detailed serum 25-hydroxyvitamin D [25(OH)D], cotinine data, and cognitive performance test scores were included in the analysis (N = 19,931). Exclusion criteria included younger than 60 years old (n = 16,299); missing data for serum 25(OH)D (n = 365); self-reported active smoking history including chewing tobacco or other forms of snus (n = 1,666); serum cotinine >10 ng/mL (the cutoff value for active smoking) (n = 13); missing data for cognitive outcomes (n = 124); abnormal energy intake (daily energy intake >5,000 kcal or < 500 kcal, n = 18). Finally, we analyzed data from a total of 1,446 individuals who were elderly non-smokers (≥ 60 years old) taken from NHANES 2011–2014. The process of participant selection is shown in Figure 1.

2.2 Assessment of cognitive impairment

The tests for cognitive function in NHANES 2011–2014 include word learning and recall modules from the Consortium to Establish a Registry for Alzheimer's disease (CERAD), the Animal Fluency test (AFT) and the Digit Symbol Substitution Test (DSST).

The CERAD consists of three consecutive learning trials and a delayed recall. During the learning trials, participants are given the instruction to pronounce 10 words that are not related to each other. They were required to remember as many of these words as possible right away. The maximum score for each trial is 10. The delayed word recall test occurred after completion of the other two cognitive exercises (AFT and DSST). Higher scores on this item indicate better cognitive performance.

Categorical verbal fluency in executive function was examined with the AFT, which has been demonstrated that scores can be used to differentiate individuals who have normal cognitive abilities from those with MCI and more severe cognitive impairments (21, 22). During the assessment, participants are given 1 min to list as many animals as they can. Each correctly named animal earns one point, and the total score is calculated by adding up all the correct answers. To familiarize participants with the task, they are initially asked to name three clothing items as a practice test. If a participant is unable to name three articles of clothing, they are not included in the subsequent assessment.

The DSST depends on speed of processing, sustained attention, and working memory. Participants are asked to fill in the blank boxes according to the symbols corresponding to the numbers and copy the corresponding symbols in the 133 boxes of adjacent numbers in 2 min. The score indicates the overall count of accurate matches.

Since the three tests mentioned above did not have established criteria for identifying low cognitive performance, we relied on the standards used in relevant published research (23). For each test, we determined the cutoff point by selecting the highest value among those in the lowest quartile. Participants who scored below these cutoff points were classified as having impaired cognitive performance, namely, < 20 for the CERAD, < 13 for the AFT, and < 34 for the DSST, respectively.

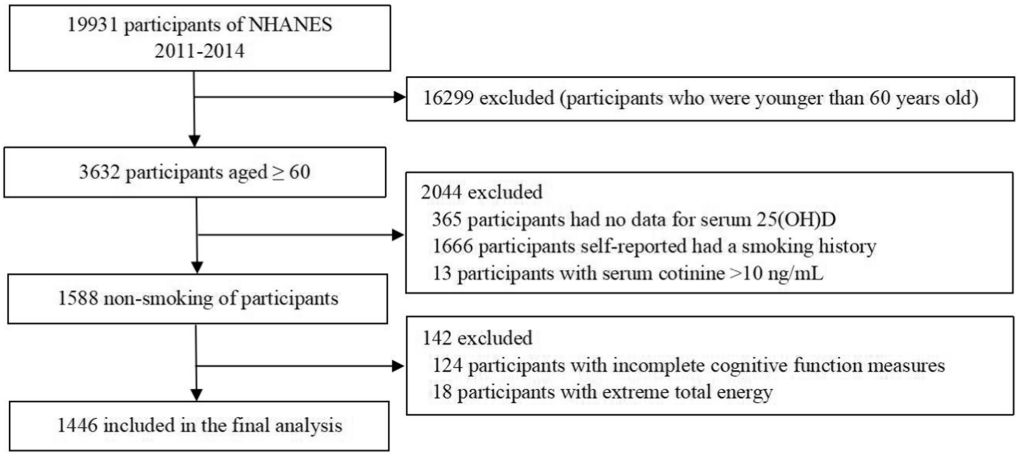

FIGURE 1
Flow chart of the screening process for the eligible participants.

2.3 Serum 25(OH)D measurement

After fasted for 9 h, blood was drawn from the subjects processed by a mobile examination center (MEC) and immediately frozen at −30°C for further measurements. Ultra-performance liquid chromatography–tandem mass spectrometry (UHPLC–MS/MS) (24) quantitative assay was used to detect serum 25(OH)D, the optimal indicator of nutritional status of VD in the body. Quantification was done by comparing the unknown analyte's peak area to the known amount of analyte in the calibrator solution. The calculation was corrected by comparing the unknown peak area with the peak area of the matching internal standard in the calibrator solution (25).

2.4 Assessment of SHS exposure

In this study, SHS was assessed using self-reported data by questionnaires combined with serum cotinine concentration. First of all, according to the answers to questions SMQ020 and SMQ040, adults surveyed responses to three questions (SMQ681, SMQ851, and SMQ863) about tobacco use (smoking and nicotine replacement therapy products) in the past 5 days to exclude active smokers. Next, if a participant reports exposure to SHS in the last 7 days, self-reported SHS is considered present. In case of missing questionnaires, SHS exposure was measured with serum cotinine and defined as exposed if the subject had a cotinine level of 0.05–10 ng/mL (26, 27). While those below 0.05 ng/mL are considered non-SHS exposed. Cotinine is determined by an isotope dilution-high performance liquid chromatography/atmospheric pressure chemical ionization tandem mass spectrometry (ID HPLC-APCI MS/MS) (28).

2.5 Covariates

We included factors of age, sex, race, educational level, marital status, poverty index (PIR), alcohol use, physical activity, body mass index (BMI), diabetes, stroke, asthma, and congestive heart failure as covariates. A computer-assisted personal interview was utilized to gather demographic information of the participants. Alcohol use (ALQ101 and ALQ110) and vigorous recreational activities (PAQ650) were defined based on self-reported data by questionnaires. We explored chronic conditions of diabetes, stroke, asthma, and congestive heart failure in the medical conditions questionnaire.

2.6 Statistical analysis

Serum 25(OH)D was treated as a categorical variable [sufficiency (≥ 75 nmol/L), insufficiency (50 ~ 75 nmol/L), and deficiency (< 50 nmol/L)] as suggested by the Institute of Medicine (IOM) (29). Depending on exposure to SHS, the participants were categorized into two groups (yes or no). Main confounders were categorized as follows: age (60 ~ 69 y, 70 ~ 79 y, and ≥ 80 y); sex (male and female); race (Mexican American, Non-Hispanic White and Black, and Other); education (high school and below/general equivalency diploma, some college/associates degrees, and college degree/above); marital status (married/living with a partner, never married/separated/widowed/divorced); PIR (< 1, and ≥ 1); BMI (< 25 kg/m^2, 25 ~ 29.99 < kg/m^2, and ≥ 30 kg/m^2). In the interaction analysis, according to their nutritional status of VD and exposure to SHS, we categorized the entire population into six groups. Logistic regression models to examine the relationship between exposure to VDD and/or SHS and the prevalence of cognitive performance. Odds ratios [OR, with 95% confidence intervals (CI)] were employed to assess the magnitude of the effect. In multivariate logistic regressions, model 1 was adjusted for age, sex, race, education level, marital status, PIR, and model 2 further adjusted for alcohol use, physical activity, BMI, diabetes, stroke, asthma, and congestive heart failure. Although there were no significant differences in sex, BMI, and the presence of asthma between subjects with or without cognitive impairment ($p > 0.05$), we still adjusted them to minimize the potential residual confounding effects. We assessed the possible synergistic effects of SHS with VDD using the multiplicative scale method. Two-sided p values were calculated to evaluate the significance of each term in the logistic regression models to compare the OR of SHS on cognitive function in different groups based on levels of serum 25(OH)D. In

order to further elucidate the associations, we conducted additional analysis by stratifying the data according to age, sex, and BMI. Considering that stroke made up only 5.7% of the participants, we performed sensitivity analysis by excluding stroke and compared the results. The statistical analysis was conducted using SPSS 22.0 software, and a significance level of $p < 0.05$ was considered statistically significant.

2.7 Ethics approval and consent to participate

The research was carried out in accordance with the principles outlined in the Declaration of Helsinki. Participants in this study are all in accordance with the study ethics guidelines and have informed consent.

3 Results

The characteristics of all participants included are shown in Table 1 Individuals with low cognitive performance in all the three tests were more likely to be older, other Hispanic and other Racial, low educated, unmarried (or not living with a partner), less physically active, poverty stricken, with higher prevalence of diabetes, stroke, and heart failure, and less proportion of alcohol drinks ($p < 0.01$). Individuals with impaired cognitive performance had relatively lower serum 25(OH)D levels in all tests, and they had higher prevalence of SHS exposure in the AFT and DSST ($p < 0.05$). Table 2 shows the effects of exposure to VDD, SHS on cognitive impairment. In binary logistic regression analyses, compared to those with sufficient VD, subjects with VDD had 62% increased odds of cognitive impairment indicated by DSST after adjusting for the possible confounders in the final model [adjusted odds ratio (aOR): 1.62; 95% CI: 1.03, 2.53]. In the AFT, a significant correlation was observed in VDD with impaired cognitive performance in the crude analysis (OR: 1.47; 95% CI: 1.06, 2.04), and a marginal significant correlation remained after adjusting for age, sex, race, education, marital status and PIR (aOR: 1.41; 95% CI: 0.97, 2.05, $p = 0.072$). In the CERAD, a marginal significant correlation was observed in VDD with impaired cognitive performance in the crude analysis (OR: 1.38; 95% CI: 0.97, 1.95, $p = 0.071$) while no significant correlations remained after adjusting for the possible confounding factors, while a statistical significant correlation remained in insufficient VD in the final multivariable model (aOR: 1.41; 95% CI: 1.01, 1.97). Exposure to SHS was associated with cognitive impairment both in the DSST (OR: 1.40; 95% CI: 1.06, 1.85) and the AFT (OR: 1.41; 95% CI: 1.08, 1.86) in the crude models. After adjusting for age, sex, race, education, marital status and PIR, only a marginal statistical significance was observed in the AFT (aOR: 1.31; 95% CI: 0.96, 1.78, $p = 0.088$).

The results of the interaction analysis of VDD and SHS on cognitive impairment was shown in Table 3. Compared with persons with sufficient VD level and non-SHS exposure, with VDD and SHS exposurers had significantly higher odds of cognitive impairment in the DSST (aOR: 3.03; 95% CI: 1.57, 5.83) and the AFT (aOR: 2.40; 95% CI: 1.34, 4.29) after adjusting for the possible confounders.

Furthermore, considering that participants with a history of stroke made up only 5.7% of the total participants, we performed sensitivity analysis by excluding them. In the fully adjusted model, the negative associations remained, and the size effect was larger in DSST. Hence, sensitivity analysis proves that the regression model is robust as shown in the Supplementary material S1.

The results of subgroup analysis of the interaction effects of VDD and SHS on cognitive impairment were shown in Figure 2; Supplementary material S1. The interaction effects on cognitive impairment remained in those aged 60 ~ 69. Sex stratified analysis showed similar results in male and female as the total population. Male may be more sensitive to combined VDD and SHS exposure in the AFT than female (aOR: 3.10; 95% CI: 1.13, 8.49 vs. aOR: 2.21; 95% CI: 1.06, 4.63), while female may be more sensitive than male in DSST (aOR: 3.53; 95% CI: 1.48, 8.39 vs. aOR: 2.73; 95% CI: 0.89, 8.35, $p = 0.078$). In BMI stratified analysis, no synergistic effects of SHS with VDD on cognitive impairment indicated by all the three tests were observed in those of underweight or normal weight (BMI < 25 kg/m^2). Compared to the total subjects, a more significant synergistic effect was observed in AFT (aOR: 5.30; 95% CI: 1.63, 17.24 vs. aOR: 2.40; 95% CI:1.34, 4.29) in overweight individuals ($25 \leq$ BMI < 30). For DSST, no synergistic effect remained in overweight elderly, while in obese individuals, we found a more significant synergistic effect (aOR: 4.73; 95% CI: 1.77, 12.68 vs. aOR: 3.03; 95% CI: 1.57, 5.83; Figure 2).

4 Discussion

Utilizing data from two continuous NHANES cycles of 1,446 eligible subjects, we found that SHS exposure had a significant synergistic effect with VDD on cognitive impairment in older adults, and the effect was more pronounced among overweight and obese participants. To our best knowledge, this is the first study of its kind which may provide important evidence to the control of cognitive impairment in older adults.

In accordence with previous studies, we found VDD was independently associated with cognitive impairment in older adults (30). VD has been reported to be involved in neuronal proliferation (31) with neuroprotective effects (32), and VDD was revealed to play an important role in the pathogenesis of dementia (33). Mechanistically, VD can have an impact on neurocognition through a variety of mechanisms, such as inducing neuroprotection, regulating calcium homeostasis, and regulating oxidative stress (34). VDD leads to dysregulations of perineuronal nets (35) and matrix metalloproteinases (36) and further contributes to cognitive decline and impairment. Older people are prior to have VDD mainly due to their reducing outdoor activities, as well as the decreasing bioavailability of VD in the body. There are differences in the results observed by different cognitive function tests in this study, which may be that the design of the test itself influenced the assessment results. Previous studies on cognition have also found more positive results for DSST and AFT than for CERAD, and this study also confirms this (37, 38). Specifically, VDD was reported to be associated with reduced processing speed and decreased verbal fluency (39), and a longitudinal study of Australian women found that individuals

TABLE 1 Characteristics of the subjects by cognitive impairment, NHANES 2011–2014 [*N* = 1,446, *n* (%)].

Characteristics	CERAD			AFT			DSST		
	Normal Cognitive Performance	Impaired Cognitive Performance	*p*-value	Normal Cognitive Performance	Impaired Cognitive Performance	P-value	Normal Cognitive Performance	Impaired Cognitive Performance	P-value
Number of subjects	1,093 (75.6)	322 (22.3)		1,067 (73.8)	348 (24.1)		1,040 (71.9)	329 (22.8)	
Age, years			<0.001			<0.001			<0.001
60~	613 (56.1)	103 (32.0)		589 (55.2)	129 (37.1)		596 (57.3)	119 (36.2)	
70~	319 (29.2)	101 (31.4)		303 (28.4)	116 (33.3)		290 (27.9)	110 (33.4)	
≥ 80 years	161 (14.7)	118 (36.6)		175 (16.4)	103 (29.6)		154 (14.8)	100 (30.4)	
Sex (%)			<0.001			0.334			0.431
Male	355 (32.5)	144 (44.7)		383 (35.9)	115 (33.0)		364 (35.0)	123 (37.4)	
Female	738 (67.5)	178 (55.3)		684 (64.1)	233 (67.0)		676 (65.0)	206 (62.6)	
Race (%)			0.407			0.020			<0.001
Mexican American	97 (8.9)	36 (11.2)		100 (9.4)	31 (8.9)		70 (6.7)	49 (14.9)	
Non-Hispanic White and Non-Hispanic Black	739 (67.6)	208 (64.6)		735 (68.9)	216 (62.1)		741 (71.2)	185 (56.2)	
Other Hispanic and Other Race	257 (23.5)	78 (24.2)		232 (21.7)	101 (29.0)		229 (22.0)	95 (28.9)	
Education level (%)			<0.001			<0.001			<0.001
College degree or above	330 (30.2)	54 (16.8)		332 (31.1)	54 (15.5)		351 (33.8)	33 (10.0)	
Some college/associates degrees	324 (29.6)	60 (18.6)		307 (28.8)	75 (21.6)		323 (31.1)	52 (15.8)	
High school and below/general equivalency diploma	438 (40.1)	208 (64.6)		428 (40.1)	218 (62.6)		366 (35.2)	243 (73.9)	
Marital status (%)			0.002			0.002			<0.001
Married/living with partner	653 (59.7)	161 (50)		638 (59.8)	175 (50.3)		639 (61.4)	160 (48.6)	
Never married/separated/widowed/divorced	438 (40.1)	160 (49.7)		428 (40.1)	171 (49.1)		399 (38.4)	169 (51.4)	
Family PIR (%)			<0.001			<0.001			<0.001
PIR ≥ 1	885 (78.2)	224 (69.6)		856 (80.2)	226 (64.9)		857 (90.1)	199 (60.5)	
PIR < 1	135 (12.4)	74 (23.0)		120 (11.2)	85 (24.4)		94 (9.9)	100 (30.4)	
BMI, kg/m^2			0.196			0.756			0.677
< 25	286 (26.2)	90 (28.0)		279 (26.1)	94 (27.0)		281 (27.0)	82 (24.9)	
25 ~ 30	368 (33.7)	116 (36.2)		378 (35.4)	113 (32.5)		357 (34.3)	118 (35.9)	
≥ 30	429 (39.2)	106 (32.9)		403 (37.8)	128 (36.8)		396 (38.1)	117 (35.6)	
Diabetes (%)	217 (19.9)	87 (27.0)	0.006	199 (18.7)	102 (29.3)	<0.001	187 (18.0)	95 (28.9)	<0.001

(Continued)

10.3389/fnut.2025.1533193

TABLE 1 (Continued)

Characteristics	CERAD			AFT			DSST		
	Normal Cognitive Performance	Impaired Cognitive Performance	*p*-value	Normal Cognitive Performance	Impaired Cognitive Performance	P-value	Normal Cognitive Performance	Impaired Cognitive Performance	P-value
Stoke (%)	50 (4.6)	31 (9.6)	0.001	49 (4.6)	31 (8.9)	0.002	41 (3.9)	33 (10.0)	<0.001
Asthma (%)	158 (14.5)	31 (9.6)	0.026	148 (13.9)	41 (11.8)	0.326	136 (13.1)	45 (13.7)	0.788
Congestive heart failure (%)	51 (4.7)	42 (13.0)	<0.001	55 (5.2)	37 (10.6)	<0.001	44 (4.2)	42 (12.8)	<0.001
Alcohol drinking (%)	558 (51.1)	137 (42.5)	0.022	560 (52.5)	134 (38.5)	<0.001	567 (54.5)	119 (36.2)	<0.001
Recreational Physical activity (%)	126 (11.5)	14 (4.3)	<0.001	122 (11.4)	20 (5.7)	0.002	132 (12.7)	6 (1.8)	<0.001
$25(OH)D_2 + 25(OH)D_3$(%)			0.001			0.056			0.010
≥ 75 nmol/L	576 (52.7)	134 (41.6)		548 (51.4)	165 (47.4)		550 (52.9)	148 (45.0)	
50 ~ 75 nmol/L	333 (30.5)	129 (40.1)		354 (33.2)	110 (31.6)		331 (31.8)	110 (33.4)	
< 50 nmol/L	184 (16.8)	59 (18.3)		165 (15.5)	73 (21.0)		159 (15.3)	71 (21.6)	
SHS (%)	266 (24.3)	75 (23.3)	0.700	242 (22.7)	102 (29.3)	0.012	234 (22.5)	95 (28.9)	0.018

with VD > 25 nmol/L had better verbal fluency performance but was not associated with the CERAD (40). Consistently, we found similar effects of VDD on the special impaired cognitive performance verbal fluency in the total subjects as well as in the sex and BMI stratified analysis.

SHS exposure may increase the risk of overall cognitive impairment in older adults. As reported, Subjects exposed to SHS had a greater decline in memory scores (41). A cohort study of 2087 non-smoking older adults in Spain found SHS exposure was related to increased risk of overall cognitive impairment with decreased working memory capacity (42). Similarly, in a longitudinal study of 6,875 Chinese women, those who lived with smoking husbands had significantly faster declines in global cognitive function (43). However, in a cohort of 970 older people, Barnes et al. did not find a relationship between SHS and the risk of dementia (44). Smoking leads to cognitive dysfunction by destroying subcortical gray matter, the frontotemporal cortex(functions of language and movement), and the medial temporal lobe pathway (functions of language, memory, and mental activity) (45). In our study, in crude analysis, exposure to SHS was associated with nearly 40% higher risk of cognitive impairment both in the DSST and the AFT. However, after adjusting for the potential confounders, no significant associations remained. It may mainly be due to different criteria for judging SHS exposure (46) in these studies and more confirmative cohort researches are needed in the future.

It is worth noting that we found SHS has a synergistic effect with VDD on cognitive impairment in the elderly. Our novel findings are plausible concerning the biological mechanisms. On one hand, SHS may share the similar biological pathway leading to cognitive impairment as VDD. Previous studies found that cigarette smoke induced dysregulation of the balance between oxidants and antioxidants, inflammasome activation, reactive oxygen species (ROS) (47) production, and Ca^{2+} influx (48), finally leading to oxidative stress (49) in the body. Likewise, as reported, VDD was accompanied by increased ROS generation and intracellular free Ca^{2+} in brain nerve terminals (50), causing oxidative stress to weaken neuroprotective effects further (8). On the other hand, SHS is associated with VDD and cognitive impairment. Tobacco itself may cause VDD by inhibiting some of the key metabolic sites of VD. Smoking inhibits the expression of CYP27B1 (51) (the key enzyme required for activation of VD), reduces serum PTH level, increases the expression of CYP24A1 (52) (the key enzyme required for breakdown of VD), thereby reducing serum VD levels and cognitive impairment (53) (Figure 3). Other than that, smoking decreases VD intake from diet, calcium absorption, and reduces the cutaneous production of VD through skin aging (52).

Moreover, we found the synergistic effect of VDD with SHS on cognitive impairment was markedly more significant in overweight or obese elderly. Obesity is widely recognized as a chronic, low-grade inflammatory state (54). It has been reported that overweight and obese persons had impaired performance on memory (55), cognitive flexibility, and executive function (56). It has been reported that obese persons have lower temporal lobe volume due to brain atrophy (57, 58), which is in accordance with the impaired cognitive function. Similarly, exposure to SHS increases the inflammatory response (59), and oxidative stress in obese subjects (60). Therefore, this may partially explain the increased synergistic effects of SHS with VDD on cognitive impairment in overweight and obese elder persons. In

TABLE 2 Odds ratios of cognitive impairment according to serum 25(OH)D concentrations and SHS as categorical using a logistics regression model, NHANES 2011–2014 (*N* = 1,446).

	CERAD						AFT					
	Crude model OR (95% CI)	*p*- value	Model 1 OR (95% CI)	*p*- value	Model 2 OR (95% CI)	*p*- value	Crude model OR (95% CI)	*p*- value	Model 1 OR (95% CI)	*p*- value	Model 2 OR (95% CI)	*p*- value
25(OH)D level												
<50 nmol/L	1.38 (0.97, 1.95)#	0.071	1.18 (0.79, 1.77)	0.423	1.10 (0.72, 1.70)	0.658	1.47 (1.06, 2.04)*	0.021	1.41 (0.97, 2.05)#	0.072	1.30 (0.87, 1.93)	0.202
50–75 nmol/L	1.67 (1.26, 2.20)*	<0.001	1.53 (1.11, 2.10)*	0.010	1.41 (1.01, 1.97)*	0.047	1.03 (0.78, 1.36)	0.823	0.99 (0.72, 1.36)	0.957	0.99 (0.71, 1.37)	0.926
≥75 nmol/L	Ref.	—	Ref.	—	Ref.	—	Ref.	—	Ref.	—	Ref.	—
SHS												
Yes	0.94 (0.70, 1.27)	0.700	0.88 (0.63, 1.23)	0.446	0.88 (0.62, 1.25)	0.746	1.41 (1.08, 1.86)*	0.013	1.31 (0.96, 1.78)#	0.088	1.24 (0.90, 1.72)	0.189
No	Ref.	—	Ref.	—	Ref.	—	Ref.	—	Ref.	—	Ref.	—

	DSST					
	Crude model OR (95% CI)		Model 1 OR (95% CI)		Model 2 OR (95% CI)	
25(OH)D level						
<50 nmol/L	1.66 (1.19, 2.32)*	0.003	1.69 (1.11, 2.56)*	0.014	1.62 (1.03, 2.53)*	0.036
50–75 nmol/L	1.24 (0.93, 1.64)	0.142	1.11 (0.79, 1.57)	0.547	1.13 (0.78, 1.64)	0.525
≥75 nmol/L	Ref.		Ref.		Ref.	
SHS						
Yes	1.40 (1.06, 1.85)*	0.019	1.27 (0.90, 1.78)	0.174	1.17 (0.81, 1.68)	0.405
No	Ref.		Ref.		Ref.	

Model 1: adjusted for age, sex, race, education level, marital status, PIR. Model 2: Model 1+ alcohol use, physical activity, BMI, diabetes, stroke, asthma, and congestive heart failure. *Significant at $p < 0.05$; #Borderline significant, $0.05 < p < 0.1$.

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TABLE 3 Interaction analysis of SHS with VD status on the risk of cognitive impairment in the elderly, NHANES 2011–2014 (N = 1,446).

	CERAD						AFT					
	Crude Model OR (95% CI)	*p*- value	Model 1 OR (95% CI)	*p*- value	Model 2 OR (95% CI)	*p*- value	Crude Model OR (95% CI)	*p*- value	Model 1 OR (95% CI)	*p*- value	Model 2 OR (95% CI)	*p*- value
Deficiency *SHS	1.42 (0.82, 2.47)	0.209	1.37 (0.72, 2.60)	0.328	1.23 (0.62, 2.44)	0.556	2.21 (1.35, 3.61)*	0.002	2.59 (1.49, 4.49)*	<0.001	2.40 (1.34, 4.29)*	0.003
Insufficiency *SHS	1.54 (0.98, 2.41)	0.061	1.28 (0.76, 2.16)	0.358	1.28 (0.75, 2.20)	0.366	1.38 (0.89, 2.13)	0.154	1.08 (0.65, 1.79)	0.780	0.98 (0.57, 1.69)	0.953
Sufficiency *SHS	0.73 (0.44, 1.20)	0.218	0.66 (0.38, 1.12)	0.125	0.59 (0.34, 1.05)	0.073	1.15 (0.75, 1.76)	0.519	0.97 (0.60,1.57)	0.910	0.94 (0.57, 1.55)	0.794
Deficiency *non-SHS	1.25 (0.82, 1.88)	0.300	0.96 (0.59, 1.55)	0.858	0.89 (0.54, 1.49)	0.663	1.23 (0.82, 1.84)	0.320	0.98 (0.61, 1.57)	0.928	0.88 (0.53, 1.45)	0.605
Insufficiency*non-SHS	1.58 (1.16, 2.17)*	0.004	1.44 (1.00, 2.07)*	0.049	1.25 (0.85, 1.84)	0.251	0.96 (0.70, 1.33)	0.806	0.95 (0.66, 1.37)	0.802	0.96 (0.66, 1.41)	0.838
Sufficiency *non-SHS	Ref.	—	Ref.	—	Ref.	—	Ref.	—	Ref.	—	Ref.	—

	DSST					
	Crude Model OR (95% CI)	*p*- value	Model 1 OR (95% CI)	*p*- value	Model 2 OR (95% CI)	*p*- value
Deficiency *SHS	2.49 (1.50, 4.11)*	<0.001	3.25(1.76, 6.00)*	<0.001	3.03(1.57, 5.83)*	0.001
Insufficiency *SHS	1.57 (1.00, 2.48)	0.051	1.11(0.64, 1.95)	0.710	1.06(0.59, 1.93)	0.839
Sufficiency *SHS	1.13 (0.72, 1.76)	0.593	0.88(0.51, 1.50)	0.633	0.74(0.42, 1.33)	0.316
Deficiency *non-SHS	1.38 (0.92, 2.09)	0.123	1.10(0.65, 1.84)	0.732	1.02(0.59, 1.77)	0.948
Insufficiency*non-SHS	1.17 (0.84, 1.62)	0.350	1.07(0.72, 1.60)	0.729	1.06(0.69, 1.62)	0.807
Sufficiency *non-SHS	Ref.		Ref.	—	Ref.	—

Model 1: adjusted for age, sex, race, education level, marital status, PIR. Model 2: Model 1+ alcohol use, physical activity, BMI, diabetes, stroke, asthma, and congestive heart failure. *Significant at $p < 0.05$.

10.3389/fnut.2025.1533193

Subgroup		DSST		
			OR (95% CI)	P-value
Age	≥60 years	Deficiency*SHS	3.58(1.45, 8.84)*	0.006
		Insufficiency*SHS	0.92(0.36, 2.40)	0.869
		Sufficiency*SHS	0.47(0.15, 1.43)	0.181
		Deficiency*non-SHS	1.81(0.79, 4.12)	0.161
		Insufficiency*non-SHS	1.44(0.71, 2.92)	0.316
		Sufficiency*non-SHS	Ref.	—
	≥70 years	Deficiency*SHS	3.21(0.80, 12.82)	0.100
		Insufficiency*SHS	1.39(0.50, 3.85)	0.531
		Sufficiency*SHS	0.74(0.23, 2.34)	0.608
		Deficiency*non-SHS	0.64(0.19, 2.23)	0.486
		Insufficiency*non-SHS	0.88(0.39, 2.00)	0.757
		Sufficiency*non-SHS	Ref.	—
	≥80 years	Deficiency*SHS	7.16(0.57, 89.837)	0.127
		Insufficiency*SHS	1.67(0.38, 7.32)	0.495
		Sufficiency*SHS	1.26(0.46, 3.47)	0.651
		Deficiency*non-SHS	0.79(0.25, 2.46)	0.683
		Insufficiency*non-SHS	0.83(0.35, 1.94)	0.664
		Sufficiency*non-SHS	Ref.	—
Gender	Male	Deficiency*SHS	2.73(0.89, 8.35)	0.078
		Insufficiency*SHS	1.39(0.54, 3.55)	0.491
		Sufficiency*SHS	1.24(0.44, 3.47)	0.689
		Deficiency*non-SHS	1.41(0.59, 3.36)	0.443
		Insufficiency*non-SHS	0.84(0.41, 1.74)	0.640
		Sufficiency*non-SHS	Ref.	—
	Female	Deficiency*SHS	3.53(1.48, 8.39)*	0.004
		Insufficiency*SHS	0.81(0.36, 1.84)	0.620
		Sufficiency*SHS	0.58(0.27, 1.21)	0.146
		Deficiency*non-SHS	0.77(0.36, 1.65)	0.495
		Insufficiency*non-SHS	1.34(0.77, 2.33)	0.298
		Sufficiency*non-SHS	Ref.	—
BMI	< 25 kg/m^2	Deficiency*SHS	2.78(0.57, 13.52)	0.205
		Insufficiency*SHS	1.48(0.39, 5.68)	0.568
		Sufficiency*SHS	0.46(0.12, 1.75)	0.252
		Deficiency*non-SHS	0.85(0.20, 3.59)	0.821
		Insufficiency*non-SHS	1.32(0.57, 3.07)	0.514
		Sufficiency*non-SHS	Ref.	—
	25 to < 30 kg/m^2	Deficiency*SHS	2.34(0.63, 8.72)	0.206
		Insufficiency*SHS	0.65(0.21, 2.02)	0.456
		Sufficiency*SHS	0.51(0.20, 1.35)	0.177
		Deficiency*non-SHS	1.30(0.52, 3.25)	0.572
		Insufficiency*non-SHS	0.59(0.27, 1.28)	0.178
		Sufficiency*non-SHS	Ref.	—
	≥ 30 kg/m^2	Deficiency*SHS	4.73(1.77, 12.68)*	0.002
		Insufficiency*SHS	1.32(0.53, 3.32)	0.553
		Sufficiency*SHS	1.76(0.64, 4.82)	0.272
		Deficiency*non-SHS	0.98(0.40, 2.40)	0.970
		Insufficiency*non-SHS	1.47(0.69, 3.12)	0.323
		Sufficiency*non-SHS	Ref.	—

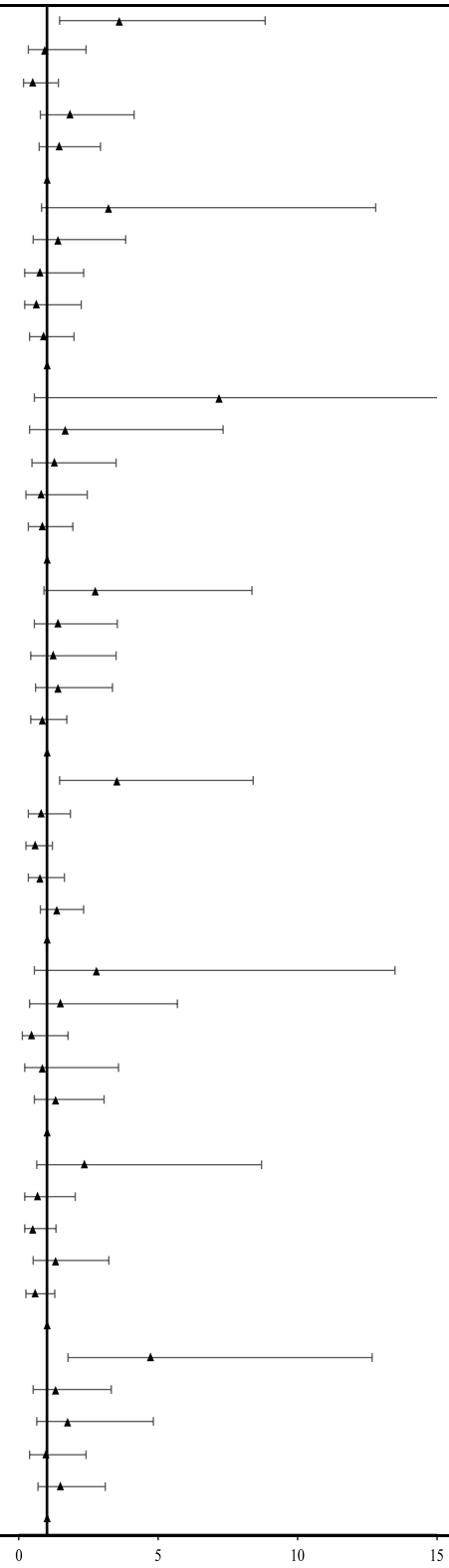

FIGURE 2
Subgroup analysis of the interaction of 25(OH)D and SHS on the risk of DSST in the elderly, NHANES 2011–2014 (*N* = 1,446). *: significant at $p < 0.05$. Abbreviations: DSST, the Digit Symbol Substitution Test; SHS, secondhand smoke; BMI, body mass index.

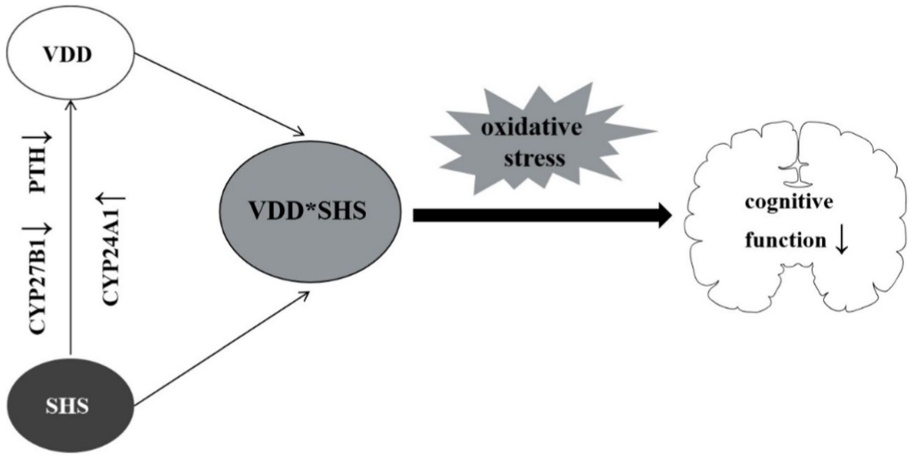

FIGURE 3
The latent mechanism.

addition, people with overweight and obese are more likely to develop VDD, mainly due to the less sun exposure than lean counterparts (61); VD levels are reduced due to volume dilution (62).

There are several strengths in our study. To begin with, our research makes use of a significant portion of the United States population as subjects and examines the impact of SHS with VDD on the deterioration of cognitive abilities. In addition, this study is the first of its kind to examine the connection between the combined exposure of VDD and SHS and the risk of cognitive decline among the general elderly population. This may have significant impact on public health. Furthermore, SHS exposure was evaluated by utilizing both self-reported data and the concentration of serum cotinine measured by ID HPLC-APCI MS/MS, which is a reliable biomarker for SHS exposure. The inclusion of serum cotinine concentration helps to minimize measurement errors and provide more accurate results regarding SHS. Nonetheless, there are certain limitations in the present study. Firstly, the cross-sectional design of the study makes it challenging to make a causal explanation of the results. Secondly, self-reported smoking among senior citizens can lead to random and systematic errors, as well as potential recall bias. Nevertheless, we mitigated this issue by incorporating serum cotinine as a biomarker for SHS exposure to ensure the reliability. Thirdly, although we adjusted for confounders as much as possible in the final model, we cannot rule out that there are still additional possible confounders.

5 Conclusion

Cognitive impairment in the elderly population was found to be associated with VDD and SHS has a synergistic effect with VDD. This effect was particularly pronounced in overweight and obese individuals. Our findings add new theoretical support for the potential risk factors of cognitive impairment due to living habits that can be modified, helping facilitate planning and guiding targeted strategies in the elderly such as stricter restrictions on smoking in the circumstance, ensuring sufficient vitamin D intake as well as sun exposure to prevent and control cognitive impairment in elderly. Furthermore, our study highlights the need for future research to investigate the underlying mechanisms of the combined effects of VDD and SHS on cognitive impairment in the elderly.

Data availability statement

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

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The research was carried out in accordance with the principles outlined in the Declaration of Helsinki. Written informed consent from the patients/ participants or patients/ participants' legal guardian/next of kin was required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

YL: Data curation, Formal analysis, Visualization, Writing – original draft, Writing – review & editing. QS: Conceptualization, Formal analysis, Methodology, Supervision, Writing – review & editing. CC: Formal analysis, Investigation, Supervision, Writing – review & editing. XuY: Data curation, Investigation, Supervision, Writing – review & editing. XW: Investigation, Supervision, Writing – review & editing. XiY: Investigation, Supervision, Writing – review & editing. XZ: Investigation, Supervision, Writing – review & editing. LC: Data curation, Funding acquisition, Investigation, Writing – review & editing. JX: Methodology, Project administration, Supervision, Writing – review & editing. GG: Conceptualization, Project administration, Supervision, Writing – review & editing.

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Conflict of interest

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

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2025.1533193/full#supplementary-material

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Alzheimer's disease and insomnia: a bibliometric study and visualization analysis

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Background: Alzheimer's disease (AD) is the fastest-growing neurodegenerative disorder globally, with patient numbers expected to rise to 130 million by 2050. Insomnia, a prevalent comorbidity, exhibits a bidirectional relationship with AD: insomnia accelerates AD pathology, while AD worsens sleep disorders. This relationship has emerged as a key area of research. Current mechanisms involve oxidative stress, inflammatory responses, and glymphatic system dysfunction, yet a comprehensive review of these processes remains absent.

Objective: To conduct a visual analysis of the relationship between Alzheimer's disease and insomnia using CiteSpace.

Methods: Literature on "insomnia" and "Alzheimer's disease" published between January 1, 2000, and October 31, 2024, was retrieved from the Web of Science Core Collection. CiteSpace and VOSviewer software were used to analyze institutions, authors, and keywords.

Results: A total of 1,907 articles were analyzed, revealing a consistent upward trend in publication volume. The United States and the Mayo Clinic were identified as leading contributors, producing 704 and 57 publications, respectively. Boeve Bradley F the most prolific author contributed 30 publications. Collaboration was actively observed among countries, institutions, and authors. High-frequency keywords identified were "Parkinson's disease," "cognitive impairment," and "sleep behavior disorder." Emerging research areas are likely to focus on "sleep quality" and the "glymphatic system."

Conclusion: This study is the first to apply bibliometric analysis to identify three key trends in AD and insomnia research: the dominance of the United States and Mayo Clinic, strong international collaboration, and a focus on critical areas such as cognitive impairment, the glymphatic system, and sleep interventions. Insomnia may accelerate AD progression via multiple pathways, indicating that enhancing sleep quality could provide new strategies for early intervention. Future research should prioritize advancing the clinical translation of sleep interventions and investigating the mechanisms of the glymphatic system.

KEYWORDS

bibliometrics, CiteSpace, VOSviewer, visual analysis, insomnia, Alzheimer's disease

1 Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder marked by progressive cognitive decline, memory loss, and behavioral changes, which significantly affect patients' daily lives and social interactions (Li et al., 2023). The prevalence of AD is increasing rapidly among aging populations and is expected to nearly triple in the next few decades (Wilkins et al., 2022). AD imposes substantial, psychological, and financial burdens on patients and their families and places significant strain on healthcare systems.

Insomnia, a prevalent sleep disorder, is strongly linked to the onset and progression of Alzheimer's disease. Studies show that AD patients frequently suffer from poor sleep quality, including difficulty falling asleep, frequent nighttime awakenings, and excessive daytime sleepiness (Webster et al., 2019). Such disturbances may result from neurotransmitter imbalances in AD, including norepinephrine and acetylcholine dysregulation, which disrupt the sleep-wake cycle (Huang et al., 2020). Insomnia impairs cognitive function and may also accelerate disease progression, perpetuating a vicious cycle (Musiek and Holtzman, 2016). Improving sleep quality is therefore essential for the overall wellbeing of AD patients.

Current treatments for AD mainly involve medications, such as donepezil, rivastigmine, and memantine, aimed at improving cognitive function (Khan et al., 2022). However, these drugs show limited effectiveness in improving sleep quality and may cause adverse effects with prolonged use, such as gastrointestinal issues, nausea, and even insomnia (Arvanitakis et al., 2019). Combining pharmacological treatments with non-pharmacological interventions, such as cognitive behavioral therapy (CBT) and sleep hygiene education, is crucial for improving sleep quality in AD patients (Qaseem et al., 2016).

The interaction between sleep and circadian rhythms plays a critical role in Alzheimer's disease. Circadian rhythm disruptions can worsen insomnia and further impair cognitive function. Borbély's "two-process model" provides a framework for understanding sleep regulation in AD, emphasizing the interaction between circadian rhythms and sleep homeostasis (Borbély, 1982). Addressing sleep disturbances and circadian rhythm dysregulation in AD may offer novel clinical intervention strategies to enhance cognitive function and quality of life.

Bibliometrics is a quantitative method used to systematically analyze academic literature (such as books, journal articles) and associated metadata (such as abstracts, keywords, and citations). Bibliometric analysis maps relationships between publications and identifies trends in specific disciplines or research fields by analyzing statistical data. Despite its limitations, bibliometrics is a widely used objective tool for understanding various aspects of research activity (Chen, 2006).

This study applied bibliometric and visual analyses with VOSviewer and CiteSpace to explore the relationship between AD and insomnia. The analysis quantitatively evaluated contributions from authors, countries, and institutions, along with their collaborative networks (Synnestvedt et al., 2005; van Eck and Waltman, 2010). Bibliometric tools were also employed to analyze keywords in the included literature, identifying research hotspots and forecasting future trends. These findings offer valuable insights for researchers aiming to understand the current state of the field.

2 Methods

2.1 Data sources and search strategy

This study's terminology is based on a frequency analysis of high-frequency terms from the MeSH database, focusing on core concepts. Insomnia is defined by the ICSD-3 criteria as difficulty falling asleep, maintaining sleep, or early awakening for at least 3 months, along with daytime functional impairment. The selected search terms include "Insomnia," "Sleep disorder," "Sleeplessness," and "Circadian rhythm disruption," while non-specific terms (e.g., "fatigue") were excluded to ensure relevance. Articles on Alzheimer's disease and insomnia were retrieved from the Web of Science Core Collection (WoSCC) between 2000 and 2024. Retrieval strategy: [TS = ("Alzheimer's disease" OR "Alzheimer's disease") AND TS = ("Insomnia" OR "Sleep disorder" OR "Sleeplessness" OR "Circadian rhythm disruption")] NOT TS = ("Parkinson's*"); Publication Date: 2000-01-01 to 2024-10-31. A total of 2,049 articles were retrieved.

2.2 Study type and exclusion criteria

Study type: This includes both original research articles and reviews, which together provide a comprehensive overview of the existing knowledge.

Exclusion criteria: Language: Only studies published in English were included to ensure consistency and reliability. Relevance: Studies not directly addressing the relationship between Alzheimer's disease and insomnia were excluded. This includes studies that focus on only one condition without exploring their potential connection.

Quality: Studies with poor methodological quality or that did not meet the standards of peer-reviewed journals were excluded to maintain the analysis's integrity.

After applying these steps, 1,907 articles were selected, and plain text files were used to export complete records and references. The extracted data were downloaded into CiteSpace and VOSviewer software for bibliometric analysis. The search strategy employed in this study is shown in Figure 1. The literature mainly consists of original articles (1,224 in total), with 683 reviews, as shown in Figure 2.

2.3 Visualization tools

This study used CiteSpace (version 6.2.R4) and VOSviewer (version 1.6.18) for co-occurrence analysis and to generate visualized graphs. The results of the analysis were imported into Microsoft Excel 2019 to produce supplementary charts and figures. In the visualized maps, nodes, and links constitute the core

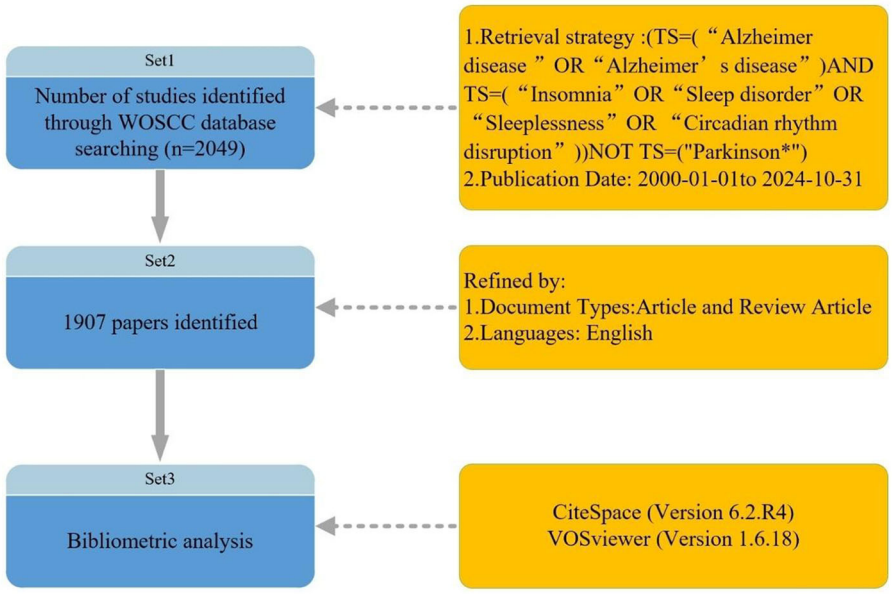

FIGURE 1
Flowchart of data screening and bibliometric analysis.

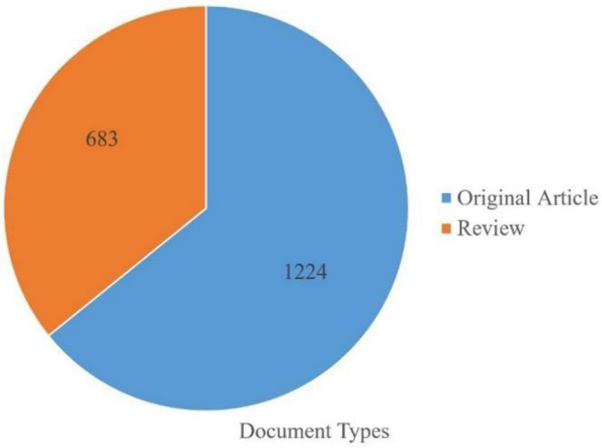

FIGURE 2
Distribution of documents by type.

structure. Each node represents an analyzed entity, such as an author, institution, or journal. Links represent co-occurrence and co-citation relationships between nodes. Generally, a larger number of nodes indicates higher frequency, whereas the number and thickness of links reflect the strength of relationships between nodes. Centrality is a critical metric for assessing the importance of nodes within a network. Nodes with more shortest paths passing through them exhibit higher centrality. Nodes with centrality values >0.1 are generally considered pivotal within a specific field.

3 Results

3.1 Annual publication trends and analysis

A literature search was conducted for studies published between 2000 and 2024. While early research laid the foundation for this field, it had limitations due to small sample sizes and lower research quality, which hindered the exploration of the complex mechanisms underlying AD pathology. Thus, focusing on high-quality research published after 2000 enables more accurate and reliable conclusions in this field. A total of 1,907 articles on AD and insomnia were retrieved between 2000 and 2024. As data collection ended on October 31, 2024, the records for 2024 are incomplete. Figure 3 illustrates a steady increase in publications from 2000 to 2023. The Joinpoint Regression model aims to identify “inflection points” or significant change points in the data, revealing trends in data changes by applying different regression models at various stages. In this study, we used this model to identify inflection points in publication volume between 2000 and 2023 ($p < 0.05$). A regression analysis of the annual number of articles published over the past 24 years yielded the linear growth formula: $y = 6.3893x$. This formula was derived using linear regression, a method that minimizes the distance (errors) between data points and the fitted line to determine the best-fitting line. The goal of this process is to use a mathematical model to describe the trend of data changes. The resulting linear growth trend indicates an annual increase of 6.4% in attention. Based on these “inflection points” or significant change points, the study divides the entire data period into four phases. The growth trajectory is divided into four phases: 2000–2005: A slow growth phase, with 20–35 articles published annually, representing the early stage of research interest. 2006–2011: A phase of modest fluctuations in

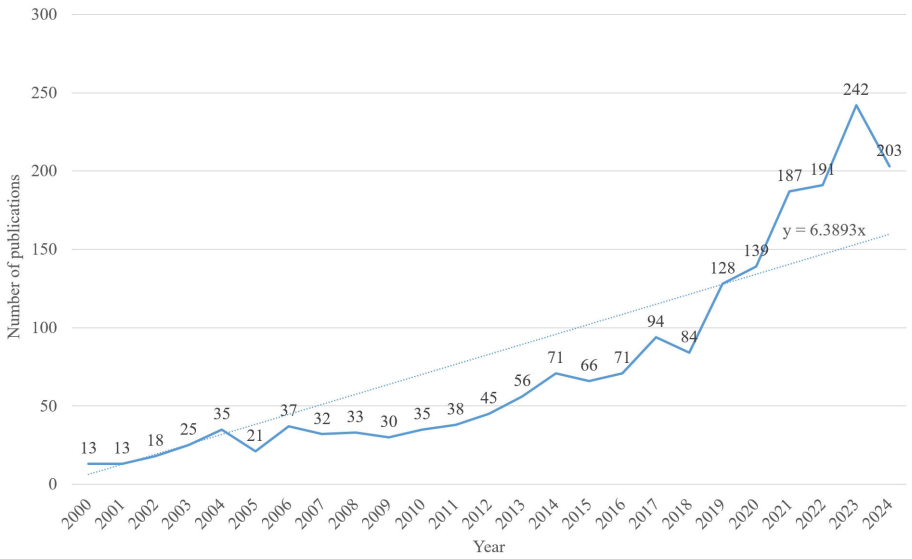

FIGURE 3
Annual publication trends. Shows the global publication volume from 2000 to 2024, with the fitted formula $y = 6.3893x$.

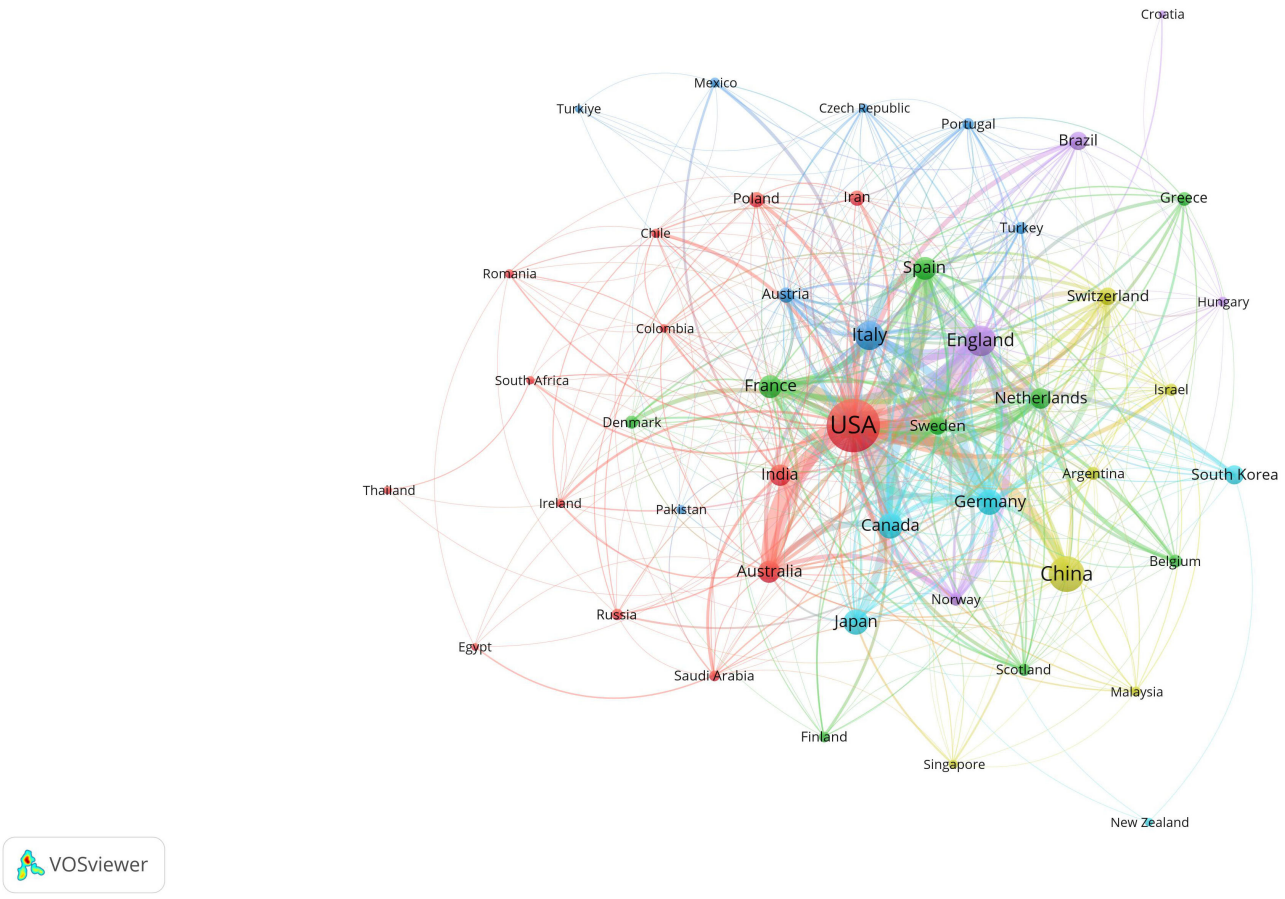

FIGURE 4
Collaboration network among countries and regions. The size of the nodes represents publication volume, while the thickness of the connecting lines indicates the strength of collaboration (TLS ≥ 10). Only 48 countries with publication volumes ≥5 are displayed. Six collaboration clusters, each represented by a different color, were formed, with a total connection strength of 1,753.

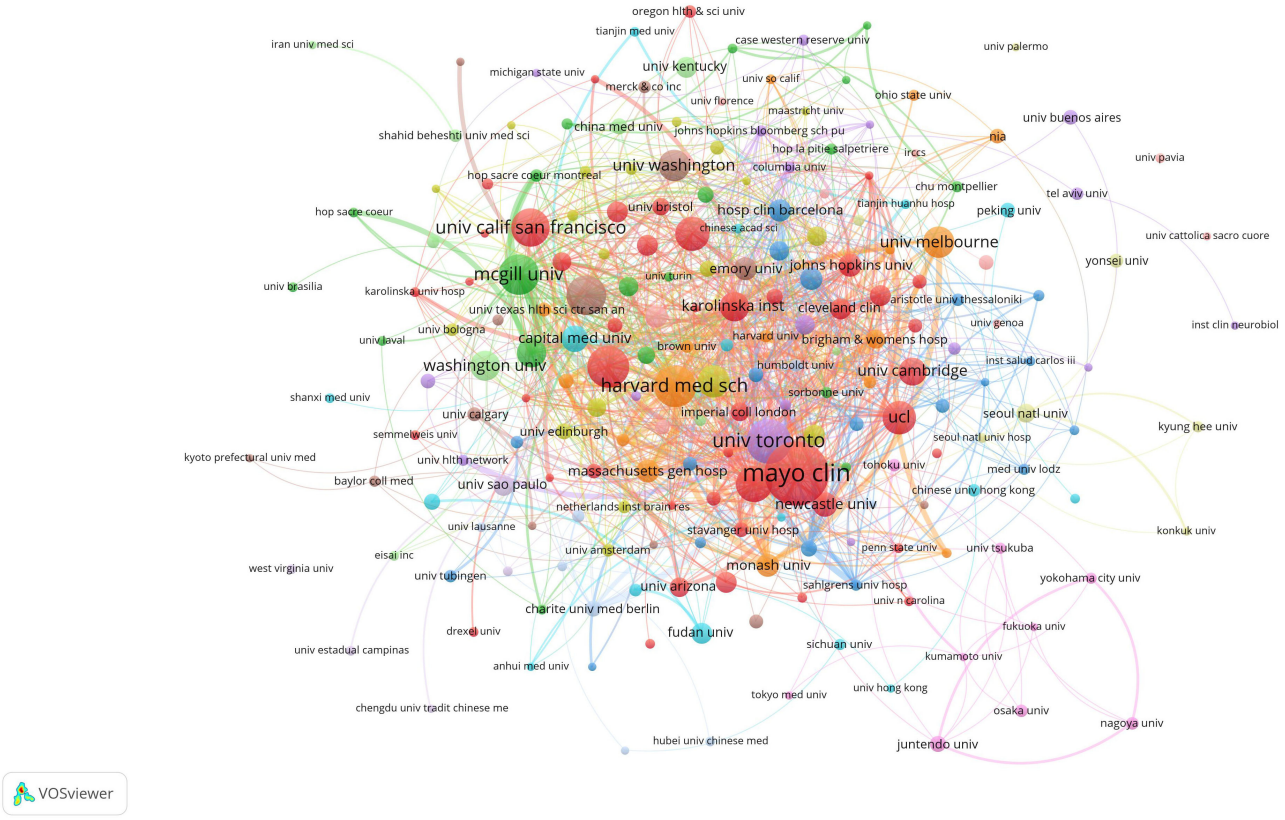

FIGURE 5
Institutional collaboration network. The size of the nodes represents publication volume, while the thickness of the connecting lines indicates collaboration strength (TLS ≥ 10). There are 2,862 institutions in total, with 216 institutions displaying a publication volume of 5 or more. Fourteen collaboration clusters, each represented by a different color, were formed, with a total connection strength of 1,913.

research attention but with overall steady growth. 2012–2017: A steady growth phase, with publications increasing from 45 to 94, reflecting significantly heightened research interest. 2018–2023: A rapid growth phase, especially after 2020, characterized by a sharp surge in publications. The highest number of publications was recorded in 2023 (242 articles), with a slight decline to 203 articles in 2024. Overall, researchers' interest in the link between AD and insomnia has remained consistently strong. Annual publication trends underscore the growing importance of this academic topic. The steady rise in annual publications over the past 24 years demonstrates the increasing attention this topic has garnered from researchers.

3.2 Bibliometric analysis of countries and institutions

Statistical analysis identified 2,862 institutions from 82 countries and regions that published articles on Alzheimer's disease and insomnia. The number of articles produced by each institution was analyzed using VOS viewer, as depicted in Figures 4–6.

Table 1 presents the top 10 contributing countries and regions. The United States led with 704 publications, followed by China with 267. The United Kingdom and Italy produced a comparable number of publications, with 179 and 159 articles, respectively. Figure 4 highlights the United States, United Kingdom, Germany, Italy, and Canada as prominent hubs with strong interconnections, indicating their significant global academic influence and collaboration in this field. Regarding collaboration, the United States ranked first with a Total Link Strength (TLS) of 500 and 44 connections, followed by the United Kingdom with a TLS of 307 and 37 connections.

Figure 5 shows 67 institutions that produced at least 10 publications. In North America, prominent institutions included the Mayo Clinic, Harvard Medical School, University of Pennsylvania, Stanford University, and University of California (San Francisco and San Diego), as well as Canada's University of Toronto and McGill University. In Europe, King's College London and University College London were significant contributors. These findings suggest that regional characteristics significantly influence institutional collaborations.

Table 2 highlights that the top ten global institutions in AD and insomnia research are dominated by North American institutions, with notable collaboration between Europe and North America. The Mayo Clinic in the United States leads with 57 publications and 3,680 total citations, focusing on the mechanisms of circadian rhythm disruption and the glymphatic system. The University of Toronto (37 publications) and McGill University (33 publications) in Canada investigate the interaction

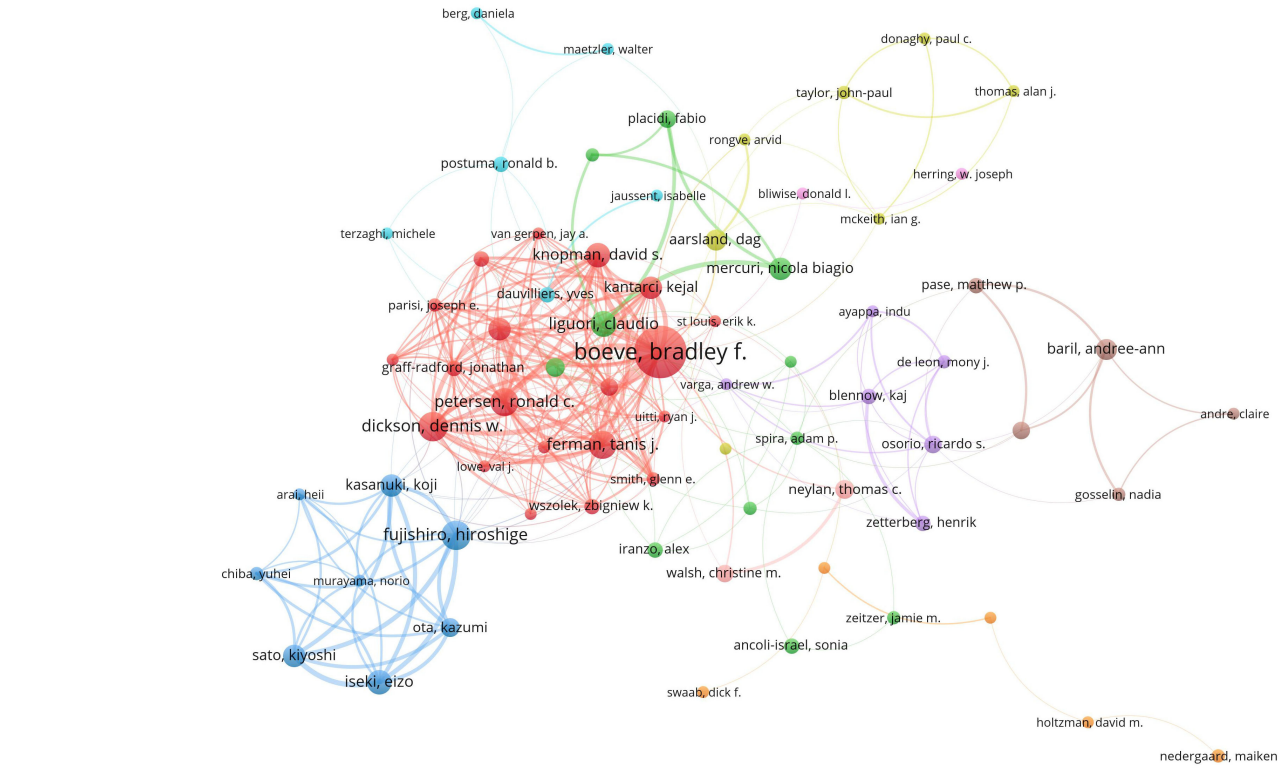

FIGURE 6
Author collaboration network. There are 9,560 authors in total. The size of the nodes represents publication volume, while the thickness of the connecting lines indicates collaboration strength (TLS ≥ 10). Only 96 authors with a publication volume of 5 or more are displayed. Eight collaboration clusters, each represented by a different color, were formed, with a total connection strength of 1,043.

between the APOE ε4 gene and sleep disorders through extensive inter-institutional collaboration (49/50 links). King's College London (29 publications) leads Europe with a total link strength of 103, advancing multidisciplinary research on the socioeconomic burden of insomnia in AD. These institutions' research directions exhibit a clinical-basic linkage. For instance, Harvard Medical School has made breakthroughs in glymphatic system imaging (Cluster #8), while the University of California, San Francisco has advanced the development of cerebrospinal fluid biomarkers. These institutions have fostered innovation in AD and insomnia mechanism research through strong collaborations (e.g., McGill's 50 links with U.S. institutions) and interdisciplinary integration (e.g., King's College London integrating neuroscience and public health), providing a model for future research that connects clinical cohorts with basic research.

Table 3 highlights the most prolific authors in the field of AD and insomnia. Boeve, Bradley F led with 30 publications, followed by Dickson, Dennis W and Fujishiro, Hiroshige, who each contributed 15 publications. Ferman, Tanis J and Petersen, Ronald C shared third place with 14 publications each.

In terms of co-citations, Braak, H, ranked first with 448, followed by Mckeith, IG, with 414. VOSviewer defined researcher collaboration as having at least five co-authored publications. Figure 6 depicts 96 authors meeting this criterion, with Boeve, Bradley F leading the first tier with a Total Link Strength (TLS) of 148.

3.3 Bibliometric analysis of keyword co-occurrence and clustering

Keyword co-occurrence identifies key research topics within a specific field. In the co-occurrence network map, nodes represent keywords, their size reflects the frequency of articles containing the keyword, and links indicate relationships among keywords. Figure 7 illustrates the intricate network of links between keywords, demonstrating their complex interconnections. High-centrality keywords signify the prominence of their associated research areas, while high-frequency keywords indicate trending topics. Table 4 presents the top 10 high-frequency keywords: "Alzheimer's disease" (Frequency: 1,181), "dementia" (Frequency: 353), "mild cognitive impairment" (Frequency: 302), "insomnia" (Frequency: 190), "cognitive impairment" (Frequency: 165), "sleep behavior disorder" (Frequency: 160), "risk" (Frequency: 146), "older adults" (Frequency: 145), "sleep" (Frequency: 131), and "diagnosis" (Frequency: 126). Table 4 also lists the top 10 high-centrality keywords: "placebo-controlled trial" (Centrality: 0.09), "oxidative stress" (Centrality: 0.08), "central nervous system" (Centrality: 0.08), "insomnia" (Centrality: 0.07), "cerebrospinal fluid" (Centrality: 0.07), "Lewy body" (Centrality: 0.07), "disturbances" (Centrality: 0.06), "REM sleep" (Centrality: 0.06), "association" (Centrality: 0.06), and "daytime sleepiness" (Centrality: 0.06).

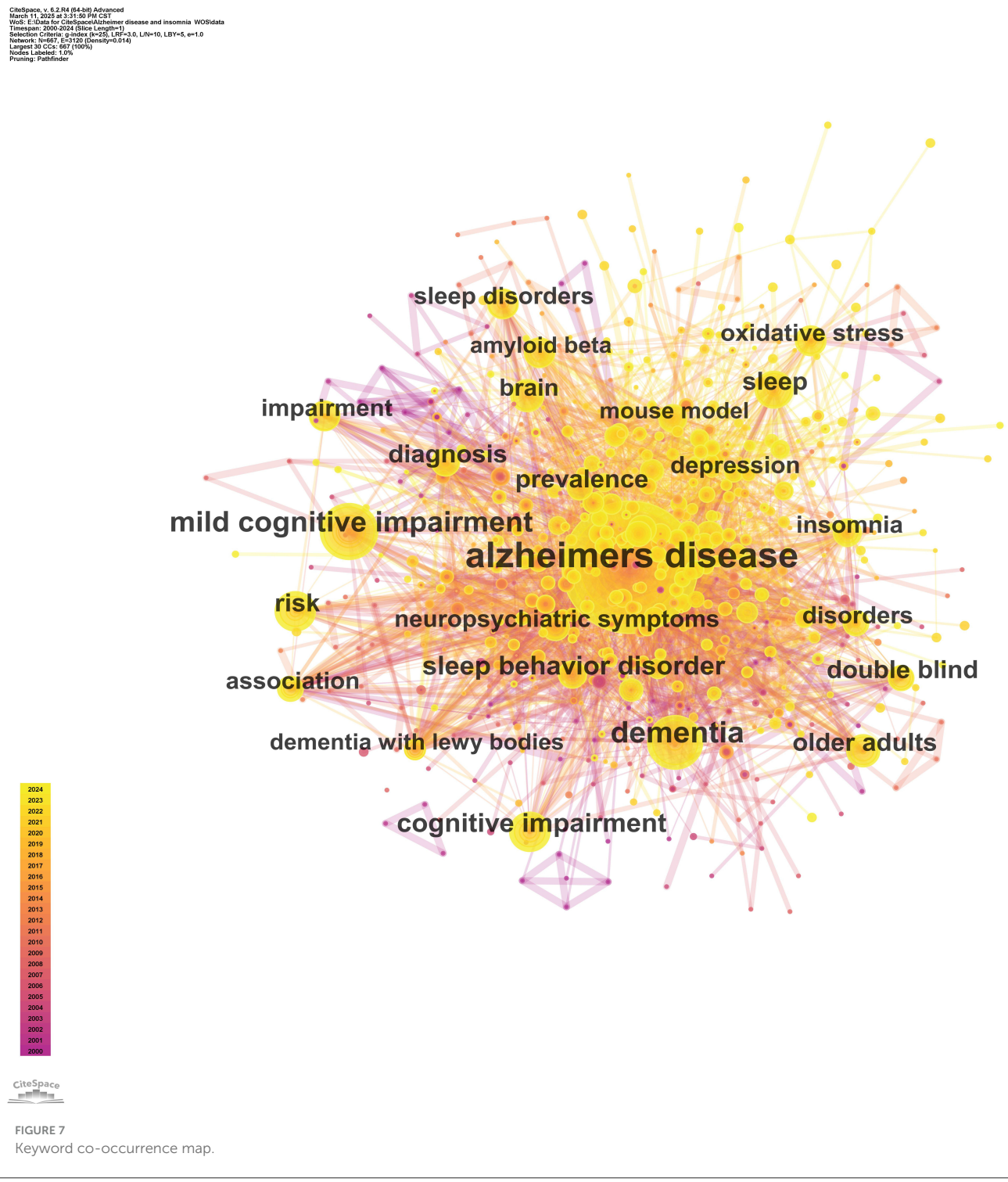

FIGURE 7
Keyword co-occurrence map.

CiteSpace cluster analysis identifies key research themes. Clustering quality is typically evaluated using the average silhouette coefficient. Clustering analysis was conducted using the built-in Log-Likelihood Ratio (LLR) algorithm in CiteSpace. The LLR algorithm maximizes intra-class similarity and inter-class differences to divide the co-occurrence network into clusters with semantic consistency. For the parameter settings, the time slice was set from 2000 to 2024, with an annual interval. The node type was keywords, and the Pathfinder algorithm was used to prune redundant weak connections, preserving the core network structure. Generally, a silhouette value above 0.5 indicates reasonable clustering, while values above 0.7 suggest highly effective and reliable clustering. This study identified 10 clusters, presented in Table 5 and Figure 8. The overall silhouette

TABLE 1 The top 10 most productive countries are ranked according to key metrics, including the number of documents, citations, total link strength (TLS), and the number of collaborative connections (Links).

Rank	Country	Documents	Citations	Links	TLS
1	USA	704	43,779	44	500
2	England	179	15,667	37	307
3	Germany	111	12,362	37	221
4	Italy	159	9,470	36	196
5	Canada	112	13,101	34	171
6	Spain	91	10,794	33	185
7	Australia	82	10,269	32	154
8	France	86	11,229	29	163
9	Peoples R China	267	7,689	25	97
10	Japan	114	9,134	25	68

TABLE 2 The top 10 most productive institutions are evaluated and ranked according to key metrics, including the number of Documents, Citations, Total link strength (TLS), and the number of collaborative links.

Rank	Organization	Documents	Citations	Links	TLS
1	Mayo Clinic	57	3,680	47	82
2	University of Toronto	37	1,719	49	80
3	Harvard Medical School	34	720	45	95
4	University of Pennsylvania	34	2,797	40	60
5	McGill University	33	1,274	50	88
6	Stanford University	32	1,490	36	47
7	University of California San Francisco	31	2,219	35	47
8	King's College London	29	1,787	66	103
9	University of California San Diego	27	1,403	28	37
10	University College London	26	1,418	38	55

score was 0.7431, and each cluster achieved a silhouette value above 0.5, indicating high reliability of the results. The modularity value (Q) of this study was 0.4323 (>0.3), indicating a meaningful and substantial clustering structure.

3.4 Bibliometric analysis of keyword bursts and temporal trends

Keyword bursts refer to keywords that are cited with high frequency during specific time periods. The distribution of keywords with strong citation bursts can predict emerging research frontiers. CiteSpace was employed to analyze high-burst keywords from 2000 to 2024. Figure 9 highlights 25 keywords exhibiting the strongest citation bursts. Green lines represent the full study period, while red lines highlight time intervals during which specific keywords experienced bursts of activity. Among these, "body disease" and "excessive daytime sleepiness" exhibited the longest burst durations. Keywords such as "sleep quality," "glymphatic system," and "sleep disorder" remain significant and are likely to serve as focal points for future research in this field. The keyword "glymphatic system" experienced a significant surge in citations after 2020, indicating growing research interest in this area. This increase is attributed to the glymphatic system being recognized as a crucial pathway for waste clearance in the brain, particularly in the removal of β-amyloid (Aβ) associated with AD. Recent studies have shown that the glymphatic system becomes more active during sleep, helping to clear metabolic waste from the brain. This process is closely linked to the pathological progression of Alzheimer's disease (Delic et al., 2021). Researchers, using functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), can now observe the activity of the glymphatic system more directly, providing new tools to study its role in brain waste clearance and advancing related research. Studies suggest that sleep quality is closely linked to glymphatic

TABLE 3 The top 10 most prolific authors and most frequently co-cited authors.

Rank	Author	Documents	Citations	TLS	Rank	Author	Co-citations
1	Boeve, Bradley F	30	2,529	148	1	Braak, H	448
2	Dickson, Dennis W	15	841	109	2	Mckeith, Ig	414
3	Fujishiro, Hiroshige	15	571	66	3	Boeve, Bf	372
4	Ferman, Tanis J	14	1,147	108	4	Liguori, C	313
5	Petersen, Ronald C	14	1,088	108	5	Aarsland, D	280
6	Liguori, Claudio	13	448	29	6	Cummings, Jl	277
7	Iseki, Eizo	12	386	54	7	Mccurry, Sm	263
8	Knopman, David S	12	1,081	98	8	Mander, Ba	259
9	Graff-radford, Neill R	11	885	92	9	Postuma, Rb	257
10	Kantarci, Kejal	11	622	82	10	Ju, Yes	256

TABLE 4 Top 10 keywords ranked by frequency and centrality.

Rank	Keywords	Frequency	Keywords	Centrality
1	Alzheimer's disease	1,181	Placebo controlled trial	0.09
2	Dementia	353	Oxidative stress	0.08
3	Mild cognitive impairment	302	Central nervous system	0.08
4	Insomnia	190	Insomnia	0.07
5	Cognitive impairment	165	Cerebrospinal fluid	0.07
6	Sleep behavior disorder	160	Lewy body	0.07
7	Risk	146	Disturbances	0.06
8	Older adults	145	Rem sleep	0.06
9	Sleep	131	Circadian rhythm	0.06
10	Diagnosis	126	Daytime sleepiness	0.06

system function, with sleep deprivation significantly reducing its clearance efficiency. This exacerbates the pathological progression of AD and has driven further research into the relationship between sleep disorders and AD (Sadeghmousavi et al., 2020). The glymphatic system, as a key pathway for brain waste clearance, has become a potential target for Alzheimer's disease treatment. Researchers are exploring therapies aimed at enhancing glymphatic system function to slow the progression of AD (Buccellato et al., 2022).

3.5 Keyword timeline analysis

A keyword timeline map visually analyzes and displays temporal trends in academic keywords. Keywords from 2000 to 2024 were analyzed using CiteSpace to identify research hotspots and trends across different time periods (Figure 10). Table 6 presents keywords with a frequency >100, excluding broad terms such as "Alzheimer's disease," "Insomnia," "Sleep disorder," and "Sleeplessness," along with their first appearance year, based on automatic software analysis. The keyword timeline map facilitated a longitudinal analysis of research hotspots from 2000 to 2024, summarized below:

Figure 10 displays a keyword timeline map that illustrates the spatiotemporal distribution of keywords in AD and insomnia research from 2000 to 2024, highlighting the field's evolution from basic associations to mechanistic analysis and precision interventions. The early stage (2000–2005) focused on disease diagnosis and basic pathologies, such as β-amyloid protein and oxidative stress. The mid-stage (2006–2015) shifted focus to molecular mechanisms, such as the glymphatic system and neuroinflammation, as well as intervention strategies like light therapy and melatonin. The recent stage (2016–2024) has adopted an interdisciplinary approach, with emerging topics such as glymphatic system regulation (which saw a breakout in 2021), Mendelian randomization for causal validation (also a breakout in 2021), and multi-omics integration research. Core nodes reveal that the bidirectional relationship between AD and insomnia persists, while the strong association between the "glymphatic system" and "sleep quality" suggests that sleep-dependent brain waste

TABLE 5 Keyword clustering analysis.

Cluster ID	Silhouette	Mean (Year)	Label (LSI)
#0 Dementia	0.686	2008	Mild cognitive impairment; mendelian randomization; sleep traits; coronary artery disease
#1 Sleep deprivation	0.674	2014	Sleep disturbance; sharp-wave ripples; neuronal reactivation; beta pathology
#2 Dementia with lewy bodies	0.756	2009	Vascular dementia; cognitive impairment; intracerebral source locations; progressive supranuclear
#3 Locus coeruleus	0.670	2017	Iron metabolism; endocrine system; animal models; neuromedin u
#4 Circadian rhythms	0.729	2011	Light therapy; sleep disturbance; irregular sleep-wake rhythm; pharmacologic interventions
#5 Fatal familial insomnia	0.856	2007	Cerebrospinal fluid; prion diseases; neurofilament light; frontotemporal dementia
#6 Toxicity	0.854	2014	Household members; healthcare resource use; healthcare costs; psychiatric symptom
#7 Rem sleep	0.912	2013	Sleep disturbance; light therapy; pharmacologic interventions; sleep management
#8 Alzheimer's disease	0.925	2009	Tau hyperphosphorylation; non-rapid eye movement sleep; amyloid beta-peptides; white matter hyperintensities
#9 Mendelian randomization	0.944	2021	Alzheimer's disease; low-density lipoprotein; coronary artery disease; cognitive decline

clearance mechanisms are becoming a major research frontier. The timeline map also reflects trends in interdisciplinary fields, such as neuroimaging and epigenetics, as well as clinical translation directions, including personalized interventions based on APOE ε4 genotype. It provides a visual basis for understanding the field's dynamics and guiding interdisciplinary research.

Table 6 presents the high-frequency keywords from 2000 to 2024, along with their first occurrence years. The keywords include "dementia," "mild cognitive impairment," "sleep behavior disorder," and "risk," among others. The frequency and first occurrence years of these keywords reflect the evolving research trends in the field.

4 Discussion

4.1 General overview

This study employed CiteSpace and VOSviewer to analyze the current state of research on the relationship between AD and insomnia, emphasizing key topics and emerging trends. A total of 1,907 articles were retrieved from the Web of Science Core Collection database. The rapid increase in publication rates after 2020 may be attributed to the surge in anxiety and sleep disorders caused by the COVID-19 pandemic, which stimulated research on sleep disorders. This likely advanced research on the relationship between AD and insomnia, establishing it as a prominent topic in medical research. Boeve, Bradley F affiliated with the Mayo Clinic, was the most prolific author, contributing 30 publications. The United States and the Mayo Clinic are leading contributors in this field, producing 704 and 57 publications, respectively. Active international and institutional collaboration has significantly advanced this research area. Research hotspots in AD and insomnia include pathological mechanisms, circadian rhythm disruptions, biomarker development, and intervention strategies. Advancing interdisciplinary research in this field offers promising avenues for early diagnosis and comprehensive treatment of these conditions.

4.2 Research hotspots in Alzheimer's disease and insomnia

Osorio et al. conducted a comprehensive study on the relationship between Alzheimer's disease and insomnia across various age groups and genetic backgrounds.

The results revealed a stronger association between Alzheimer's disease and insomnia in middle-aged and older populations. This finding underscores the importance of considering age-related factors in studies on the relationship between Alzheimer's disease and insomnia (Osorio et al., 2011). Furthermore, individuals carrying the APOEε4 gene exhibited a higher risk in the relationship between Alzheimer's disease and insomnia (Zhang et al., 2023).

Keyword timeline analysis highlights the evolving trends in Alzheimer's disease and insomnia research. From 2000 to 2024, the focus of research expanded from initial topics such as "Alzheimer's disease" and "insomnia" to include "cognitive impairment" and "mild cognitive impairment." These changes reflect the continuous expansion and deepening of the research field. For example, "Alzheimer's disease" and "insomnia" were the main research focuses around 2000, while "cognitive impairment" emerged as a key focus after 2010. These trends suggest that as research advanced, scholars increasingly focused on specific pathological mechanisms and related diseases.

Keyword clustering reflects the core themes and their inherent connections within the research field. This study identified 10 clusters using CiteSpace (Table 5). The following sections, in

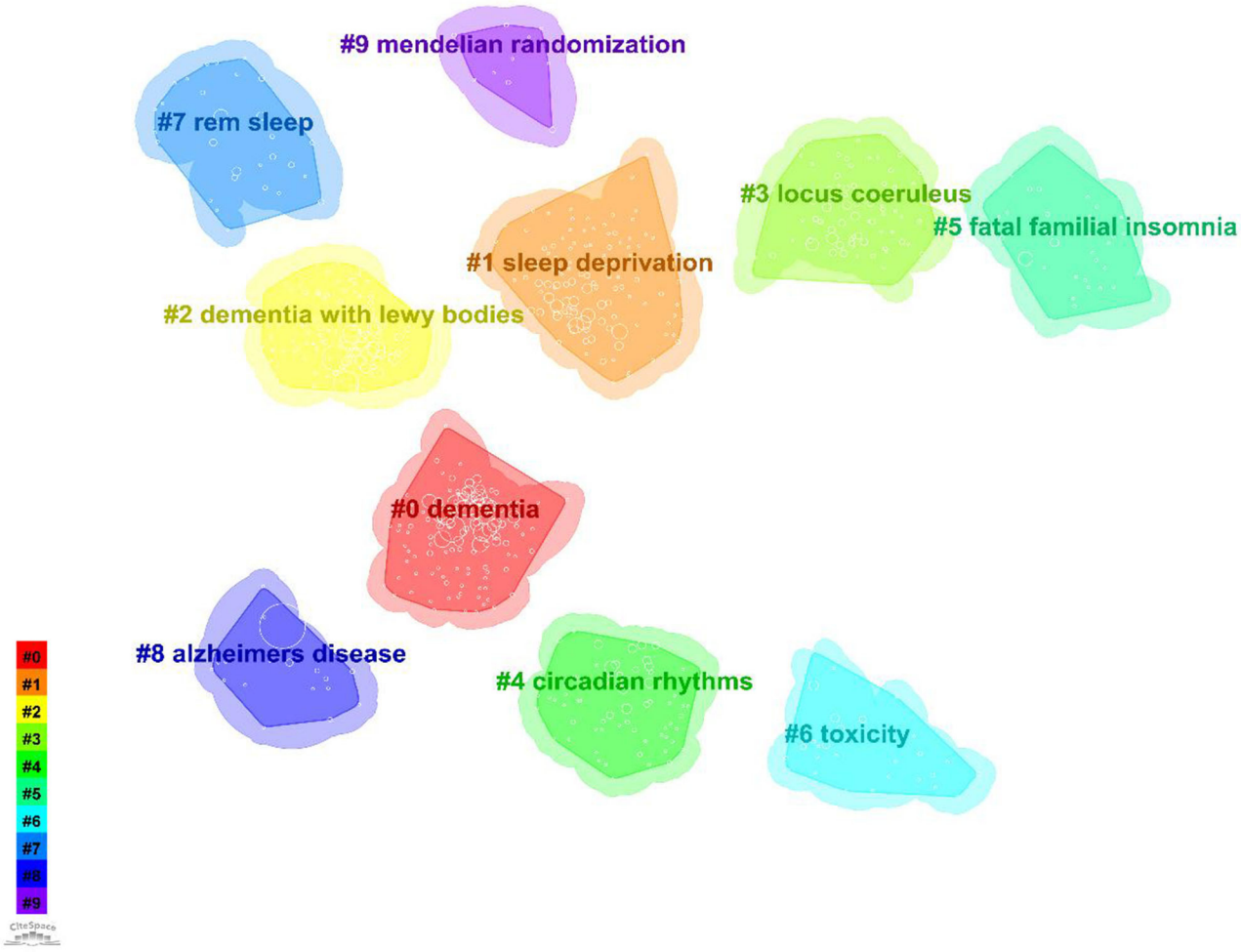

FIGURE 8
Keyword clustering map. The map illustrates ten distinct research clusters, each represented by a unique color. Cluster #0 dementia, Cluster #1 sleep deprivation, Cluster #2 dementia with lewy bodies, Cluster #3 locus coeruleus, Cluster #4 circadian rhythms, Cluster #5 fatal familial insomnia, Cluster #6 toxicity, Cluster #7 rem sleep, Cluster #8 Alzheimer's disease, Cluster #9 mendelian randomization.

conjunction with the discussion, highlight the significance of key clusters in AD and insomnia research.

Cluster #0 "dementia" (Silhouette = 0.686): this cluster reflects the connection between the early stages of Alzheimer's disease (mild cognitive impairment, MCI) and cardiovascular diseases. Studies suggest that sleep disorders may increase Alzheimer's risk by affecting vascular health, indicating that sleep interventions may reduce this risk by improving vascular health (Section 4.2.4). Cluster #1 "sleep deprivation" (Silhouette = 0.674): this cluster focuses on the effects of sleep deprivation on the brain, particularly how it exacerbates Alzheimer's pathology by affecting neuronal activity and the accumulation of β-amyloid protein. It emphasizes the importance of sleep quality in Alzheimer's disease (Section 4.2.1). Cluster #2 "dementia with Lewy bodies" (Silhouette = 0.756): this cluster explores the relationship between Lewy body dementia and Alzheimer's disease, highlighting the overlap in pathology and clinical manifestations of different types of dementia. It suggests that future research should focus on the interactions between different dementia types (Section 4.2.2). Cluster #3 "locus coeruleus" (Silhouette = 0.67): This cluster focuses on the role of the locus coeruleus in Alzheimer's disease, particularly in relation to iron metabolism and neurotransmitter function in sleep disorders. It suggests that dysfunction of the locus coeruleus may play a key role in sleep disturbances in Alzheimer's disease (Section 4.2.3). Cluster #4 "circadian rhythms" (Silhouette = 0.729): this cluster explores the role of circadian rhythm disruptions in Alzheimer's disease, particularly the effectiveness of light therapy in improving circadian rhythm synchronization. It emphasizes the importance of circadian rhythms in Alzheimer's and suggests that future research should focus on the clinical

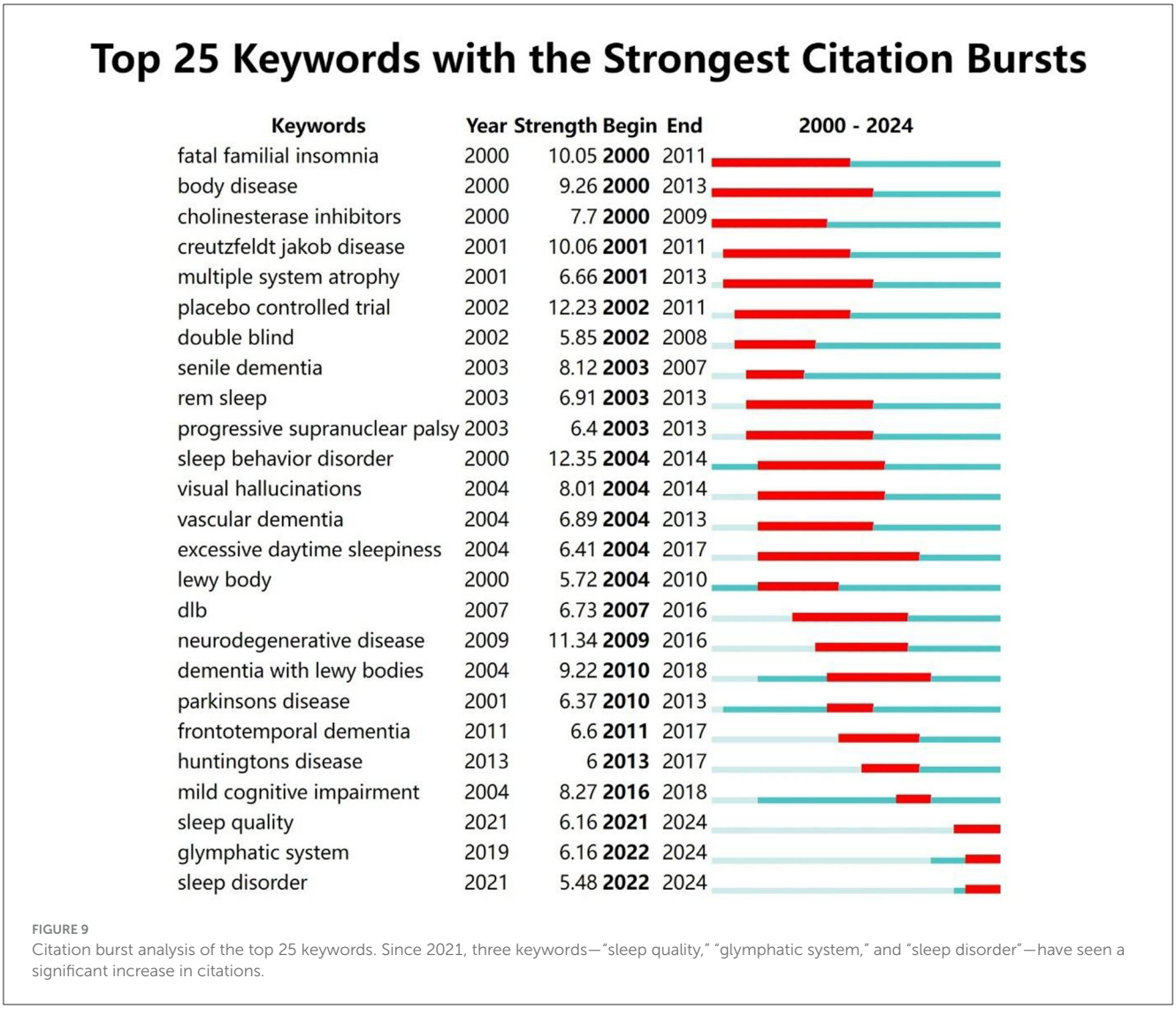

FIGURE 9
Citation burst analysis of the top 25 keywords. Since 2021, three keywords—"sleep quality," "glymphatic system," and "sleep disorder"—have seen a significant increase in citations.

application of light therapy (Section 4.2.5). Cluster #5 "fatal familial insomnia" (Silhouette = 0.856): this cluster focuses on fatal familial insomnia, emphasizing the role of genetic factors in both sleep disorders and Alzheimer's disease. It suggests that future research should explore the relationship between genetic sleep disorders and Alzheimer's disease (Section 4.2.4). Cluster #6 "toxicity" (Silhouette = 0.854): this cluster examines the burden of sleep disorders on family members and healthcare systems, particularly the impact of sleep disorders on healthcare resource use and costs. It suggests that future research should address the social and economic impacts of sleep disorders (Section 4.2.6). Cluster #7 "REM sleep" (Silhouette=0.912): This cluster focuses on the role of REM sleep in Alzheimer's disease, particularly the effectiveness of light therapy and drug interventions in improving REM sleep disorders. It highlights the importance of REM sleep in Alzheimer's and suggests that future research should focus on managing REM sleep disorders (Section 4.2.5). Cluster #8 "Alzheimer's disease" (Silhouette = 0.925): this cluster focuses on the core pathological mechanisms of Alzheimer's disease, particularly the role of tau protein hyperphosphorylation and Aβ peptides in sleep disorders. It suggests that sleep deprivation may accelerate cognitive decline through the Aβ/tau pathway (Sections 4.2.1–4.2.2). Cluster #9 "Mendelian randomization" (Silhouette = 0.944): this cluster uses Mendelian randomization to validate the causal relationship between sleep and Alzheimer's disease, emphasizing the application of genetic markers in Alzheimer's research. It suggests that future studies should focus on gene-targeted interventions (Section 4.2.4).

4.2.1 The bidirectional relationship between Alzheimer's disease and insomnia

Numerous studies confirm the bidirectional relationship between AD and insomnia: insomnia accelerates AD progression, while AD exacerbates sleep disturbances.

Insomnia accelerates AD onset and progression through various mechanisms. It increases neuronal metabolic load, resulting in excessive production of reactive oxygen species (ROS). Impaired ROS clearance causes oxidative stress, damaging neurons, and promoting β-amyloid (Aβ) aggregation and tau protein phosphorylation, thereby advancing AD pathology (Xie

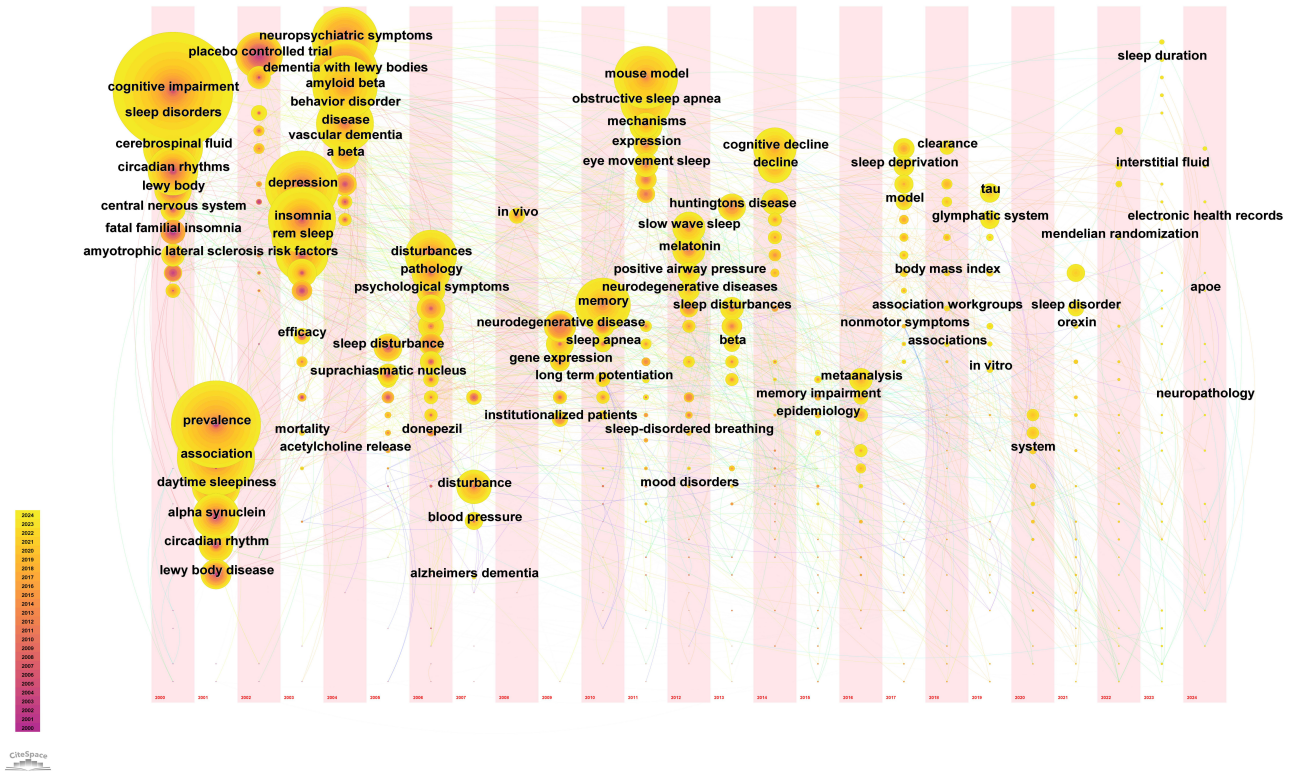

FIGURE 10
Timeline map of keywords related to Alzheimer's disease and insomnia (2000–2024).

et al., 2013; Ye et al., 2014). Oxidative stress induces mitochondrial dysfunction, exacerbating apoptosis and inflammatory responses—key pathways through which insomnia drives disease progression (Cao et al., 2020). Chronic insomnia activates central and peripheral inflammatory pathways, increasing pro-inflammatory markers such as IL-6, TNF-α, and CRP. This activation triggers microglial responses, intensifying neuroinflammation and worsening the toxic effects of Aβ (Dzierzewski et al., 2020; Sadeghmousavi et al., 2020). Sleep deprivation impairs glymphatic system function, reducing Aβ clearance and causing its accumulation in the brain. Reduced or fragmented NREM sleep weakens waste clearance, aggravating Aβ deposition (Iliff et al., 2012; Xie et al., 2013). Reduced REM sleep disrupts synaptic plasticity and memory consolidation, whereas insufficient NREM sleep impairs metabolic waste clearance. Insomnia often co-occurs with sleep apnea, characterized by intermittent hypoxia, triggering inflammatory responses and worsening the toxic effects of Aβ and tau proteins (Ju et al., 2013). In summary, insomnia accelerates AD pathology via oxidative stress, inflammatory responses, impaired Aβ clearance, and disrupted sleep architecture.

AD worsens sleep disturbances through mechanisms including circadian rhythm disruptions, fragmented sleep, and neural network degeneration. Circadian rhythm disruption is an early characteristic of AD and may serve as a predictive marker. Pathological changes in AD, including Aβ plaque deposition and tau tangles, disrupt neuronal networks in the suprachiasmatic nucleus (SCN), the primary regulator of circadian rhythms. These disruptions reduce melatonin secretion and disturb the sleep-wake cycle, causing frequent nighttime awakenings, excessive daytime sleepiness, and inverted circadian behavior, which severely impact quality of life (Wu et al., 2019; Niu et al., 2021; Baril et al., 2023). Patients with AD often experience fragmented sleep, marked by reduced deep sleep and frequent nighttime awakenings, closely associated with neurodegeneration in the hypothalamus, and brainstem. Dysfunction of the locus coeruleus severely impairs sleep-wake transitions (Sethi et al., 2015; Liguori et al., 2020; Egroo et al., 2021). AD damages neural networks across multiple brain regions, including the hypothalamus (regulating circadian rhythms and deep sleep), the hippocampus (responsible for sleep and memory consolidation), and the prefrontal cortex (involved in REM sleep and emotional regulation). This neural degeneration further disrupts sleep continuity and restorative quality, exacerbating symptoms and diminishing quality of life (Kent and Mistlberger, 2017; Lew et al., 2021; Canever et al., 2024).

The bidirectional relationship between insomnia and AD perpetuates a vicious cycle. Insomnia accelerates AD onset and progression through oxidative stress, inflammation, and impaired Aβ clearance. Conversely, AD worsens sleep disturbances

TABLE 6 Frequency and first appearance year of keywords related to Alzheimer's disease and insomnia (2000–2024).

Frequency	Keywords	Year
353	Dementia	2001
302	Mild cognitive impairment	2004
160	Sleep behavior disorder	2000
146	Risk	2006
145	Older adults	2007
126	Diagnosis	2001
123	Prevalence	2001
122	Double blind	2002
109	Oxidative stress	2006
101	Depression	2003

via circadian rhythm disruption, fragmented sleep, and neural network degeneration. This mutual interaction accelerates disease development and progression.

4.2.2 Molecular mechanisms of sleep deprivation

Recent studies suggest that insomnia or sleep deprivation (SD) is a major risk factor for AD. Sleep deprivation increases the production of reactive oxygen species (ROS), overwhelming the cell's antioxidant defenses. This leads to oxidative stress, mitochondrial dysfunction, and apoptosis, particularly in the hippocampus. It also facilitates β-amyloid (Aβ) production and aggregation, as well as tau protein hyperphosphorylation (Qiu et al., 2016; Tönnies and Trushina, 2017). Sleep deprivation activates inflammatory pathways in the central and peripheral nervous systems, increasing levels of inflammatory markers, including IL-6, TNF-α, and CRP. This process overactivates microglia, disrupts the blood-brain barrier (BBB), exacerbates neuroinflammation, and destabilizes brain homeostasis (Wisor et al., 2011; Hurtado-Alvarado et al., 2017). These mechanisms collectively lead to Aβ deposition in the brain and reduced cerebrospinal fluid flow, further impairing NREM sleep's metabolic waste clearance function. Abnormal tau phosphorylation disrupts microtubule stability and neuronal transport, aggravating cognitive dysfunction (Šimić et al., 2016; Lee et al., 2017). A vicious bidirectional cycle emerges between sleep deprivation and AD. Aβ and tau deposition impair the circadian rhythm regulation function of the suprachiasmatic nucleus (SCN), while neuroinflammation damages neural networks in the hypothalamus and brainstem. This aggravates sleep fragmentation, while cognitive dysfunction further impairs sleep quality and waste clearance efficiency, accelerating disease progression. Improving sleep quality through interventions such as cognitive behavioral therapy, melatonin treatment, or light therapy, as well as developing biomarkers based on sleep deprivation's molecular mechanisms (such as inflammatory marker levels or cerebrospinal fluid Aβ concentrations), may reduce the risk of AD (Holth et al., 2016; Wang and Holtzman, 2020; Lew et al., 2021). Future research should investigate the molecular mechanisms of sleep regulation and conduct large-scale longitudinal studies to clarify the causal relationship between sleep deprivation and AD, identifying new targets for intervention strategies. Recent studies have confirmed that the activity of the glymphatic system is closely linked to sleep quality. The system's ability to clear Aβ peaks during non-rapid eye movement (NREM) sleep, while insomnia-induced sleep fragmentation significantly impairs its efficiency (the term "glymphatic system" saw a surge in citations after 2021, as shown in Figure 10; Cordone et al., 2019; Yan et al., 2021). The clustering analysis in this study (Cluster #8) shows a strong association between "NREM sleep" and "Aβ peptides," supporting this mechanism. Based on these findings, clinical implications include developing biomarkers based on sleep depth (such as the proportion of NREM sleep) to quantify glymphatic function (e.g., monitoring cerebrospinal fluid flow with dynamic contrast-enhanced MRI), and exploring non-invasive interventions (such as acoustic stimulation) to enhance glymphatic clearance efficiency (Harrison et al., 2020; Kjaerby et al., 2022).

4.2.3 Circadian rhythm disturbance

Circadian rhythm disturbance (CRD) is a prevalent non-cognitive symptom in AD, marked by disrupted sleep-wake cycles, inverted day-night behavior, and fragmented sleep. Studies suggest that CRD is not merely a symptom of AD but also accelerates disease progression by impairing metabolic waste clearance and neuronal repair mechanisms (Uddin et al., 2020). Core pathological features of AD, including β-amyloid (Aβ) deposition and tau protein hyperphosphorylation, disrupt the regulatory functions of the hypothalamic suprachiasmatic nucleus (SCN), contributing to CRD. SCN damage reduces deep sleep and melatonin secretion, impairing cerebrospinal fluid clearance of Aβ and further aggravating neurodegeneration (Holth et al., 2016; Uddin et al., 2020). CRD is also associated with neuroinflammation activation. Inflammatory markers, including IL-6 and TNF-α, activate microglia, further impairing SCN function and perpetuating a vicious cycle of circadian rhythm dysregulation. Patients often exhibit frequent nighttime awakenings, daytime sleepiness, reduced deep sleep and lower REM sleep proportions, disrupting normal activity patterns, and social behavior rhythms (Fonken et al., 2016; Kress et al., 2018; Pillai et al., 2021). Phototherapy has proven effective in improving circadian rhythms and reducing nighttime awakenings by controlling light exposure intensity and timing (Léger et al., 2018). Melatonin and its analogs improve nighttime sleep initiation and maintain circadian stability, with combined phototherapy providing optimal results (Saeed and Abbott, 2017). Behavioral interventions, including sleep hygiene education and exercise, alongside pharmacological treatments, provide supplementary benefits in symptom management. CRD accelerates AD progression by reducing waste clearance efficiency, aggravating neural network damage, and perpetuating neuroinflammation. Future efforts should prioritize early diagnosis and multimodal intervention strategies for CRD, investigating its interaction with AD's core pathology to develop more effective treatment plans.

4.2.4 Research based on genetics and epigenetics

AD onset and progression result from the combined influence of genetic and environmental factors. Studies show that insomnia and other sleep disorders are not only potential risk factors for AD but are also closely linked to genetic and epigenetic regulation. Recent Mendelian randomization (MR) studies have used genetic variations as instrumental variables to overcome confounding biases in traditional observational research. MR has led to significant methodological breakthroughs in understanding the causal relationships between sleep characteristics, cardiovascular health, and AD. For instance, MR analysis based on sleep-related genetic polymorphisms confirmed a significant association between abnormal sleep duration (either too short or too long) and AD risk (OR = 1.14, 95% CI: 1.02–1.27). Genetic correlations were also found between cardiovascular health indicators, such as elevated LDL levels, and AD, suggesting that sleep disorders may indirectly influence AD risk through cardiovascular health (Yuan et al., 2021; 2023). The APOE ε4 genotype notably enhances the pathogenic effect of insomnia on AD risk, emphasizing the crucial role of gene-environment interactions in the disease process.

The bibliometric analysis in this study further reinforces the previous conclusion. Keyword clustering results reveal a significant increase in citations of "Mendelian randomization" (Cluster #9) since 2021 (Table 5), emphasizing its widespread application in AD research. This study systematically identified the central role of MR technology in AD-insomnia association research through co-occurrence network and clustering analysis, prioritizing relevant evidence in literature selection and mechanism discussions. For example, MR studies provided causal evidence supporting the hypothesis that "insomnia accelerates AD progression through oxidative stress" and identified the enhanced pathogenic effect of insomnia in individuals with the APOE ε4 genotype. Based on this, the study proposes targeted intervention strategies for APOE ε4 carriers, recommending enhanced sleep management (e.g., prolonged light therapy) to reduce AD risk. This finding provides a crucial theoretical basis for integrating genetic evidence into clinical practice, advancing the development of personalized intervention strategies.

The causal relationship between insomnia symptoms and cognitive decline has been validated, reinforcing that sleep disorders are critical risk factors for early cognitive impairment in AD. Epigenetic studies reveal that sleep patterns influence AD pathology through the regulation of gene expression. For instance, reduced DNA methylation of the APOE gene, caused by chronic insomnia, is closely linked to Aβ metabolic dysregulation (Hwang et al., 2018). Histone modifications contribute to disease progression by regulating tau-related pathological processes. Insomnia-induced inflammatory responses may worsen pathology by altering histone-modifying enzyme activity (Klein et al., 2018). Sleep disorders disrupt the expression of circadian rhythm-related genes (such as CLOCK and BMAL1) via epigenetic mechanisms, further worsening neuronal damage (Hor et al., 2019). The interplay between genetics and epigenetics is central to understanding the impact of insomnia on AD. Moreover, sleep disorder-induced neuroinflammation exacerbates inflammatory responses by modifying the epigenetic states of inflammation-related genes (Chen et al., 2022). Research on genetics and epigenetics provides new avenues for early AD diagnosis and intervention. Sleep-related genetic markers and epigenetic modification sites identified via MR studies may serve as biomarkers, while drugs targeting epigenetic modifications could offer effective strategies for AD intervention (Fani et al., 2021). Future studies should conduct large-scale longitudinal research to explore genetic and epigenetic interactions in sleep disorders and AD, with the goal of identifying novel pathways for targeted interventions.

4.2.5 Sleep intervention strategies

Interventions for AD-related insomnia are broadly classified into pharmacological and non-pharmacological approaches. Pharmacological treatments encompass melatonin, GABA agonists, and sedative-hypnotic drugs. Melatonin supplementation aids sleep initiation and reduces nighttime awakenings; however, its efficacy varies among individuals, and the safety of prolonged use remains unclear (Javed et al., 2023). GABA agonists like zolpidem enhance GABA activity to promote deep sleep, but prolonged use may lead to tolerance and dependence, limiting their suitability for older adults. Antihistamines (e.g., diphenhydramine) and antidepressants (e.g., trazodone) are also used for insomnia relief, but their side effects are especially concerning in elderly patients (Abad and Guilleminault, 2018; Atkin et al., 2018). Non-pharmacological therapies are increasingly gaining attention. Mindfulness meditation shows promise in reducing anxiety, improving sleep quality, and potentially slowing cognitive decline (Russell-Williams et al., 2018). Sleep hygiene education, which optimizes the sleep environment and establishes regular routines, is a foundational intervention that can be combined with other methods. Phototherapy, which regulates light exposure intensity and timing, helps align circadian rhythms and is particularly effective for managing day-night behavioral disturbances in late-stage AD patients (Forbes et al., 2014). Cognitive Behavioral Therapy for Insomnia (CBT-I) is a structured, non-pharmacological approach using techniques like stimulus control, sleep restriction, and cognitive restructuring. CBT-I significantly improves insomnia symptoms, reduces medication dependence, and is especially suitable for early-stage AD patients or those at high risk of mild cognitive impairment (MCI) (Bennett, 2020; Blackman et al., 2021). Multimodal interventions combining pharmacological and non-pharmacological approaches may have synergistic effects, improving sleep quality and potentially delaying AD progression by optimizing circadian rhythms. Future research should prioritize developing personalized intervention plans tailored to patients' genetic backgrounds, sleep patterns, and cognitive status to maximize treatment efficacy. Additionally, large-scale longitudinal studies and mechanistic research are essential to clarify the long-term effects of various strategies on AD progression, offering a robust scientific basis for improving sleep and cognitive health in AD patients.

4.2.6 Integrated studies on multidimensional impacts

Insomnia exacerbates AD progression through pathological mechanisms like β-amyloid (Aβ) deposition and tau hyperphosphorylation, while also increasing caregiving costs

and harming caregivers' mental health. Insomnia imposes significant social and economic burdens on AD patients, including higher caregiving expenses, increased professional care costs, and reduced caregiver income due to long-term commitments. Long-term caregiving for AD patients with insomnia increases caregiver anxiety and depression, resulting in burnout and reduced care quality (Okuda et al., 2019). Insomnia and mood disorders, including anxiety and depression, have a bidirectional relationship. Insomnia activates the hypothalamic-pituitary-adrenal (HPA) axis, elevating stress hormone levels, triggering neuroinflammation, and worsening emotional disorders. Conversely, anxiety and depression worsen sleep quality by disrupting circadian rhythms (Alvaro et al., 2013). Anxiety and depression are significant risk factors for AD, accelerating the progression from mild cognitive impairment (MCI) to AD through neuroinflammation and cognitive decline. Managing anxiety and depression is essential for improving insomnia in AD patients. Comprehensive intervention strategies are vital for mitigating the multidimensional impacts of AD-related insomnia. These strategies include interdisciplinary research with long-term follow-up to clarify causal relationships, psychological interventions (e.g., CBT), and policy measures (e.g., nighttime caregiving subsidies). These measures improve the quality of life for patients and caregivers, reduce AD risk by optimizing sleep, and advance multidimensional research to foster intervention development. The bidirectional link between AD and insomnia is a critical focus in neurodegenerative disease research. Recent multimodal studies combining molecular imaging, genetics, and neurobiology have illuminated insomnia's role in AD onset and progression. Concurrently, sleep-related biomarkers are emerging as promising tools for early AD diagnosis. Long-term cohort studies tracking changes in sleep patterns provide insights into how insomnia affects AD risk across age groups. Molecular imaging techniques, such as PET, are invaluable for monitoring dynamic changes in Aβ and tau pathology in AD patients. Combined with sleep deprivation experiments, these technologies help establish causal links between insomnia and pathological accumulation (Wang et al., 2016). Future research should utilize multimodal technologies to develop non-invasive biomarkers for efficient screening of high-risk populations. Large-scale cohort studies and interdisciplinary collaborations are essential to explore insomnia's influence on AD risk across age groups and to develop targeted intervention strategies. Multidimensional research can improve sleep quality, reduce AD risk, and pave the way for early diagnosis and intervention.

4.2.7 Interdisciplinary collaboration driving AD-insomnia research

The collaboration between neuroimaging, genetics, and sleep medicine offers new perspectives for understanding the complex relationship between AD and insomnia. In neuroimaging, the combination of PET and MRI technologies has shown that the joint analysis of tau-PET and functional MRI (fMRI) can dynamically monitor the effects of sleep deprivation on AD pathology, particularly the reduction in the functional connectivity of the default mode network (Ding et al., 2023). Additionally, glymphatic system imaging, particularly dynamic contrast-enhanced MRI (DCE-MRI), has revealed how insomnia accelerates Aβ deposition through glymphatic dysfunction by quantifying the relationship between sleep stages and cerebrospinal fluid flow velocity (Dong et al., 2024).

In genetics and epigenetics, a study using a two-sample MR approach assessed the causal relationship between insomnia and AD. The results suggest a potential causal link between insomnia and AD (Anderson et al., 2021). Furthermore, in epigenetic regulation, the study examined the generation of formaldehyde (FA) during DNA demethylation. Abnormal accumulation of FA may lead to Aβ deposition and tau protein phosphorylation, thereby triggering AD. The findings indicate that epigenetic mechanisms play a critical role in the onset and progression of AD (Ma et al., 2023).

4.2.8 From mechanism to clinic: the translational pathway of sleep interventions

Based on bibliometric and clinical trial evidence, a three-level translational framework is proposed to advance research and clinical applications of the relationship between AD and insomnia. The first level of translation focuses on intervention strategies targeting core pathological mechanisms. Light therapy research ($n = 120$) shows that morning exposure to bright light (10,000 lux, 30 min/day) significantly improves circadian rhythm synchronization in AD patients ($p < 0.01$) and lowers the cerebrospinal fluid Aβ42/Aβ40 ratio ($\beta = -0.28$, $p = 0.02$) (Zang et al., 2023). In terms of acoustic stimulation, a study by Murdock et al. (2024) demonstrated that low-frequency focused ultrasound (0.5 MHz) enhances astrocyte AQP4 channel activity, improving glymphatic Aβ clearance efficiency, resulting in a 37% reduction in Aβ deposition in animal models. The second level of translation emphasizes precision drug-behavior combined interventions. A randomized crossover trial (n=80) showed that cognitive behavioral therapy for insomnia (CBT-I) combined with melatonin treatment increased sleep efficiency by 25% ($p < 0.001$) and reduced plasma phosphorylated tau (p-tau181) levels by 18% compared to the control group ($p = 0.03$) (Clynes et al., 2019). Based on the high-frequency occurrences in the bibliometric analysis (Table 4), an enhanced intervention plan is proposed for APOE ε4 carriers, such as extending light therapy duration to 45 min/day. The third level of translation focuses on personalized management based on biomarkers. This involves combining polysomnography (PSG), cerebrospinal fluid Aβ42/tau ratio, and dynamic contrast-enhanced MRI (DCE-MRI) glymphatic activity indicators to further build an AD risk prediction model.

4.3 Limitations

This study has several important limitations. First, due to the data format limitations of VOSviewer and CiteSpace, which are compatible only with certain data sources, literature

related to Alzheimer's disease and insomnia was retrieved from a single database (WOSCC). This study did not include other data sources in the bibliometric analysis to minimize selection bias. WOSCC provides better coverage of clinical medicine than interdisciplinary research, which may lead to the omission of studies spanning multiple disciplines. Future studies should integrate PubMed, Scopus, and Embase to address the gaps in WOSCC's coverage. Moreover, WOSCC predominantly includes high-impact English-language journals, which may exclude non-English studies, resulting in the omission of regional research and introducing bias. Future efforts should focus on developing multilingual bibliometric tools (e.g., CiteSpace plugins integrated with translation APIs) to support the automated analysis of non-English literature. Third, the presence of several synonyms may result in overlap between content categories during keyword clustering.

5 Conclusion

Using CiteSpace and VOSviewer, we analyzed collaborative networks among countries, institutions, and authors, and identified emerging trends in the literature. Our findings indicate that the bidirectional relationship between AD and insomnia is a key research focus, with particular emphasis on insomnia's role in accelerating AD onset and progression.

Additionally, recent research has focused on the relationships between circadian rhythm disturbances, sleep-disordered breathing, and AD. Circadian rhythm disturbances have been identified as a critical link between AD and insomnia. Molecular mechanisms of sleep deprivation, particularly its links to oxidative stress and inflammatory factors, have gained prominence in recent literature. Methodologically, multimodal approaches are increasingly adopted, integrating molecular imaging, genetics, and epigenetics to uncover the mechanisms linking AD and insomnia. These findings will help professionals develop a comprehensive understanding of key challenges in this field, advancing research and clinical applications.

Author contributions

Z-YT: Data curation, Formal analysis, Methodology, Writing – original draft. BJ: Data curation, Formal analysis, Methodology, Writing – original draft. MJ: Data curation, Investigation, Writing – review & editing. X-KY: Methodology, Visualization, Writing – review & editing. Q-LC: Data curation, Formal analysis, Methodology, Writing – original draft. J-HW: Funding acquisition, Supervision, Writing – review & editing.

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Conflict of interest

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

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Generative AI statement

The author(s) declare that no Gen AI was used in the creation of this manuscript.

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Research progress on resistance exercise therapy for improving cognitive function in patients with AD and muscle atrophy

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Alzheimer's disease (AD) significantly reduces the quality of life of patients and exacerbates the burden on their families and society. Resistance exercise significantly enhances the overall cognitive function of the elderly and patients with AD while positively improving memory, executive function, and muscle strength, reducing fall risks, and alleviating psychological symptoms. As AD is a neurodegenerative disorder, some nerve factors are readily activated and released during exercise. Therefore, several prior studies have concentrated on exploring the molecular mechanisms of resistance exercise and their impact on brain function and neural plasticity. Recent investigations have identified an intrinsic relationship between individuals with AD and the pathological mechanisms of skeletal muscle atrophy, establishing a correlation between patients with AD cognitive level and skeletal muscle content. Resistance exercise primarily targets the skeletal muscle, which improves cognitive impairment in patients with AD by reducing vascular and neuroinflammatory factors and further enhances cognitive function in patients with AD by restoring the structural function of skeletal muscle. Furthermore, the effects of resistance training vary among distinct subgroups of cognitive impairment. Individuals exhibiting lower cognitive function demonstrate more pronounced adaptive responses in physical performance over time. Consequently, further investigation is warranted to determine whether tailored guidelines—such as variations in the frequency and duration of resistance exercise—should be established for patients with varying levels of dementia, in order to optimize the benefits for those experiencing cognitive impairment. This study aimed to review the relationship between AD and skeletal muscle atrophy, the impact of skeletal muscle atrophy on AD cognition, the mechanism by which resistance exercise improves cognition through skeletal muscle improvement, and the optimal resistance exercise mode to elucidate the additional advantages of resistance exercise in treating cognitive function in patients with AD and skeletal muscle atrophy.

KEYWORDS

Alzheimer's disease, cognitive function, skeletal muscle atrophy, resistance exercise, neuromuscular

1 Introduction

Recently, with the aggravation of population aging, social development, the incidence rate of Alzheimer's disease (AD) has increased significantly, placing a substantial burden on families and society. The latest released statistics by the International AD Association indicate that the global prevalence of dementia is projected to reach 75 million by 2030 (Stephan et al., 2018). Therefore, AD research has gradually become a prominent subject of interest. Despite the ability of pharmacological interventions to improve cognitive function and behavioral symptoms in patients with AD, most patients do not receive effective treatment because of the large patient population and slow progress in drug development. The pertinent literature suggests that approximately 40% of global cognitive dysfunction is caused by 12 controllable risk factors, and AD constitutes over 60% of all cognitive dysfunction (Stephan et al., 2018). Consequently, patients, families, and society need to reduce the incidence of AD and delay cognitive decline by changing living environments, daily living habits, and other controllable risk factors. Current guidelines recommend resistance exercise as a non-pharmacological preventive intervention for cognitive impairment (Bangsbo et al., 2019). Although certain previously conducted randomized controlled trials (RCTs) have indicated that resistance training can improve and delay the behavior and cognition of AD, most trials have concentrated on the effects of resistance exercise on brain structure and function, including cerebrovascular function and cerebral blood flow perfusion, brain structure, synaptic development, and neurotrophic factors, to elucidate the mechanism by which resistance exercise enhances cognitive function in patients with AD (Ben-Zeev et al., 2022). Skeletal muscle atrophy can affect the cognition of patients with AD (Liu et al., 2023), and resistance exercise can improve the physiological structure and function of the skeletal muscles (Rahmati et al., 2023). Therefore, resistance exercise may directly improve skeletal muscle function and further enhance the cognitive function of patients with AD. Furthermore, there is a lack of recent research examining the physical and cognitive effects of resistance exercise on individuals with varying levels of cognitive impairment, indicating a need for further investigation. At the same time, there are multiple treatment options available for AD, such as resistance exercise, medication, cognitive training, yoga, Baduanjin, and other mind-body therapies. However, studies on the effectiveness of combining these treatments, particularly for patients with different levels of cognitive impairment, are scarce. Future research is essential to develop targeted and personalized treatment approaches.

2 The relationship between AD and skeletal muscle atrophy

AD is a neurodegenerative disease characterized by the progressive deterioration of cognitive behavior and ability (Jack et al., 2010). The characteristic pathological features of AD are the accumulation of extracellular amyloid plaques and intracellular neurofibrillary tangles in the brain (Querfurth and LaFerla, 2010). Starch-like protein plaques primarily comprise amyloid beta (Aβ) peptides, whereas over-phosphorylated tau is the principal component of intracellular neurofibrillary tangles. AD presents two manifestations: Early familial and late sporadic. The early familial type has a low incidence rate, accounting for only 1–2%. The premature-onset familial type is generally associated with amyloid precursor protein (APP), premature aging protein 1 (PS1 or PSEN1), and premature aging protein 2 mutations at the (PS2 or PSEN2) site, which are associated with excessive production of Aβ. Late sporadic type onset is a prevalent form of AD in patients aged 65 years or older exhibiting the APOE4 genotype. Changes in lifestyle, genetics, and environmental factors significantly affect the onset of the late sporadic type. As a result, current research has focused on the late sporadic type of AD.

2.1 AD impacts skeletal muscle atrophy

Several risk factors have been identified for the late sporadic type of AD, with aging being the principal cause (Robinson et al., 2023). Aging increases the risk of skeletal muscle atrophy. Although Aβ accumulation in the brain is primarily associated with AD, Aβ deposition and APP have been detected in the skeletal muscles of humans and certain animal models. Progressive loss of skeletal muscle function, including decreased muscle mass and strength, can also be observed in patients with AD (Ogawa et al., 2018; Burns et al., 2010; Fukuchi et al., 1998). Previous studies (Burns et al., 2010) have demonstrated a positive correlation between progressive cerebral atrophy and muscle mass reduction in patients with AD. Since 1984, abnormal weight loss and cachexia have been considered the clinical manifestations of AD. Previous studies (Sugimoto et al., 2016) have indicated that the risk of muscle loss in patients with AD is higher than in a population without cognitive impairment in the same age group. A study using magnetic resonance imaging (MRI) and dual-energy X-ray absorptiometry (DEXA) revealed that compared with the normal control group, patients with AD experienced significant weight loss, accompanied by cognitive decline and reduced brain volume (Burns et al., 2010). A subsequent study confirmed using an AD transgenic mouse model (3xTgAD mice) that compared to young (2–4 months) mouse models, elderly (18–20 months) mouse with AD exhibited better performance, including more phenotypes related to muscle atrophy, including neuromuscular junction injury, reduced gastrocnemius muscle mass, sciatic nerve induction, and direct muscle stimulation to decrease the induced contraction force (Xu et al., 2022). Moreover, Aβ levels were elevated in the skeletal muscle and neurogenic groups of elderly 3xTgAD mice, and the TGF-β-mediated atrophy signaling pathway was activated in elderly 3xTgAD mice, potentially contributing to muscle atrophy in this group. This study suggests that the pathological mechanism of AD involves peripheral alterations in the skeletal muscle. A prospective study elucidated the relationship between muscle loss and the AD continuum (Kim et al., 2024), which includes preclinical AD, mild cognitive impairment (MCI) caused by AD, and AD dementia (Sperling et al., 2011; Albert et al., 2011; McKhann et al., 2011). A total of 142 participants with AD continuum and 58 Aβ-negative cognitively normal patients were evaluated using DEXA and grip strength measurements. This study

discovered an independent association between muscle loss and AD continuum. The skeletal muscles of patients with AD may be more susceptible to oxidative and inflammatory stress (Monteiro-Cardoso et al., 2015).

2.2 Skeletal muscle atrophy affects AD cognition

Numerous investigations have revealed that elderly individuals with Aβ in their brains exhibit minimal or no expression (Aizenstein et al., 2008; Johnson et al., 2013; Roberts et al., 2018). Consequently, in addition to cognitive impairment caused by Aβ, other factors may be linked to the deterioration of brain function. In elderly patients or patients with dementia, muscle atrophy and cognitive decline occur almost simultaneously. Skeletal muscle atrophy may also exacerbate the severity of cognitive impairment or accelerate its progression of cognitive impairment in patients with AD (Brisendine et al., 2024). Certain researchers (Brisendine et al., 2024) have identified that neuromuscular dysfunction occurs before cognitive dysfunction in a Transgenic mice with five familial AD (5xFAD) mouse model. Accordingly, researchers hypothesize that neural conduction in skeletal muscles is a precursor to significant cognitive dysfunction, indicating that muscle structure and function alterations may influence cognitive function. This aligns with a human study (Qian et al., 2022) that identified a positive correlation between decreased peripheral motor nerve conduction velocity and cognitive impairment in patients diagnosed with MCI and AD compared with a control group without cognitive impairment. Epidemiological evidence suggests a bidirectional relationship between musculoskeletal health and the occurrence of AD (Sui et al., 2022).

However, due to the predominance of cross-sectional studies, accurately establishing the causal relationship between skeletal muscle atrophy and AD cognitive impairment remains challenging. Future longitudinal studies are essential to elucidate the relationship between the two, facilitating more targeted interventions for the disease and focusing on improving skeletal muscle atrophy or alleviating AD cognition to maximize patient outcomes.

3 Possible mechanisms of skeletal muscle atrophy affecting cognitive function in AD

In recent years, the concept of a bidirectional relationship between bones and the brain, known as the bone-brain axis (Zhang and Zhang, 2024), has gained attention and this theory (Brazill et al., 2019; Millar et al., 2019) suggests that the brain not only influences bone health (efferent pathway) but that skeletal muscles can also send signals to the brain by releasing bone-derived factors (efferent pathway). These molecules may have effects on brain function, and studies have identified their presence in the brain (Brazill et al., 2019; Millar et al., 2019). An animal study (Kim et al., 2024) demonstrated a correlation between skeletal muscle atrophy and decreased hippocampal volume and cognitive function in patients with AD continuum. Skeletal muscle atrophy impacts cognitive abilities in AD, likely due to the interplay of several systems, primarily consisting of Oudbier et al. (2022): (1) systemic inflammation including decreased neurotrophic factors and myokines; (2) insulin irregularities; (3) disruptions in protein metabolism; (4) compromised mitochondrial function; (5) Others. These interconnected pathological processes collectively establish the biological foundation for the degenerative alterations in the bone-brain network.

3.1 Systemic inflammation

3.1.1 Role of proinflammatory cytokines

In generally (Ramsey et al., 2021), older adults tend to be less physically active and have a greater presence of pro-inflammatory cells in their bodies. As a result, their muscle strength is often diminished compared to those who are more active. Increased levels of inflammatory markers in the bloodstream, like C-reactive protein and IL-6, have been linked to dementia (Darweesh et al., 2018). When released by type I and type II skeletal muscle fibers during muscle contraction, IL-6 acts as an anti-inflammatory cytokine (Pedersen and Febbraio, 2005). Research indicates (Schumertl et al., 2022) that IL-6 is crucial for maintaining balance in the central nervous system within the brain.

3.1.2 Role of myokine

Research indicates that metabolically active tissues, including skeletal muscle, release neurotrophic factors for brain synapses, one of which is brain-derived neurotrophic factor (BDNF; Lu et al., 2014). BDNF is released during skeletal muscle contraction and is a neurotrophic factor required for maintaining synaptic connections and adaptive neuronal plasticity in adults. It can regulate cognitive processes, including learning and memory; its deficiency is associated with neurodegenerative processes (Lu et al., 2014).

Irisin is a newly identified muscle factor that is released during exercise. It is produced from the precursor protein fibronectin type III domain protein 5 (FNDC5) when skeletal muscles contract, and then it is cleaved and enters the bloodstream (Boström et al., 2012). In mice, 72% of irisin originates from skeletal muscle, while 28% comes from fat (Ruan et al., 2019; Shirvani and Rahmati-Ahmadabad, 2019). Irisin has the ability to influence various cellular signaling pathways across different organs, it is secreted by skeletal muscles during physical activity and can cross the blood-brain barrier (Ruan et al., 2019; Shirvani and Rahmati-Ahmadabad, 2019). A study (Sanesi et al., 2023) examining the effects of FNDC5/irisin on muscle atrophy revealed that after 4 weeks of muscle atrophy, FNDC5 levels and serum irisin concentrations decreased. However, treatment with recombinant irisin was able to reverse muscle atrophy. The primary mechanism appears to involve irisin's ability to directly inhibit muscle protein degradation and promote myosin synthesis, as well as its role in maintaining bone health by regulating the balance of osteoprotegerin (OPG) and receptor activator of nuclear factor kappa-B ligand (RANKL) and the apoptosis pathway. Recent research has highlighted the

importance of FNDC5/irisin in providing neuroprotection in AD. In a recent study (Kim et al., 2025) using a three-dimensional cell culture model of AD, it was found that irisin can reduce A β protein levels, suggesting that it mitigates Aβ pathology by enhancing the activity and levels of neprilysin (NEP) secreted from astrocytes.

Research indicates that certain bone-derived factors, such as osteocalcin (Jaberi and Fahnestock, 2023), lipocalin 2 (LCN2; Mosialou et al., 2017), sclerostin (Shi et al., 2024), and Dickkopf-related protein (Dkk; Sato et al., 2024), can cross the blood-brain barrier via the bloodstream. Additionally, extracellular vesicles, which are secreted by nearly all cell types, play a vital role in cell communication and the exchange of biological information (Couch et al., 2021). The transmission of information through these vesicles is linked to various diseases (Faraldi et al., 2021). Evidence suggests that extracellular vesicles from skeletal muscles can be taken up by different organs, including the brain (Aswad et al., 2014). Studies (Aswad et al., 2014; Rodríguez and Cabello-Verrugio, 2024) have shown that when skeletal muscles with nerve connections experience injury, there are significant alterations in the miRNA profiles of the extracellular vesicles they release. These changes can significantly affect brain functions related to neuroplasticity, memory, sleep, and emotions (Delezie and Handschin, 2018). This points to the existence of pathways mediated by extracellular vesicles between the brain and bones, although more research is needed in this area.

3.2 Insulin metabolism

Skeletal muscle is crucial for regulating blood glucose levels, serving as a key organ for glucose storage and metabolism (Sylow et al., 2021). Muscle atrophy is linked to insulin resistance (Kim and Park, 2018), a significant risk factor for cognitive decline (Ekblad et al., 2017). A sustained rise in insulin levels in the body is associated with lower insulin levels in the brain, which decreases the clearance of Aβ (Cholerton et al., 2013). Another hypothesis suggests that elevated insulin levels in the body compete with enzymes that break down insulin, resulting in the buildup of A β and impaired degradation, which may contribute to increased tau formation (Nguyen et al., 2020).

3.3 Protein metabolism

The decline in skeletal muscle mass is caused by a reduction in muscle protein synthesis and an increase in muscle protein breakdown, resulting in a negative net protein balance (Kim et al., 2020). This negative balance can also lower protein levels in the brain, which can indirectly impact cognitive function. Furthermore, studies (Poddar et al., 2019) have shown that not only does protein content decrease, but the extent of oxidative damage to proteins also rises, contributing to cognitive impairment. Additionally, skeletal muscle atrophy is linked to the upregulation of the ubiquitin-proteasome system (UPS; Al Mamun et al., 2020), which is a system that promotes protein breakdown. The amyloid precursor protein (APP), associated with AD, has been confirmed to be related to the UPS (Al Mamun et al., 2020).

3.4 Mitochondrial function

The primary energy source for skeletal muscle contraction is adenosine triphosphate (ATP) (Gan et al., 2018), which is largely produced through mitochondrial oxidative phosphorylation. Mitochondrial issues, such as changes in quantity, function, and structure, are frequently observed in atrophied skeletal muscle (Picca et al., 2018). Additionally, mitochondrial dysfunction in the brain may contribute to cognitive decline. When skeletal muscle atrophy occurs, it can lead to mitochondrial dysfunction, resulting in the buildup of reactive oxygen species (ROS). An overproduction of ROS heightens oxidative stress, which in turn increases the production of Aβ (Leuner et al., 2012). Furthermore, it is understood that oxidative stress serves as a common underlying mechanism for both skeletal muscle atrophy and cognitive impairment (Liguori et al., 2018).

3.5 Others

Recent clinical studies have found that atrophied skeletal muscle releases hemoglobin, which can lead to cognitive dysfunction.

Elevated hemoglobin levels are linked to the progression of AD and are inversely related to cognitive function (Ashraf et al., 2020). In 2024, Iki and Tohda (2024) conducted experiments using both 5XFAD and non-transgenic wild-type mice, inducing skeletal muscle atrophy by immobilizing their hind limbs for 14 days. They found that continuous infusion of recombinant hemoglobin into the ventricles impaired object recognition memory in the 5XFAD mice with simulated muscle atrophy. Proteomic analysis showed that hemoglobin levels in the skeletal muscle, plasma, and hippocampus of these mice were higher than in typical 5XFAD mice. Furthermore, injecting hemoglobin into 5XFAD mice led to increased levels of lipocalin-2 (Lcn2), messenger RNA (mRNA), and neuroinflammatory markers in the hippocampus. The rise in LCN2 mRNA levels in the hippocampus of the simulated muscle atrophy mice indicates that skeletal muscle atrophy negatively impacts memory impairment in young 5XFAD mice, mediated by hemoglobin secretion from atrophied muscle. Thus, hemoglobin could be a potential therapeutic target for preventing cognitive decline in AD patients with skeletal muscle atrophy.

There is substantial research indicating that the factors mentioned earlier contribute to skeletal muscle atrophy and cognitive decline. However, it remains uncertain whether these mechanisms are exclusively a result of muscle atrophy or if there is a reciprocal relationship between muscle atrophy and cognitive impairment. Further investigation is required to clarify this issue in the future.

The atrophy and muscle loss of skeletal muscles are associated with chronic neurodegeneration and oxidative stress (Migliavacca et al., 2019), exacerbating the Aβ-related neurodegeneration process (Maltais et al., 2019). More longitudinal studies are needed to determine the relationship between the two, especially the relationship between muscle atrophy and Aβ deposition, which may be more convincing for the relationship between skeletal muscle atrophy and cognitive changes in AD. Since skeletal muscle

functions as an endocrine organ capable of releasing various muscle factors, peptides, and growth factors (García-Llorente et al., 2024; Nicola et al., 2024), further research is necessary to investigate the pathways and molecular mechanisms involved in their signaling to the brain. Additionally, this research should aim to identify new targets for addressing bone-brain comorbidities based on these findings.

4 Impact of resistance exercise on skeletal muscles

4.1 The concept of resistance motion

Resistance exercise is any form of physical activity requiring muscle strength to counteract external resistance to increase muscle size, strength, and/or endurance (McArdle et al., 2015). Resistance exercise, or strength training, is a periodic form of physical exercise that uses external weight to overload and contract skeletal muscles, stimulating their strength and mass to lift more weight and increase muscle volume (Bodine et al., 2001). Resistance training includes exercises that increase muscle strength, endurance, and function by causing muscles to contract under external resistance. There are various types and forms of resistance exercises, including but not limited to bicep bending, overhead push, sitting rowing, squats, leg curling, knee extension, side hip elevation, and stretching exercise.

4.2 Impact of resistance exercise on AD

Over the past decade, RCTs have demonstrated that resistance training can improve cognitive function in healthy individuals and elderly people with cognitive impairments. Furthermore, recent studies indicate (Fonseca et al., 2025) that the effects of resistance training vary among distinct subgroups of cognitive impairment. Individuals exhibiting lower cognitive function demonstrate more pronounced adaptive responses in physical performance over time. The Excel for Cognition and Everyday Living study (Weier et al., 2012) is a 6-month randomized trial. Eighty-six elderly women aged 70–80 were randomly assigned to twice-weekly resistance, aerobic, and balance and tension training. It was observed that the resistance exercise group significantly improved their Stroop test and associative memory task abilities while also causing changes in the encoding and recall associations of three cortical regions (the fusiform gyrus of the right tongue and occipital region and the right frontal pole). In another RCT study on resistance training and cognitive training (Fiatarone Singh et al., 2014), patients with MCI were randomly assigned to two groups for 2–3 days/week of exercise for 6 months, followed up at 18 months and the AD Assessment Scale cognitive subscale (ADAS Cog), functional independence and Bayer Activities of Daily Living were observed. The ADAS Cog scores were significantly improved by resistance training.

In animal experiments, it has been observed that resistance exercise may improve cognitive impairment by promoting the clearance of Aβ in the hippocampus, reducing Aβ plaques and tau protein in the brain (Pena et al., 2020; Liu et al., 2020; Campos et al., 2023). AD is a neurodegenerative and neuroinflammatory disease characterized by the Aβ deposition, the formation of tau protein fiber tangles, excessive deposition of Aβ, and imbalance of inflammatory factors caused by neurotoxic activation of microglia. In the early stages of AD, microglia can promote the clearance of Aβ, but as the disease progresses, the neurotoxicity of microglia activates, causing them to lose their ability to clear Aβ. Microglia play a crucial function in the inflammatory factor signaling pathway in neurodegenerative diseases, including influencing the balance of pro-inflammatory [interleukin (IL)-1 β and tumor necrosis factor-alpha (TNF-α)] and anti-inflammatory factors (IL-4 and IL-10). A study suggests that moderate-intensity physical exercise, including resistance exercises, can suppress neurotoxic attacks by inhibiting the activation of microglia and reducing the expression of pro-inflammatory factors, including IL-1β and TNF-α (Mee-Inta et al., 2019; Spielman et al., 2016). Exercise can also increase the content of BDNF (López-Ortiz et al., 2021), reducing the levels of pro-inflammatory factors, including TNF-α, and alleviating cognitive impairment in AD. In 2007 research indicated that the expression of cytokines such as IL-4 and IL-13 was first identified in skeletal muscle following resistance exercise training. Furthermore, it was observed that the intensity of resistance exercise correlates positively with the levels of IL-4 in skeletal muscle (Prokopchuk et al., 2007). Subsequent investigations revealed that resistance exercise enhances the levels of anti-inflammatory cytokines, including IL-4 and IL-10, by modulating the activity of dendritic cells and microglia through the influence of TREM2, a transmembrane protein. This modulation facilitates a transition from a pro-inflammatory to an anti-inflammatory state, resulting in increased expression of IL-4 and IL-10, which may alleviate symptoms associated with AD (López-Ortiz et al., 2021; Forloni and Balducci, 2018; Leuchtmann et al., 2021). A recent study on the effects of resistance exercise on AD-related neurodegenerative diseases revealed that (Hashiguchi et al., 2020)resistance exercise reduces the volume of Aβ plaques in the hippocampus of APP/PS1 mice and maintains relatively stable levels of related cytokines in the hippocampus. Despite the absence of a significant decrease in Aβ protein levels under the combined action of anti-inflammatory and pro-inflammatory factors, the deposition of Aβ plaques was reduced, further improving cognitive impairment (Hashiguchi et al., 2020).

4.3 Effect of resistance exercise on skeletal muscles and the mechanism of improving cognition through the treatment of muscle atrophy

Resistance exercise improves cognitive function by reducing inflammation and enhancing muscle strength and physiological function. Multiple studies (McLeod et al., 2024; Vossel et al., 2024). have demonstrated that resistance exercise increases muscle mass, strength, and physical function compared to non-exercise. Enhancing muscle strength can lead to a greater release of irisin, which in turn raises the levels of IGF-1 and BDNF. This process helps reduce oxidative stress, encourages the growth of new neurons, and boosts insulin sensitivity (Someya et al., 2019). Moreover, resistance exercise can induce hypertrophy of skeletal

muscle cells under the action of skeletal muscle satellite cells (Burns et al., 2010). In an animal experiment (Rahmati et al., 2023), 1–42 amyloid protein was injected in a single dose into the hippocampal Cornu Ammonis 1 region (1 μL/site). Rats with AD were compared with healthy rats after 5 weeks of resistance training. The findings indicated that AD induced significant skeletal muscle atrophy and reduced the number of muscle nuclei and muscle stem cell (SC) content in the gastrocnemius muscle in the entire muscle cross-section and isolated muscle fibers. Compared with the control group, there was no significant difference in the distribution of different myosin heavy chains (MyHC) in rats with AD, while resistance training significantly increased the muscle cross-sectional area of MyHC IIb fibers in AD and healthy animals. These results indicate that the skeletal muscles of AD animals are more prone to atrophy, and the number of muscle nuclei and satellite cell content are more easily lost, while resistance exercise can successfully restore these injuries. The increase in muscle nuclei and the recovery of satellite cells promoted muscle regeneration and anti-aging through related mechanisms (Sousa-Victor et al., 2022). This further indicates the role of resistance exercise in improving skeletal muscle physiological function and subsequently enhancing cognitive function. In an RCT study to determine whether improvements in aerobic capacity and strength after progressive resistance training (PRT) mediate cognitive function improvement, it was found that high-intensity PRT can significantly improve cognitive function in patients with MCI through increased muscle strength and aerobic capacity (Mavros et al., 2017). Moreover, a study on the effects of 12-week resistance training on the metabolism of the elderly brain found (Sheoran et al., 2023) that resistance exercise maintains the stability of various neurotransmitters to keep the brain at a relatively healthy level and significantly improves muscle strength. This increases the motor dependence of brain neurons to some extent, enhancing neural transmission and cognition. This may be because resistance exercise may promote the production and expression of myokines and angiogenic factors in large muscle groups (Fournier and Duman, 2012; Yeo et al., 2012), which cross the blood-brain barrier and promote long-term synaptic enhancement-induced signaling pathways, thereby enhancing the possibility of exercise-induced neuroplasticity (Vints et al., 2022) and improving brain function.

Resistance exercise can induce oxidative stress and exert anti-inflammatory effects on cognitive function by increasing the release of neurotrophic factors, regulating inflammatory response, and reducing Aβ load in patients with AD (Navarro et al., 2018; de Almeida et al., 2022). Moreover, according to existing research, it directly affects skeletal muscle and cognitive function (Figure 1). Therefore, further research is required to elucidate the connection mechanism between resistance exercise, the physiological function of skeletal muscle, and the brain function of patients with cognitive impairment to further explore the potential of exercise in alleviating dementia, particularly in patients with skeletal muscle atrophy.

5 Best mode of resistance movement

In recent years, exercise has been extensively researched as a non-drug treatment for individuals with cognitive impairment. According to the American Physical Activity Guidelines (Piercy and Troiano, 2018), we categorized exercise interventions into four types: (1) aerobic exercise; (2) resistance exercise (RE); (3) multicomponent exercise (ME); and (4) mind-body exercise (MBE). A study by Bosserrs et al. in 2016 indicated (Bossers et al., 2016) that exercise can enhance daily living activities (ADL) in dementia patients, with a combination of aerobic and RE proving to be more effective than either type alone. A recent 12-week randomized controlled trial (RCT) conducted in 2023 highlighted (Papatsimpas et al., 2023) the benefits of resistance exercise in improving cognitive decline and instrumental activities of daily living (IADL) in dementia patients, particularly when paired with AE. This supports earlier findings that RE may offer greater advantages for cognitive function and knowledge-related outcomes (Li et al., 2018). This could be attributed to RE not only improving motor coordination and balance but also activating specific cerebellar-cortical connections, which may enhance both cognitive function and balance (Fonseca et al., 2025). A study investigating the impact of aerobic and RE on inflammatory factors and their relationship with neurocognitive performance found (Tsai et al., 2019) that after 16 weeks, both types of exercise positively influenced certain neurocognitive outcomes. The AE group experienced a notable increase in peripheral serum BDNF levels and a decrease in insulin, TNF-α, and IL-15 levels, while the RE group saw a significant rise in IGF-1 levels and a reduction in IL-15 levels. This suggests that in older adults with MCI, while both AE and RE can affect inflammatory factor levels and enhance neurocognition, the distinct inflammatory factors influenced by each type may indicate different molecular mechanisms at play in how they improve cognitive function.

The specific form, frequency, intensity, and duration of resistance exercise and the need to combine it with other non-pharmacological treatment methods to improve and delay the optimal combination mode of AD cognitive impairment remain the subjects of ongoing research. Aerobic exercise is more prevalent in daily life than resistance exercise because it can usually be completed without any specialized equipment, the movements are simpler, the exercise cost is lower, and it is more flexible. However, guidelines for patients with MCI recommend aerobic exercise and resistance exercise (Lautenschlager et al., 2018). This is because different forms of exercise have high specificity, and regular and appropriate resistance exercises also have unique effects on the skeletal muscles and cognition of patients with AD. The appropriate frequency, intensity, duration, and mode of resistance exercise are the manifestations of its specificity, which can more fully induce adaptation to the characteristics of the neuromuscular system and improve cognitive function.

5.1 Resistance exercise intensity

Research reveals that moderate-intensity resistance exercises achieve the greatest cognitive advantages (Chow et al., 2021). Moderate intensity training is defined as Chen et al. (2024) exercises that can be performed while maintaining uninterrupted dialogue, typically lasting 30–60 min (3–6 metabolic equivalents, 55–70% heart rate maximum, 40–60% heart rate recovery, 40–60% maximum oxygen consumption, the Rate of Perceived Exertion (PRE; C): 11–13, PRE (C-R): 3–4 [METs: metabolic

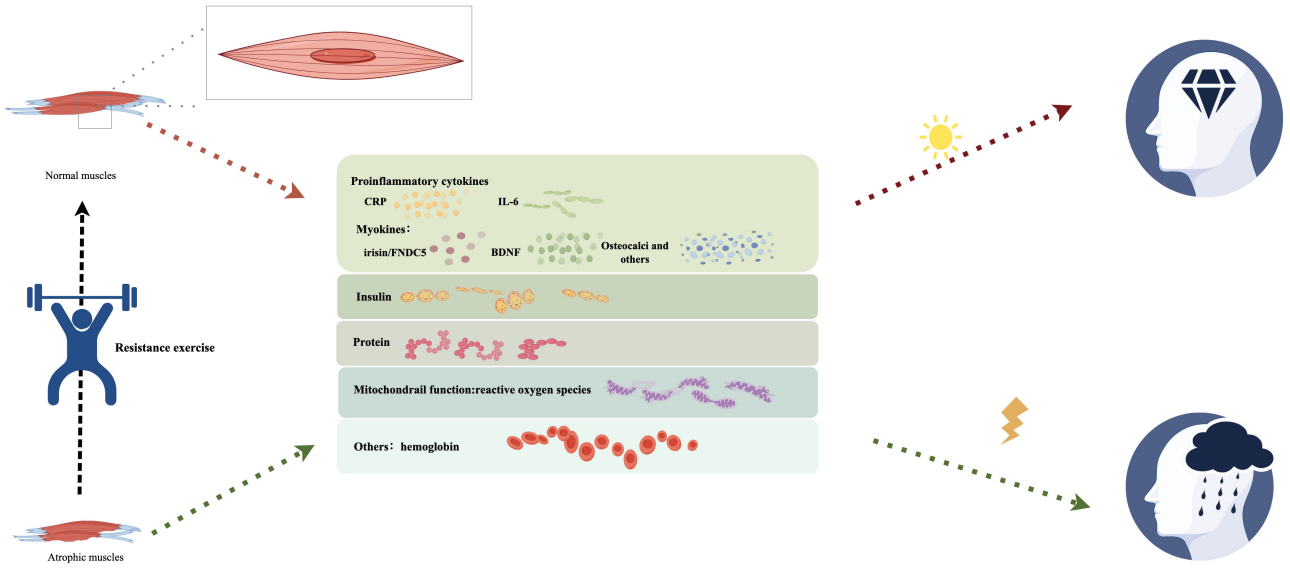

FIGURE 1
Resistance exercise, muscle atrophy and cognitive function.

equivalents; HRmax: heart rate maximum; HRR: heart rate recovery; VO_2max: maximum oxygen consumption; Borg's RPE scales C=category scale (6–20) and C-R=category-ratio scale (0–10)]. This may be because moderate-intensity training optimally stimulates hormones, neurotransmitters, and other factors in the body through psychological and physiological factors, thereby promoting cognitive function. Low-intensity training is more conducive to physiological adaptation, whereas high-intensity induces fatigue and heightened wakefulness, reducing cooperation and completion for patients with cognitive impairment (Komiyama et al., 2020; Liu X. et al., 2024). A 2023 review report (Liu S. et al., 2024) examining the impact of acute exercise (both aerobic and resistance) on cognitive function in individuals with AD and MCI suggests that moderate-intensity acute aerobic and resistance exercise can improve inhibitory control (IC) in MCI patients. Conversely, high-intensity acute exercise does not appear to enhance IC, potentially due to the influence of BDNF and insulin-like growth factor 1 (IGF-1).

5.2 Duration of resistance exercise

Most trials last 12–52 weeks, with weekly exercise frequency varying from 1 to 3 times. Research reveals that regardless of the duration and frequency, regular resistance exercise can significantly improve the cognition of the elderly population. A preliminary study indicated that for female patients with MCI, resistance exercises were performed twice-weekly, with each group of exercises lasting 6–8 sessions for 6 months, and the cognitive abilities of this group of patients improved (Nagamatsu et al., 2012). This study was further supported by subsequent researchers, who conducted upper limb resistance training (2.4 kg dumbbells) and lower limb resistance training (chair test) separately on the patients, with 3 × 10 repetitions, 3 times weekly, for 12 weeks. The experimental group increased upper body strength by 58%, lower body strength by 68%, and cognitive ability by 19% (Smolarek Ade et al., 2016). In a recent study, participants aged 55 and older with MCI were subjected to resistance exercise for 6 months, 2–3 times a week. Physical and metabolic tests, a series of neuropsychological scale tests, and an MRI evaluation determined that regular resistance exercise can improve cognitive function and behavioral ability (Broadhouse et al., 2020). There was no significant statistical difference in the effectiveness of high-dose intervention (> 150 min/week) compared to low-dose intervention (<150 min/week) in elderly individuals with cognitive impairment. Subsequently, certain scholars observed no significant correlation between cognitive function improvement and overall duration but suggested shorter and more frequent resistance exercises (Sanders et al., 2019). Although there is no clear requirement for the duration of resistance exercise in improving cognition, a minimum intervention time of ≥ 8 weeks is necessary to increase muscle strength and restore muscle function (Mayer et al., 2011). Moreover, skeletal muscles exhibit adaptability to resistance exercise; therefore (Liu S. et al., 2024), it is recommended that resistance exercise must be performed at least 2–3 times per week, lasting more than 12 weeks.

5.3 The form of resistance movement

The World Health Organization recommends that older adults must perform at least three major muscle exercises per week (Bull et al., 2020). A 12-week study comparing the effects of upper and lower-body resistance exercise on cognitive changes and physical function in older adults revealed (Sanchez-Lastra et al., 2022) that resistance exercise positively influences cognitive function and functional independence. Moreover, upper-body exercise was more effective for cognitive function, while lower-body exercise demonstrated superior improvements in physical function parameters. Resistance exercise training usually includes

leg exercises, sitting rowing, chest exercises, latissimus dorsi pull-down, leg stretches, and triceps brachii flexion and extension (Timmons et al., 2018). For elderly patients with AD, the above movements can be optimized to avoid using heavy equipment and achieve the same objective by resisting their own weight. Each training session must be completed comfortably within 60 s while ensuring training safety and to ensure gradual overload throughout the entire training intervention process, thereby fully activating the function of skeletal muscles in resistance exercise.

We recommend resistance exercise programs targeting many major muscle groups throughout the body, with exercise frequency of 2 to 3 times a week, lasting over 12 weeks. Moderate-intensity training should be conducted, increasing weight gradually when each exercise's repetitions become easy. To optimize health outcomes, combine aerobic exercise with resistance exercise regularly.

6 Conclusion

In conclusion, restoring partial physiological structure and function of skeletal muscles can improve cognitive levels. Researchers have discovered that atrophied skeletal muscles can affect cognition through the secretion of hemoglobin. Conversely, resistance exercise can promote muscle secretion of related muscle factors and growth factors and directly improve skeletal muscle atrophy by increasing muscle strength, thereby reversing AD-related brain atrophy and alleviating cognitive dysfunction Consequently, resistance exercise can improve cognitive function and delay cognitive impairment in patients with AD by restoring skeletal muscle function. Currently, there is relatively little research regarding the causal relationship between AD and skeletal muscle atrophy, as most patients with late to scattered AD exhibit relatively late onset age, often accompanied by unavoidable complications, including osteoporosis and skeletal muscle atrophy. For the elderly, further research is essential to elucidate whether skeletal muscle atrophy affects cognitive function or if cognitive dysfunction exacerbates skeletal muscle atrophy. A precise comprehension of the relationship between the two can be achieved through targeted interventions to delay the disease's overall progression.

Among all treatment methods for AD, exercise is widely acknowledged and has a lesser economic burden on patients and their families. Accordingly, for patients with AD, especially those with skeletal muscle atrophy, resistance exercise can improve inflammation and brain function through vascular and nerve pathways and restore skeletal muscle physiological function, thereby achieving twice the result with half the effort in improving cognitive function. The optimal resistance exercise mode should involve as many major parts of the body as possible and may be integrated with aerobic exercise. Moderate-intensity exercise should be performed 2–3 times weekly for over 12 weeks. Currently, we recommend the most effective resistance exercise approach for all AD patients. Future research should explore whether tailored exercise regimens are necessary for individuals with varying levels of cognitive impairment, and if these can be integrated with other non-drug therapies to maximize clinical benefits for patients.

Author contributions

WL: Investigation, Software, Writing – original draft, Writing – review & editing. WF: Writing – original draft, Writing – review & editing. YZ: Writing – review & editing. QC: Writing – review & editing. WS: Writing – review & editing. QL: Methodology, Writing – review & editing. LC: Methodology, Writing – review & editing. SY: Writing – review & editing. QK: Supervision, Writing – review & editing. SQ: Supervision, Writing – review & editing, Methodology.

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Conflict of interest

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

Generative AI statement

The author(s) declare that no Gen AI was used in the creation of this manuscript.

Publisher's note

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Correlation of cognitive impairment with Mediterranean diet and mortality: a prospective cohort study

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Background and aim: Long-term adherence to the Mediterranean Diet has been shown to improve cognitive function in patients. However, there is a lack of evidence regarding the impact of the Mediterranean diet and cognitive impairment on long-term mortality outcomes. This study aims to explore whether there is an interaction between the degree of adherence to the Mediterranean diet and cognitive impairment on long-term mortality outcomes.

Methods: The study included 2,520 participants from the National Health and Nutrition Examination Survey (NHANES) conducted between 2011 and 2014. The adherence to the Mediterranean diet was assessed using the 9-point alternative Mediterranean diet index (aMED index). Cognitive function was assessed using the Consortium to Establish a Registry for Alzheimer's disease (CERAD), the Animal Fluency Test (AFT), and the Digital Symbol Substitution Test (DSST). By accessing public records from the National Death Index (NDI), NHANES participants' information was linked to death certificate records to determine mortality and causes of death during the follow-up period, up to December 31, 2019, with causes specified according to ICD-10. Participants were categorized based on the median aMED score into low adherence (scores 0–3), moderate adherence (score 4), and high adherence (scores 5–9) groups. Cognitive impairment was assessed by calculating the arithmetic mean of standardized scores (Z-scores) for each cognitive test. Participants with scores below the first quartile of the arithmetic mean were considered to have cognitive impairment. Cox proportional hazards regression models were used to assess the relationship between cognitive impairment, aMED, and all-cause and cardiovascular mortality outcomes. Additionally, the interaction between cognitive impairment and aMED on these outcomes was evaluated.

Results: The study included 2,520 participants, with 481 deaths during the follow-up period, of which 129 (26.8%) were cardiovascular-related. The median aMED score in the population was 4, and 632 individuals (25.1%) were considered to have cognitive impairment. A higher aMED score was associated with a reduced risk of long-term all-cause mortality and cardiovascular-related mortality (HR, 0.65; 95% CI, 0.52–0.81, $p < 0.001$; HR, 0.73; 95% CI, 0.47–0.91, $p = 0.039$). Cognitive impairment was associated with an increased risk of long-term all-cause mortality and cardiovascular mortality (HR, 1.78; 95% CI, 1.46–2.18, $p < 0.001$; HR, 1.80; 95% CI, 1.22–2.64, $p = 0.003$). Individuals with both lower aMED scores and cognitive impairment had higher risks of all-cause and cardiovascular mortality. Subgroup analysis indicates that only in the cognitive impairment subgroup is a higher Mediterranean diet score associated with a

reduced risk of cardiovascular mortality. There is an interaction between lower aMED scores and cognitive impairment in increasing cardiovascular-related mortality (p for interaction = 0.028).

Conclusion: There is an interaction between adherence to the Mediterranean diet and cognitive impairment concerning cardiovascular-related mortality, but not all-cause mortality. Among individuals with cognitive impairment, adherence to the Mediterranean diet has a more significant impact on cardiovascular-related mortality.

KEYWORDS

Mediterranean diet, cognitive impairment, all-cause mortality, NHANES, cardiovascular mortality

1 Introduction

The global trend of aging is rapidly intensifying. Data shows that in 2019, the global population aged 65 and older reached 703 million. This number is projected to more than double, reaching 1.5 billion by 2050 (Economic and Affairs, 2020). As age increases, cognitive function typically declines, which is particularly concerning in our current aging society (Murman, 2015). Cognitive impairment generally includes conditions such as mild cognitive impairment (MCI) and dementia, which not only affect the quality of life of the elderly but are also closely associated with an increased risk of mortality (Bae et al., 2018). The occurrence of cognitive impairment may be related to various factors, including genetics, lifestyle, and chronic diseases (Gil-Peinado et al., 2023). Cognitive impairment is also associated with the development of cardiovascular diseases. However, there is relatively limited research on the relationship between cognitive impairment and long-term outcomes, especially all-cause and cardiovascular mortality, and the findings are somewhat controversial.

The Mediterranean diet, characterized by its emphasis on fruits, vegetables, whole grains, nuts, legumes, and fish, is rich in healthy unsaturated fats, antioxidants, and fiber. It is widely recognized for its protective effects on the cardiovascular system (Widmer et al., 2015; Aznar de la Riera et al., 2025). Numerous studies have shown that adherence to the Mediterranean diet can significantly reduce the risk of developing cardiovascular diseases (Grosso et al., 2017; Estruch et al., 2018; Esmaeilinezhad et al., 2025; Molani-Gol and Rafraf, 2025). In addition, the Mediterranean diet may beneficially influence cognitive function by improving inflammatory responses and oxidative stress, thereby reducing the risk of cognitive impairment (Frisardi et al., 2010; Cardelo et al., 2022; Pontifex et al., 2024). However, systematic research on the role of the Mediterranean diet in patients with cognitive impairment and its impact on long-term mortality risk is lacking. Given the significant association of both the Mediterranean diet and cognitive impairment with cardiovascular health, we hypothesize that within the context of cognitive impairment, the Mediterranean diet may offer stronger protective effects against all-cause and cardiovascular mortality.

This study aims to explore the interaction between cognitive impairment and the Mediterranean diet on the risks of all-cause and cardiovascular mortality. We utilized data from the National Health and Nutrition Examination Survey (NHANES), which collects health and nutrition information from a representative sample of the U.S. population and conducts long-term follow-up with participants. By analyzing NHANES data, we sought to determine whether adherence to the Mediterranean diet could reduce long-term mortality risk and to further investigate whether cognitive impairment might alter the risks of all-cause and cardiovascular mortality by influencing the effects of the Mediterranean diet.

2 Materials and methods

2.1 Population

NHANES is a nationwide cross-sectional survey that assesses the health and nutritional status of the U.S. population. With a design based on complex sampling, the survey includes a population representative of all age groups and various ethnicities in the United States. Conducted in two-year cycles, NHANES collects data through interview questionnaires, standardized physical examinations, and laboratory tests (Ahluwalia et al., 2016). The survey is approved by the Institutional Review Board of the Centers for Disease Control and Prevention, with informed consent obtained from all participants.[1] The study adheres to the principles of the Declaration of Helsinki. This analysis included data from the 2 cycles spanning 2011 to 2014. Follow-up data on mortality status and causes of death were linked to the National Death Index (up until December 31, 2019). The National Death Index, published annually by the National Center for Health Statistics (NCHS), provides epidemiologists with comprehensive mortality data for the entire U.S. population (MacMahon, 1983). The inclusion and exclusion criteria for the study population are detailed in Figure 1. Individuals younger than 60, those who did not complete the nutrition intake or cognitive questionnaires, and those lost to follow-up were excluded. Ultimately, 2,520 individuals were included in the final analysis.

2.2 Data collection

2.2.1 Dietary assessment and aMED calculation

Relevant dietary information was obtained from the 24-h dietary recall questionnaires in the NHANES database. Participants completed the first 24-h dietary recall in a Mobile Examination Center

1 https://www.cdc.gov/nchs/nhanes/irba98.htm

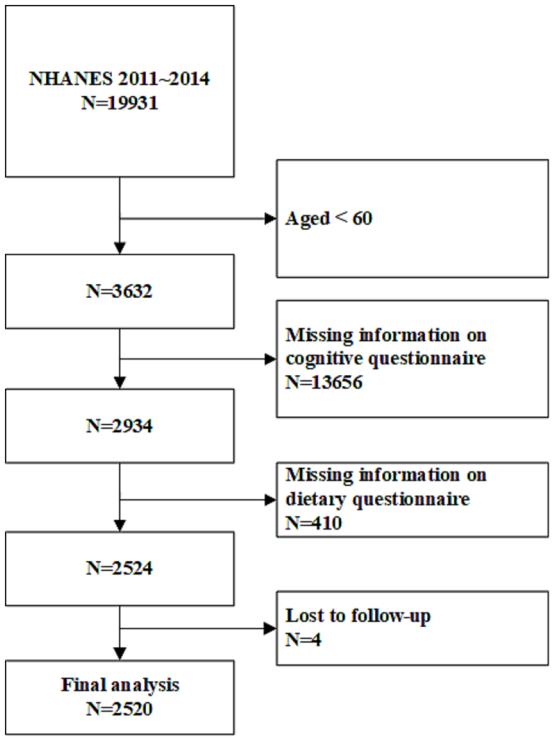

FIGURE 1
Study flowchart. NHANES, National Health and Nutrition Examination Survey. A total of 2,520 participants were included in the final analysis.

(MEC) on Day 1, and the second 24-h dietary recall within 10 days of the MEC assessment was completed through telephone follow-up on Day 2. We used data from these two 24-h dietary recalls to estimate the average dietary intake over the 2 days.

To assess adherence to the Mediterranean diet, we employed a two-step process. First, the 24-h dietary recall data were linked to the United States Department of Agriculture (USDA) Food Patterns Equivalents Database to convert different foods and beverages into standardized food pattern components (Fan et al., 2022).

In the second step, we calculated the alternative Mediterranean diet (aMED) index to evaluate adherence to the Mediterranean diet (Fung et al., 2005). The aMED index measures the intake of 9 types of food pattern components, including total fruits, vegetables (excluding potatoes), whole grains, legumes, nuts, fish, red and processed meat, the ratio of monounsaturated to saturated fats (MUFA/SFA), and alcohol. For each type of food component, a single point will be assigned to the participants if their intake was above the median of the study cohort, except for red/processed meat and alcohol. Participants were assigned a single point for below-median intake of red/processed meat and a single point for moderate alcohol intake (defined as 10–25 g/day for men and 5–15 g/day for women). If a participant does not meet the specified condition for a given item, the score for that item is set to 0 (for example, if the participant's fruit intake is below the median level of the total population, the score for the fruit component is 0). Finally, the scores for each item are summed to obtain the aMED score.

The total aMED score ranged from 0 to 9, with higher scores indicating greater adherence to the Mediterranean diet (Chang et al., 2022). Based on their aMED scores, participants were categorized into three groups: low adherence (aMED score 0–3), moderate adherence (aMED score 4), and high adherence (aMED score 5–9).

2.2.2 Assessment of cognitive impairment

Cognitive function was assessed using three standardized tests: the Consortium to Establish a Registry for Alzheimer's disease (CERAD) Word List Learning test, the Animal Fluency test, and the Digit Symbol Substitution Test (DSST). The CERAD Word List Learning test includes three immediate recall trials and one delayed recall trial, which evaluate the ability to learn and retain new verbal information. Each trial is scored from 0 to 10, with total possible scores ranging from 0 to 30 for the immediate recall and 0 to 10 for the delayed recall (Fillenbaum and Mohs, 2023). The Animal Fluency test measures verbal fluency within a specific category, where participants are asked to name as many animals as possible within 1 min. Scores for this test range from 0 to 40 (Lv et al., 2024). The DSST assesses cognitive domains such as processing speed, attention, and working memory by requiring participants to match symbols to numbers within a set time limit. Scores range from 0 to 133 (Tang et al., 2024). Higher scores across these tests indicate better cognitive performance. The individual scores from each test were then standardized using Z-score transformation. An overall cognitive score was calculated as the average of these standardized scores. Participants with overall cognitive scores in the lowest quartile of the study population were classified as having cognitive impairment, reflecting potential cognitive impairment.

2.2.3 Assessment of other covariates

Collected baseline and sociodemographic data included age, gender, race, education level, marital status, family income poverty ratio (PIR), smoking status, BMI, and average systolic/diastolic blood pressure. Smoking was defined as smoking at least 100 cigarettes in life or smoking at the time of the survey. Laboratory tests included fasting glucose, glycated hemoglobin, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, HOMA-IR, albumin, and eGFR. Medical condition data included histories of hypertension, diabetes, heart failure, coronary heart disease, and stroke. Hypertension history was defined as a self-reported physician diagnosis of hypertension, use of oral antihypertensive drugs, or elevated blood pressure (systolic $\geq$130 and/or diastolic $\geq$85 mmHg). Diabetes history was defined as meeting any of the following: self-reported physician diagnosis of diabetes, self-reported use of insulin or oral hypoglycemic drugs, fasting glucose concentration > 126 mg/dL, glycated hemoglobin $\geq$6.5%, or Oral Glucose Tolerance Test (OGTT) $\geq$ 200 mg/dL. Other medical histories were collected through questionnaires.

2.2.4 Assessment of death

Patients were followed up until December 31, 2019. Mortality outcomes, causes of death, and follow-up time were determined based on the National Death Index as of December 31, 2019, available for download from the National Center for Health Statistics website. Causes of death were coded according to ICD-10. This study included mortality from all causes and cardiovascular disease (CVD), specifically codes I00-I09, I11, I13, and I20-I51.

2.3 Statistical analysis

All analyses were conducted using the R statistical package (R Foundation).[2] This study followed the NHANES data usage guidelines for statistical analysis, taking into account the complex survey design factors.[3] Using conventional estimations is inappropriate; thus, all analyses were weighted to represent the U.S. population. We calculated weighted estimates according to the NHANES analytic guidelines.[4] Participants were divided into above-median, median, and below-median groups based on aMED scores, and baseline data for these groups were described. Continuous variables were presented as means (95% confidence intervals). Categorical variables were expressed as numbers (percentages). Differences in continuous variables among groups were analyzed using ANOVA with *p*-values obtained by survey-weighted linear regression (svyglm); differences in categorical variables were analyzed with the Chi-square test, with p-values from the survey-weighted Chi-square test (svytable). Cox proportional hazards regression models were used to calculate hazard ratios (HR) and 95% confidence intervals for cognitive impairment, aMED on all-cause and cardiovascular mortality. Further analysis grouped according to aMED and cognitive impairment (presence or absence) was conducted using Cox proportional hazards models to explore the relationship with mortality outcomes. The interaction effect of cognitive impairment with aMED on outcomes was assessed by the likelihood ratio test, considering two-sided interaction *p*-values of 0.1 as statistically significant. Kaplan–Meier survival curves were plotted for groups based on aMED and cognitive impairment, and compared using the log-rank test. Additionally, restricted cubic spline plots were used to evaluate the non-linear relationship between aMED scores and mortality outcomes. All analyses were repeated with complete data to examine the robustness of the results. Two-sided p-values of 0.05 were considered statistically significant.

3 Results

3.1 Baseline characteristics

A total of 2,520 participants were included in the study, categorized into low (0–3), median (4), and high (5–9) aMED score groups. The mean age of participants was 69.1 years (95% CI, 68.6–69.6), with no significant difference between groups ($p = 0.6499$). Female participants comprised 53.2% of the cohort, with a slightly higher percentage in the high aMED group (55.3%) compared to the low aMED group (50.6%), though this difference was not statistically significant ($p = 0.3545$).

There were significant differences in race distribution ($p = 0.0019$), with a higher proportion of non-Hispanic White participants in the high aMED group (77.4%) compared to the low aMED group (69.6%). Participants in the high aMED group also had a significantly higher family income-to-poverty ratio ($p < 0.0001$) and higher levels of education, with more participants having a college degree or above (41.3%) compared to the low aMED group (25.8%) ($p < 0.0001$).

Regarding lifestyle factors, participants in the high aMED group had lower smoking rates (13.3%) compared to the low aMED group (19.2%) ($p = 0.0024$). BMI was also significantly lower in the high aMED group (mean 28.3) than in the low aMED group (mean 29.7) ($p = 0.0046$). Additionally, participants in the high aMED group had lower fasting serum glucose levels ($p = 0.0049$), lower systolic blood pressure ($p = 0.0464$), and reported higher levels of physical activity ($p = 0.0244$) compared to the low aMED group (Table 1).

A total of 19.1% participants were categorized as having cognitive impairment. Participants with cognitive impairment were older, had lower PIR, higher rate of CHD, stroke and diabetes, have higher level of HbA1c, and have lower level of TC, LDL-C, and eGFR. There were no significant differences in TG and HDL-C levels between the cognitive impairment group and the non-cognitive impairment group. Males, the widowed, the divorced or the separated had higher risk of cognitive impairment (Supplementary Table 1).

3.2 Association between aMED, cognitive impairment, and mortality

3.2.1 All-cause mortality

In the unadjusted model, higher aMED scores were associated with a significantly lower risk of all-cause mortality. Participants in the high aMED group had a hazard ratio (HR) of 0.56 (95% CI 0.45–0.69, $p < 0.001$) compared to the reference low aMED group. The median aMED group also showed a reduced risk of all-cause mortality (HR 0.73, 95% CI 0.58–0.92, $p = 0.007$). When aMED was analyzed as a continuous variable, there was a consistent protective effect (HR 0.86, 95% CI 0.81–0.91, $p < 0.001$). Confounders were chosen from univariate regression analysis and clinical experience. To detect multicollinearity of the confounders, we calculated Variance Inflation Factors (VIFs) for all covariates included in the adjusted Cox regression model. The VIF values ranged between 1.0 and 1.5 (Supplementary Table 2). These results suggest that multicollinearity among covariates is negligible in our model, and therefore does not significantly inflate standard errors or destabilize hazard ratio estimates. After adjusting for confounding variables (Model III), the protective effect of a high aMED score remained significant (HR 0.65, 95% CI 0.52–0.81, $p < 0.001$). The association for the median aMED group, however, was attenuated and no longer significant (HR 0.82, 95% CI 0.64–1.05, $p = 0.115$). Cognitive impairment was strongly associated with an increased risk of all-cause mortality in both unadjusted (HR 2.80, 95% CI 2.34–3.35, $p < 0.001$) and adjusted models (HR 1.78, 95% CI 1.46–2.18, $p < 0.001$).

3.2.2 Cardiovascular mortality

For CVD mortality, in the unadjusted model, the high aMED group had a significantly lower risk compared to the low aMED group (HR 0.60, 95% CI 0.40–0.89, $p = 0.011$), while the median aMED group showed a non-significant reduction in risk (HR 0.76, 95% CI 0.49–1.18, $p = 0.221$). aMED as a continuous variable was associated with a lower risk of CVD mortality (HR 0.77, 95% CI 0.63–0.94, $p = 0.002$).

In the fully adjusted model (Model III), the protective effect of a high aMED score persisted (HR 0.73, 95% CI 0.47–0.91, $p = 0.039$),

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

3 https://wwwn.cdc.gov/nchs/nhanes/tutorials/sampledesign.aspx

4 https://wwwn.cdc.gov/nchs/nhanes/analyticguidelines.aspx#sample-design

TABLE 1 Baseline demographics among patients with low, median, and high aMED.

Characteristics	Total	aMED (above median)	aMED (Median)	aMED (below median)	*P**	*P***
		Score 0–3	Score 4	Score 5–9		
Number of subjects	2, 520	955	571	994		
Age (year)	69.1 (68.6, 69.6)	69.3 (68.7, 69.9)	68.8 (67.8, 69.8)	69.1 (68.3, 69.9)	0.6499	0.6311
Female	53.2 (51.0, 55.5)	50.6 (46.2, 55.0)	53.7 (48.2, 59.1)	55.3 (50.7, 59.9)	0.3545	0.1581
Race					0.0019	0.0013
Mexican American	3.4 (2.1, 5.5)	3.0 (1.4, 6.0)	3.3 (2.0, 5.4)	3.8 (2.4, 6.1)		
Other Hispanic	4.0 (2.6, 5.9)	3.9 (2.2, 6.8)	4.3 (2.5, 7.1)	3.8 (2.6, 5.4)		
Non-Hispanic White	79.1 (74.7, 82.9)	81.0 (74.8, 85.9)	78.9 (72.7, 84.1)	77.4 (72.5, 81.7)		
Non-Hispanic Black	8.5 (6.2, 11.5)	9.3 (6.4, 13.3)	9.3 (6.3, 13.5)	7.3 (5.2, 10.3)		
Other Race	5.1 (4.1, 6.3)	2.9 (1.9, 4.2)	4.2 (2.5, 7.0)	7.6 (5.6, 10.2)		
Family PIR	3.1 (3.0, 3.3)	2.8 (2.6, 3.0)	3.1 (2.7, 3.4)	3.5 (3.3, 3.7)	<0.0001	<0.0001
Educational level					<0.0001	<0.0001
Less than 9th grade	5.5 (4.1, 7.4)	7.4 (4.9, 11.2)	5.7 (3.9, 8.3)	3.6 (2.6, 4.9)		
9–11th grade	9.5 (7.1, 12.5)	11.6 (8.7, 15.3)	10.6 (7.5, 14.9)	7.0 (4.5, 10.7)		
High school graduate	22.3 (18.7, 26.4)	26.4 (21.2, 32.3)	25.1 (18.0, 33.9)	17.0 (13.4, 21.2)		
College	30.1 (26.9, 33.5)	31.4 (25.5, 38.0)	26.0 (20.9, 31.9)	31.2 (26.3, 36.6)		
College graduate or above	32.6 (28.0, 37.7)	23.2 (18.1, 29.3)	32.5 (24.5, 41.6)	41.3 (35.1, 47.7)		
Marital status					0.0001	0.0004
Married	66.7 (63.4, 69.9)	60.7 (54.5, 66.6)	67.2 (61.4, 72.6)	71.8 (68.2, 75.2)		
Never married	3.7 (2.9, 4.8)	4.4 (3.1, 6.2)	1.9 (1.0, 3.4)	4.2 (2.8, 6.1)		
Widowed/Divorced/Separated	29.6 (26.6, 32.8)	34.9 (29.4, 40.9)	30.9 (25.7, 36.6)	24.0 (21.0, 27.4)		
Smoking	19.0 (16.9, 21.4)	26.6 (21.9, 31.8)	16.5 (11.2, 23.5)	13.3 (9.1, 19.0)	0.0024	0.0015
BMI	29.1 (28.6, 29.6)	30.1 (29.4, 30.8)	29.1 (28.0, 30.3)	28.3 (27.7, 28.8)	0.0046	0.0011
CHD	9.9 (7.9, 12.4)	11.7 (9.5, 14.4)	8.4 (4.2, 16.1)	9.1 (6.4, 12.8)	0.4202	0.1848
Stroke	6.0 (5.0, 7.1)	7.7 (5.7, 10.3)	5.7 (3.7, 8.7)	4.6 (3.0, 6.9)	0.1283	0.076
Diabetes mellitus	25.2 (22.8, 27.7)	29.5 (24.7, 34.9)	23.8 (17.7, 31.1)	22.0 (19.1, 25.2)	0.0685	0.0133
Hypertension	73.9 (70.7, 76.8)	76.8 (69.4, 82.9)	72.0 (65.7, 77.6)	72.3 (68.5, 75.7)	0.3813	0.2269
Cognitive impairment	19.1 (17.1, 21.3)	23.8 (20.9, 26.9)	16.6 (12.9, 21.0)	16.4 (13.3, 20.0)	0.0014	0.0009
TG (mmol/L)	1.4 (1.3, 1.5)	1.5 (1.4, 1.6)	1.3 (1.2, 1.4)	1.4 (1.2, 1.5)	0.0139	0.0505
TC (mmol/L)	5.0 (4.9, 5.1)	4.9 (4.8, 5.1)	5.0 (4.8, 5.2)	5.0 (4.9, 5.1)	0.6827	0.43
HDL-C (mmol/L)	1.4 (1.4, 1.5)	1.4 (1.3, 1.4)	1.4 (1.3, 1.5)	1.5 (1.5, 1.6)	0.0027	0.0007
LDL-C (mmol/L)	2.9 (2.8, 2.9)	2.8 (2.7, 2.9)	2.9 (2.7, 3.1)	2.9 (2.8, 3.0)	0.5872	0.311
Fasting glucose (mmol/L)	6.2 (6.0, 6.4)	6.3 (6.1, 6.6)	6.5 (5.8, 7.1)	6.0 (5.8, 6.1)	0.0464	0.0188
HbA1c, %	5.9 (5.9, 6.0)	6.0 (5.9, 6.1)	5.9 (5.8, 6.0)	5.9 (5.8, 5.9)	0.1311	0.0484
HOMA-IR	4.0 (3.4, 4.6)	4.1 (3.2, 4.9)	4.9 (3.4, 6.4)	3.5 (3.0, 3.9)	0.1842	0.2383
Albumin	42.0 (41.8, 42.2)	41.7 (41.3, 42.0)	42.2 (41.8, 42.5)	42.3 (41.9, 42.6)	0.0244	0.0122
eGFR, mL/min	72.1 (70.8, 73.5)	69.5 (66.2, 72.8)	71.5 (69.1, 73.9)	74.8 (73.5, 76.1)	0.0049	0.0063
CERAD W-L immediate recall	19.8 (19.4, 20.3)	19.1 (18.5, 19.7)	19.9 (19.2, 20.6)	20.4 (19.9, 20.9)	0.0005	0.0001
CERAD W-L delayed recall	6.3 (6.1, 6.5)	6.1 (5.8, 6.4)	6.4 (6.0, 6.7)	6.6 (6.3, 6.8)	0.0568	0.0197
Animal fluency test	18.2 (17.7, 18.6)	17.0 (16.4, 17.6)	18.3 (17.6, 19.0)	19.1 (18.5, 19.7)	<0.0001	<0.0001
Digit symbol substitution test	52.6 (51.3, 53.8)	49.0 (47.5, 50.6)	52.8 (50.3, 55.3)	55.6 (53.8, 57.4)	<0.0001	<0.0001

*Comparison among three groups. **Comparison between aMED Below Median and above median. aMED, alternative Mediterranean diet; PIR, poverty income ratio; BMI, body mass index; SBP, systolic pressure; DBP, diastolic pressure; CHF, congestive heart failure; CHD, coronary heart disease; TG, triglycerides; TC, total cholesterol; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; HbA1c, glycated hemoglobin A1c; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; eGFR, estimated glomerular filtration rate. Data are presented as mean (95% CI) or percentage (95% CI). For continuous variables, *p*-value was by survey-weighted linear regression (svyglm). For categorical variables, *p*-value was by survey-weighted Chi-square test (svytable).

whereas the association for the median aMED group was not significant (HR 0.88, 95% CI 0.56–1.35, $p = 0.597$). Cognitive impairment was associated with a higher risk of CVD mortality, both in the unadjusted model (HR 2.99, 95% CI 2.12–4.23, $p < 0.001$) and in the fully adjusted model (HR 1.80, 95% CI 1.22–2.64, $p = 0.003$) (Table 2).

3.3 Interaction between aMED and cognitive impairment on mortality

In participants without cognitive impairment, the unadjusted hazard ratio (HR) for all-cause mortality was significantly higher in the low aMED group compared to the high aMED group (HR 1.63, 95% CI 1.23–2.17, $p = 0.001$). After adjusting for confounding factors, the risk remained elevated in the low aMED group, but with reduced significance (HR 1.30, 95% CI 0.96–1.77, $p = 0.09$). In participants with cognitive impairment, the risk of all-cause mortality was even higher in the low aMED group, with an unadjusted HR of 1.76 (95% CI 1.29–2.40, $p < 0.001$). The association remained significant after adjustment, with an adjusted HR of 1.78 (95% CI 1.25–2.52, $p = 0.001$). There was no significant interaction between aMED and cognitive impairment in influencing all-cause mortality (p for interaction = 0.408).

For cardiovascular (CVD) mortality, participants without cognitive impairment in the low aMED group had a higher but not statistically significant unadjusted risk (HR 1.10, 95% CI 0.62–1.93, $p = 0.749$) compared to the high aMED group. After adjustment, the HR remained non-significant (HR 0.76, 95% CI 0.41–1.40, $p = 0.379$).

In participants with cognitive impairment, the low aMED group had a significantly higher risk of CVD mortality in both the unadjusted (HR 2.22, 95% CI 1.22–4.06, $p = 0.009$) and adjusted models (HR 2.00, 95% CI 1.02–3.95, $p = 0.045$). The interaction between aMED and cognitive impairment was significant for CVD mortality (p for interaction = 0.028), indicating that cognitive impairment and low aMED scores together significantly increased the risk of cardiovascular mortality (Table 3).

3.4 Sensitivity analysis

Further analysis using RCS curves evaluated the nonlinear relationship between aMED and both all-cause and cardiovascular mortality (Figure 2). A clear monotonic dose–response relationship was observed between aMED and all-cause mortality, indicating that higher aMED scores were associated with a lower risk of mortality. A similar linear relationship was found between aMED and cardiovascular mortality, although this association was not statistically significant. When participants were stratified by the presence or absence of cognitive impairment, the RCS curves for all-cause mortality were similar across the groups. However, for cardiovascular mortality, among those with cognitive impairment, aMED scores below 4 were associated with a more pronounced reduction in cardiovascular mortality risk compared to those without cognitive impairment. This suggests that the protective effect of a higher aMED score on cardiovascular mortality is more evident in participants with cognitive impairment.

The Kaplan–Meier survival curves stratified by aMED scores and the presence of cognitive impairment (CI) demonstrate a clear difference in survival probability across groups ($p < 0.0001$). Participants were categorized into three aMED score groups: High aMED, Medium aMED, and Low aMED. Each group was further divided into those without cognitive impairment (−) and with cognitive impairment (+), resulting in six groups: High aMED (−), Medium aMED (−), Low aMED (−), High aMED (+), Medium aMED (+), and Low aMED (+) across all groups, participants with high aMED scores exhibited the highest survival probability over the 10-year follow-up period, regardless of cognitive impairment status. In contrast, participants with low aMED scores had the lowest survival probability, particularly those with cognitive impairment [Low aMED (+)], who experienced a steep decline in survival compared to other groups. Participants with cognitive impairment generally had lower survival probabilities within each aMED category. Notably, the Low aMED (+) group had the poorest survival outcomes, suggesting that low aMED scores combined with cognitive

TABLE 2 Association between aMED, cognitive impairment and mortality.

Mortality outcomes	Unadjusted		Model I		Model II		Model III	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
All-cause mortality								
Lower aMED	Reference							
Median aMED	0.73 (0.58–0.92)	0.007	0.82 (0.65–1.03)	0.095	0.83 (0.65–1.06)	0.0001	0.82 (0.64–1.05)	0.115
Higher aMED	0.56 (0.45–0.69)	<0.001	0.57 (0.46–0.7)	<0.001	0.64 (0.51–0.8)	<0.0001	0.65 (0.52–0.81)	<0.001
aMED (continuous)	0.86 (0.81–0.91)	<0.001	0.87 (0.82–0.92)	<0.001	0.9 (0.85–0.96)	0.001	0.9 (0.84–0.96)	0.001
Cognitive impairment*	2.8 (2.34–3.35)	<0.001	1.86 (1.53–2.25)	<0.001	1.9 (1.55–2.32)	<0.001	1.78 (1.46–2.18)	<0.001
CVD mortality								
Lower aMED	Reference							
Median aMED	0.76 (0.49–1.18)	0.221	0.86 (0.55–1.35)	0.522	0.95 (0.6–1.23)	0.217	0.88 (0.56–1.35)	0.597
Higher aMED	0.6 (0.4–0.89)	0.011	0.62 (0.42–0.93)	0.022	0.75 (0.49–0.92)	0.042	0.73 (0.47–0.91)	0.039
aMED (continuous)	0.77 (0.63–0.94)	0.002	0.85 (0.77–0.95)	0.005	0.91 (0.81–1.02)	0.101	0.9 (0.8–1.01)	0.082
Cognitive impairment*	2.99 (2.12–4.23)	<0.001	1.86 (1.29–2.69)	0.001	1.92 (1.31–2.8)	0.001	1.8 (1.22–2.64)	0.003

CVD, cardiovascular disease; Model I initially was adjusted for age, sex, and race (Mexican American, non-Hispanic white, non-Hispanic black, other races); model II was further adjusted for education level (below high school, high school or equivalent, college or above), marital status (married, widowed, divorced, and never married), and family PIR based on model I; model III further adjusted for BMI, smoking status, comorbidities including diabetes mellitus, hypertension, and stroke. *No cognitive impairment was set as the reference group.

TABLE 3 Interaction analysis of aMED and cognitive impairment on mortality.

aMED categories	Cognitive impairment	Unadjusted HR 95% CI	*P*-value	P for interaction	Adjusted HR 95% CI	*P*-value	*P* for interaction
All-cause mortality				0.768			0.408
Higher aMED	Without				1 (Ref)		
Median aMED	Without	1.36 (0.98–1.88)	0.066		1.22 (0.86–1.72)	0.261	
Lower aMED	Without	1.63 (1.23–2.17)	0.001		1.3 (0.96–1.77)	0.090	
Higher aMED	With				1 (Ref)		
Median aMED	With	1.23 (0.83–1.83)	0.294		1.41 (0.91–2.17)	0.124	
Lower aMED	With	1.76 (1.29–2.4)	<0.001		1.78 (1.25–2.52)	0.001	
CVD mortality				0.056			0.028
Higher aMED	Without	1 (Ref)			1 (Ref)		
Median aMED	Without	1.41 (0.78–2.54)	0.253		1.31 (0.71–2.4)	0.391	
Lower aMED	Without	1.1 (0.62–1.93)	0.749		0.76 (0.41–1.4)	0.379	
Higher aMED	With	1 (Ref)			1 (Ref)		
Median aMED	With	1.03 (0.45–2.36)	0.938		0.97 (0.38–2.46)	0.951	
Lower aMED	With	2.22 (1.22–4.06)	0.009		2 (1.02–3.95)	0.045	

Adjusted for age, sex, race (Mexican American, non-Hispanic white, non-Hispanic black, other races), education level (below high school, high school or equivalent, college or above), marital status (married, widowed, divorced, and never married), family PIR, BMI, smoking status, comorbidities including diabetes mellitus, hypertension, and stroke.

impairment are associated with a significantly increased mortality risk (Figure 3).

A forest plot also revealed that in the presence of cognitive impairment, the risk of all-cause mortality was notably higher. The HR for Low aMED (+) compared to High aMED (−) was 2.71 (95% CI 2.01–3.66, $p < 0.001$), and a significant trend was observed across all aMED categories (p for trend <0.001). A similar trend was observed for CVD mortality (Figure 4).

4 Discussion

Our study identifies a critical interaction between Mediterranean diet adherence and cognitive impairment in modulating cardiovascular mortality risk (p for interaction = 0.028). This finding implies that the protective effect of the Mediterranean diet on cardiovascular outcomes is amplified in individuals with cognitive impairment, a population traditionally excluded from dietary intervention trials. Mechanistically, this synergy may arise from two pathways: (1) Mitochondrial and vascular benefits: the Mediterranean diet's high antioxidant content (e.g., polyphenols, omega-3 fatty acids) may counteract oxidative stress and endothelial dysfunction—processes exacerbated in cognitive impairment due to neurodegenerative and vascular comorbidities (Caturano et al., 2025; Ilari et al., 2025). (2) Behavioral mediation: cognitive impairment often correlates with poor dietary choices and metabolic dysregulation (Młynarska et al., 2024). Adherence to the Mediterranean diet may mitigate these downstream effects, disproportionately benefiting this high-risk group. Clinically, our results advocate for prioritizing dietary interventions in cognitively impaired older adults, who face elevated mortality risk yet are rarely targeted in preventive guidelines.

The Mediterranean diet, characterized by its abundance of plant-based foods and minimally processed ingredients, has been associated with a reduced risk of various chronic diseases and increased longevity. Although the precise mechanisms by which the Mediterranean diet promotes health are not yet fully understood, a growing body of research suggests that this dietary pattern may exert its effects through multiple pathways. These include lowering blood lipids, countering oxidative stress, reducing inflammation and platelet aggregation, and regulating hormones and growth factors related to cancer development (Tosti et al., 2018). In previous cohort studies and randomized controlled trials, the Mediterranean diet has been shown to have a significant beneficial impact on all-cause mortality, cardiovascular risk factors, and the incidence and mortality of cardiovascular diseases (CVD) (Guasch-Ferré and Willett, 2021). A systematic review and dose–response meta-analysis showed that for every 2-point increase in the Mediterranean diet score, the risk of all-cause mortality decreased by 10% (95% CI: 9–11%) (Soltani et al., 2019). In patients with cardiovascular disease, higher adherence to the Mediterranean diet is associated with a reduced risk of all-cause mortality (Tang et al., 2021). Additionally, clinical trials indicate that adhering to the MD can improve endothelial function in patients with coronary heart disease (Yubero-Serrano et al., 2020) and reduces low-density lipoprotein (LDL) cholesterol related to atherosclerosis in individuals at high cardiovascular risk (Hernáez et al., 2017). Thus, it demonstrates the potential to reduce the risk of cardiovascular mortality. Our results are consistent with previous studies. Using NHANES data from the U.S. population, we found a linear association between stricter adherence to the MD and a reduced long-term risk of all-cause and cardiovascular-related mortality in the general population.

Cognitive impairment is a chronic condition that affects a person's ability to remember, learn, focus, and make decisions in daily life (Mitchell et al., 2010). Due to changes in the global age structure, the increase in the number of individuals with dementia is a major public health concern. By 2050, the prevalence is expected to double (Livingston, 2017). The presence of cognitive impairment has been shown to be an independent predictor of mortality (Sachs et al., 2011; Perna et al., 2015; Batty et al., 2016; Lee et al., 2018). Several studies

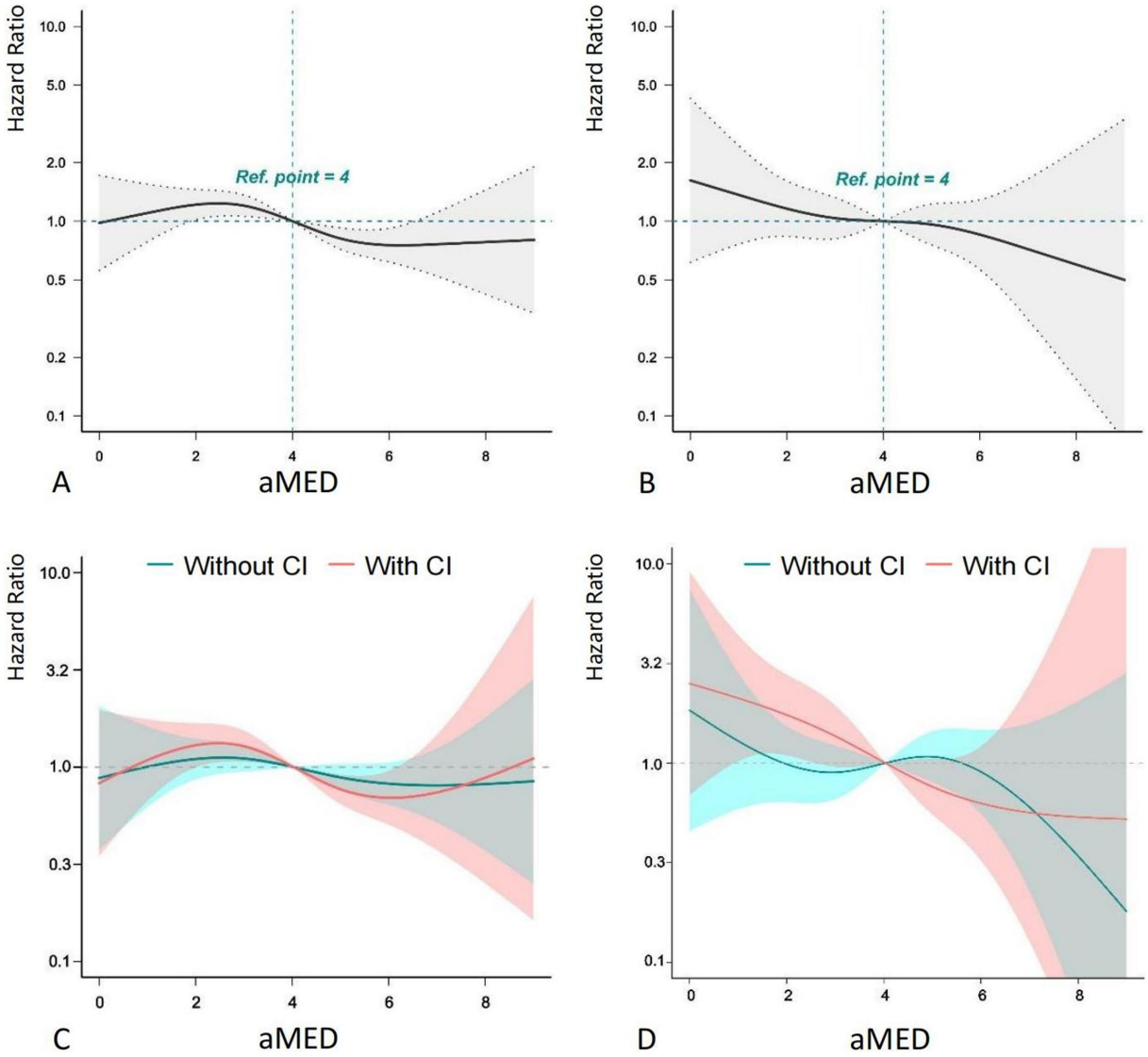

FIGURE 2
RCS plot of aMED, cognitive impairment and mortality. aMED, alternative Mediterranean Diet; HR, hazard ratio; CI, cognitive impairment. Higher aMED scores show a monotonic dose–response association with reduced all-cause mortality risk.

on cognitive impairment and mortality have found that elderly individuals with cognitive impairment have an increased risk of all-cause and cardiovascular mortality. Additionally, when cognitive impairment is accompanied by cardiovascular risk factors such as diabetes, chronic kidney disease, high blood pressure, or hypotension, the risk of mortality further increases (Zhu and Liao, 2020). Moreover, a study on cognitive impairment and mortality among elderly Chinese individuals suggested a dose–response relationship between baseline cognitive function and mortality. There was a monotonic increase in mortality risk observed across the range of cognitive severity (An and Liu, 2016). Our study found an association between cognitive impairment and an increased risk of long-term all-cause and cardiovascular mortality, consistent with previous research findings. However, our study did not analyze the relationship between cognitive impairment and cancer-related mortality. Previous research has indicated that tumor patients undergoing systemic therapy or radiotherapy may experience a decline in neurocognitive abilities (Olson and Marks, 2019). Under cognitive impairment, patients' adherence to treatment may decrease compared to those without impairment, thereby increasing cancer-related mortality. Although the exact mechanisms linking peripheral tumors and cognitive impairment remain elusive, it can be speculated that there is a mutual interaction and influence between the two. Further research is needed to explore the related mechanisms.

Increasing evidence supports the role of mitochondrial dysfunction and increased oxidative stress in the pathogenesis of neurodegenerative diseases such as Alzheimer's disease (AD). Both *in vitro* and *in vivo* experimental models have demonstrated the relevance of oxidative stress in dementia pathogenesis. The Mediterranean diet, known for its antioxidant properties including essential fatty acids, polyphenols in olive oil, and vitamins, may offer protective benefits (Cenini et al., 2019; Jurcau, 2021). The cumulative effects of the Mediterranean diet (MedD) on cardiometabolic health and glucose metabolism—both risk factors for cognitive decline—as

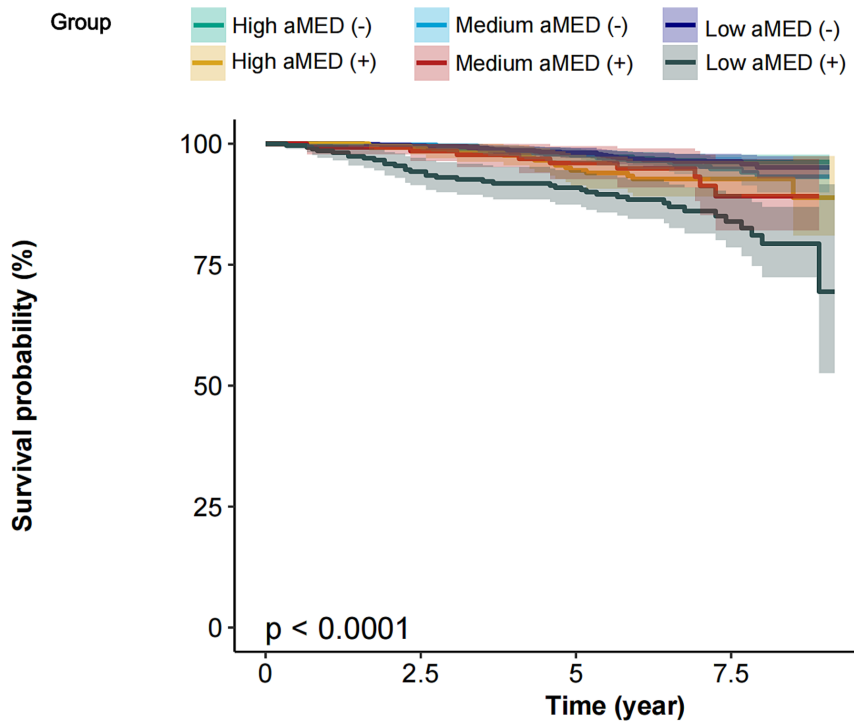

FIGURE 3
Survival curves of participants stratified by aMED scores and the presence of cognitive impairment. aMED, alternative Mediterranean Diet; High aMED (–), high aMED score without cognitive impairment; Medium aMED (–), medium aMED score without cognitive impairment; Low aMED (–), low aMED score without cognitive impairment; High aMED (+), high aMED score with cognitive impairment; Medium aMED (+), medium aMED score with cognitive impairment; Low aMED (+), low aMED score with cognitive impairment. The Low aMED (+) group had the poorest survival outcomes, suggesting that low aMED scores combined with cognitive impairment are associated with a significantly increased mortality risk.

well as the diet's nutritional density, may influence cognitive outcomes through multiple mechanisms (Georgoulis et al., 2014; Stranges et al., 2019). An observational study covering 2016–2021 indicated that adherence to the MD positively impacts both cognitively impaired and unimpaired older adults, especially concerning their memory, in both the short and long term (Klimova et al., 2021). Additionally, changes in Alzheimer's disease biomarkers, such as beta-amyloid (Aβ) deposition, tau phosphorylation, cortical thickness, or brain glucose metabolism, can occur 10–20 years before the clinical symptoms of AD appear (Vassilaki et al., 2018). A meta-analysis investigating the relationship between diet and hallmark AD biomarkers (tau and beta-amyloid) found that most studies on the MD indicate that adhering to it can significantly reduce the burden of AD biomarkers (Hill et al., 2019). Despite the current lack of robust clinical trial evidence, we still believe in the beneficial effects of the Mediterranean diet on cognitive function. Larger clinical trials are needed to further explore this potential.

Current research indicates that both the Mediterranean diet and cognitive impairment significantly impact mortality, particularly regarding all-cause mortality and cardiovascular death risk. Higher adherence to the Mediterranean diet has been shown to have a better effect on overall cognitive performance in older adults. This raises a question: do the Mediterranean diet and cognitive impairment jointly influence long-term mortality risk, and is there an interaction between the two?

Previous studies, such as those by Féart (2009) and Moustafa et al. (2022), have provided critical insights into the association between Mediterranean diet adherence and cognitive outcomes, including cognitive decline and dementia incidence. While these works established the protective role of the Mediterranean diet in neurodegeneration, our study extends this paradigm by focusing on mortality outcomes, a clinically significant yet underexplored endpoint in this context. Notably, our analysis revealed a novel interaction between low adherence to the Mediterranean diet and cognitive impairment in elevating cardiovascular mortality risk, a finding not previously reported in these prior studies. By integrating mortality outcomes, interaction effects, and a focus on vulnerable populations, our findings provide actionable evidence for tailoring dietary recommendations to mitigate excess mortality risk in older adults with cognitive impairment.

There may be a bidirectional relationship between adherence to the Mediterranean diet and cognitive abilities. Cognitive ability is closely linked to health literacy; individuals with lower cognitive abilities often find it challenging to maintain a healthy lifestyle. This can also affect their ability to adhere to the Mediterranean diet (Sabia et al., 2010; Kochan et al., 2017). Additionally, vascular dementia, a major component of cognitive impairment, has been shown in several studies to benefit from the Mediterranean diet's positive effects on risk factors such as insulin resistance, inflammation, and endothelial dysfunction (Esposito et al., 2004; Shai et al., 2008). The interaction between the two can exacerbate disease severity and increase mortality risk for patients. Therefore, our study explored the interaction between adherence to the Mediterranean diet and cognitive impairment on long-term

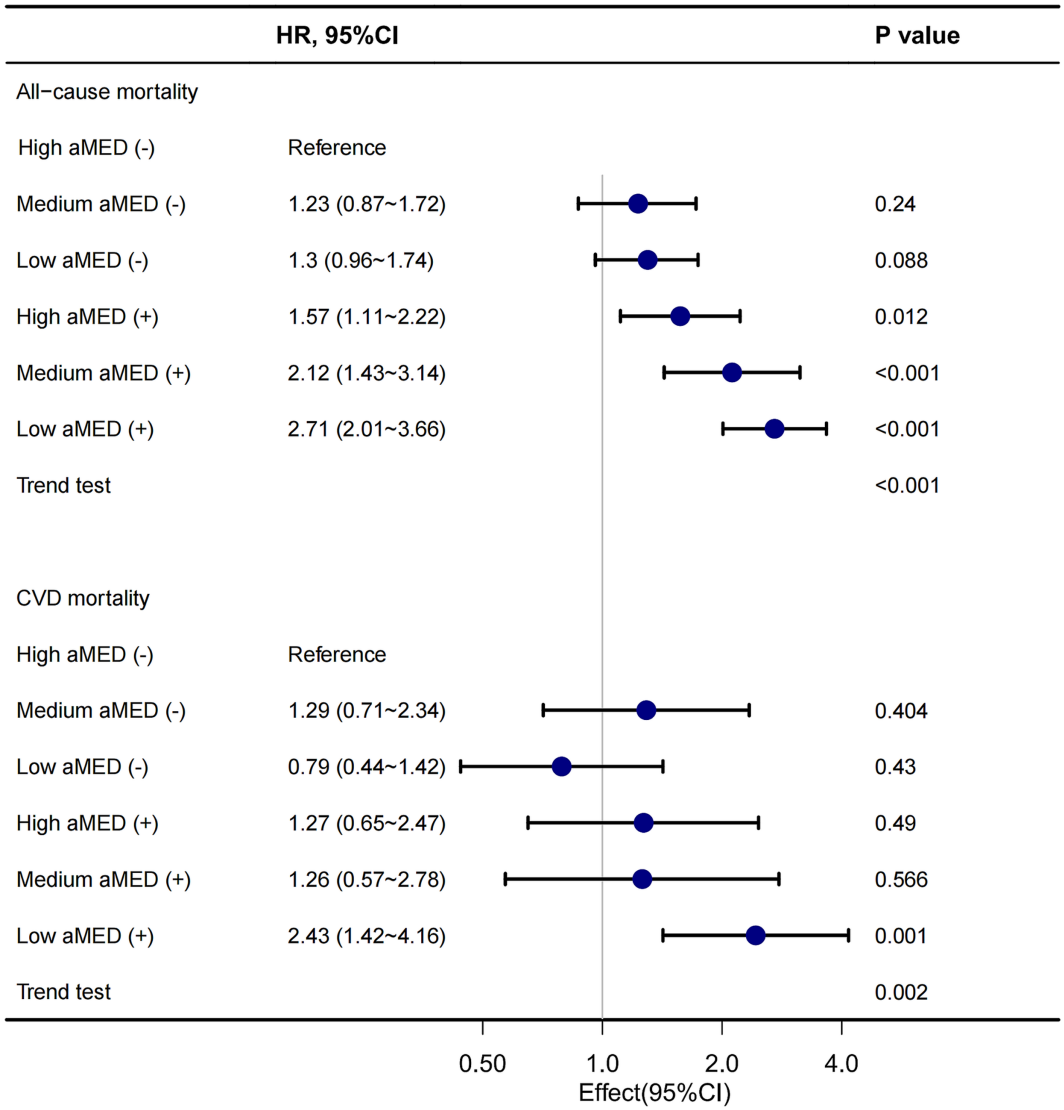

FIGURE 4
Forest plot of association between aMED, cognitive impairment and mortality. aMED, alternative Mediterranean Diet; HR, hazard ratio; CVD, cardiovascular disease. High aMED (–), high aMED score without cognitive impairment; Medium aMED (–), medium aMED score without cognitive impairment; Low aMED (–), low aMED score without cognitive impairment; High aMED (+), high aMED score with cognitive impairment; Medium aMED (+), medium aMED score with cognitive impairment; Low aMED (+), low aMED score with cognitive impairment. The stratified forest plot demonstrated that individuals with cognitive impairment and low adherence to the aMED had a 2.71-fold higher risk of all-cause mortality compared to those with high adherence, with a significant dose-dependent trend across ascending aMED categories. A consistent risk gradient was observed for CVD mortality.

mortality outcomes. The results indicated that individuals with low adherence to the Mediterranean diet and cognitive impairment had higher risks of all-cause and cardiovascular mortality. Further subgroup analysis showed that only in individuals with cognitive impairment was higher adherence to the Mediterranean diet associated with reduced cardiovascular mortality risk. Low adherence to the Mediterranean diet and cognitive impairment exhibited a synergistic effect in increasing the risk of cardiovascular-related mortality. Our use of a continuous, validated aMED score and nationally representative NHANES data improves the robustness of observed associations compared to studies relying on binary dietary assessments or homogeneous cohorts. The dose–response relationship observed via restricted cubic splines (Figure 2) further supports biological plausibility, suggesting that even incremental improvements in MedDiet adherence may reduce mortality risk, particularly in cognitively vulnerable populations. Therefore, this study highlights the importance of the Mediterranean diet for individuals with cognitive impairments. Whether for prevention or treatment, the Mediterranean diet holds significant value in improving cognitive impairments.

However, this study has several limitations. First, since the research involved regression analysis with adjustment for various covariates, missing data for some covariates may affect the robustness of the results. Second, due to the cross-sectional design of NHANES, the causal relationship between the Mediterranean diet and cognitive impairment cannot

be determined. Third, detailed information on smoking intensity (e.g., cigarettes per day) was unavailable in the NHANES dataset due to substantial missing data (>80%), precluding analysis of dose–response relationships. Fourth, the assessment of adherence to the Mediterranean diet was based on a 24-h dietary recall questionnaire, which could introduce recall bias and affect the accuracy of the results.

5 Conclusion

Adherence to the Mediterranean diet and cognitive impairment correlate in relation to cardiovascular-related mortality, but not all-cause mortality. In individuals with cognitive impairment, the effect of adherence to the Mediterranean diet on cardiovascular-related mortality is more pronounced. Future research and clinical practice could focus more on the dietary patterns of those with cognitive impairment to reduce disease severity.

Data availability statement

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

Ethics statement

The studies involving humans were approved by the Institutional Review Board of the Centers for Disease Control and Prevention. 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

LL: Data curation, Formal analysis, Writing – original draft, Writing – review & editing. XZ: Formal analysis, Writing – original draft. HM: Writing – original draft. MZ: Data curation, Writing – original draft. XL: Writing – original draft. XF: Conceptualization, Supervision, Writing – review & editing.

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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.2025.1556608/full#supplementary-material

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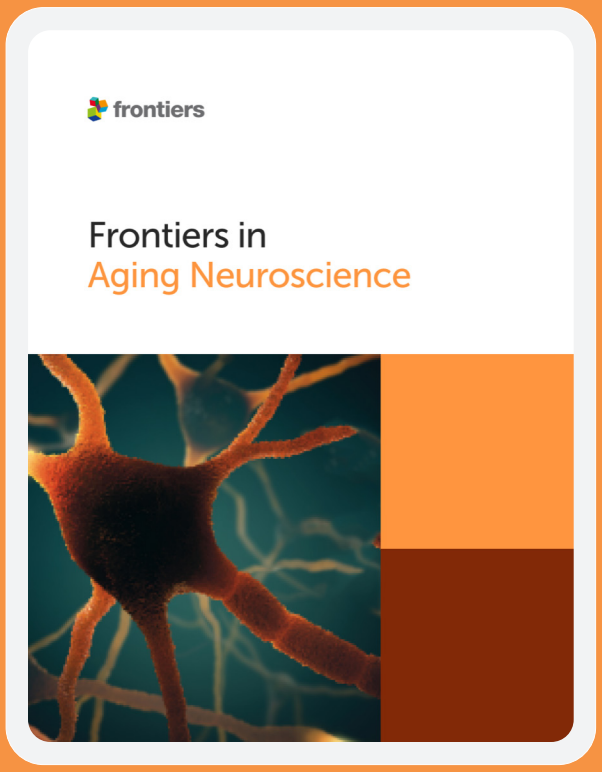

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