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Frailty- and age-associated diseases: possibilities for intervention, volume II

Edited by
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Published in
Frontiers in Medicine
Frontiers in Aging

ISSN 1664-8714
ISBN 978-2-8325-7387-7
DOI 10.3389/978-2-8325-7387-7

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Frailty- and age-associated diseases: possibilities for intervention, volume II

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Citation

Borras, C., Vina, J., Mas Bargues, C., eds. (2026). *Frailty- and age-associated diseases: possibilities for intervention, volume II*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-7387-7

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frontiers | Frontiers in Aging

TYPE Editorial
PUBLISHED 07 January 2026
DOI 10.3389/fragi.2025.1759325

OPEN ACCESS

EDITED AND REVIEWED BY
Frontiers Editorial Office,
Frontiers Media SA, Switzerland

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RECEIVED 02 December 2025
ACCEPTED 22 December 2025
PUBLISHED 07 January 2026

CITATION
Borrás C, Viña J and Mas-Bargues C (2026) Editorial: Frailty- and age-associated diseases: possibilities for intervention (Volume 2). *Front. Aging* 6:1759325. doi: 10.3389/fragi.2025.1759325

Editorial: Frailty- and age-associated diseases: possibilities for intervention (Volume 2)

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KEYWORDS

age-associated diseases, aging, biomarker, frailty, intervention

Editorial on the Research Topic
Frailty-and age-associated diseases: possibilities for intervention (Volume 2)

Introduction

Frailty and age-associated diseases represent a growing challenge for healthcare systems worldwide as populations age at unprecedented rates. Sarcopenia, cognitive impairment, osteoporosis, stroke-related complications, and chronic metabolic diseases reduce the physiological reserve, increase the vulnerability to stressors, and accelerate the functional decline. This second volume of the *Frailty- and Age-Associated Diseases* Research Topic brings together twelve complementary contributions that collectively highlight emerging opportunities for risk stratification, early identification, and intervention in older adults. From functional and biological biomarkers to multicomponent interventions and methodological roadmaps, this Research Topic provides a multidimensional overview of the current and future directions in frailty research.

Main contributions to the Research Topic

A first group of articles focuses on assessment and biomarker screening, emphasizing the need for reliable, simple, and scalable tools and biomarkers to support clinical decision-making. Sun et al. demonstrate that handgrip strength, an accessible, low-cost, and functional measure, is strongly associated with all-cause mortality in individuals with low bone mass, underscoring its utility as a routine screening tool (Sun et al). Complementing this, a narrative synthesis of frailty scales provides clinicians with a practical overview of existing instruments and their applicability across settings. Additional contributions explore nutritional and metabolic biomarkers, such as folate-related indicators, and their

associations with cognitive impairment (Lv et al), as well as a meta-analysis linking cognitive frailty to increased fall risk (Liu et al). Together, these studies converge on a key message: early identification of frailty requires both functional metrics and biologically informed markers (Wang et al).

A second set of studies examines interventions aimed at mitigating frailty progression or improving outcomes. A *post hoc* analysis of a large cohort of older adults with sarcopenia shows that multicomponent interventions (combining exercise, nutrition, and behavioral support) can extend institutionalization-free survival, demonstrating the value of integrated approaches (Ji et al). Preclinical work evaluating high-intensity interval training (HIIT) in middle-aged mice further highlights the potential for exercise to improve both physical and cognitive parameters (Stephenson et al). Deng et al. present a network meta-analysis investigating acupuncture-based therapies for postmenopausal osteoporosis, where several modalities appear to enhance bone health when combined with standard treatment (Deng et al). Despite methodological heterogeneity, these findings encourage continued exploration of combined lifestyle, rehabilitative, and complementary interventions.

Other contributions explore the underlying mechanisms and contextual factors, offering a bridge between biology and clinical practice. A review of the microbiota–aging axis in sarcopenia suggests that gut dysbiosis contributes to muscle decline and may become a therapeutic target in the future (Cheng et al). Moreover, a comprehensive epidemiological analysis of dementia and cognitive impairment emphasizes the intertwined roles of frailty, malnutrition, and healthcare utilization, illustrating the complexity of managing multimorbidity in older adults (Merchant et al). Indeed, two studies on sarcopenia in type 2 diabetes mellitus highlight the importance of rigorous methodology when studying high-risk subgroups (Whaikid et al; Xu et al). Finally, Wang et al. provide an in-depth review of post-stroke dysphagia, identifying substantial gaps in diagnostic consistency, treatment protocols, and inclusion of patients with cognitive impairment; thereby mapping a clear agenda for future rehabilitation research (Wang et al).

Convergencies and discrepancies

Across these diverse studies, several common themes emerge. First, frailty is reaffirmed as a multidimensional syndrome that requires integrated approaches. Second, there are simple screening tools with high clinical value (e.g., handgrip strength, standardized scales). Third, multicomponent interventions (exercise + nutrition + rehabilitation) are the most promising strategies for preserving independence and avoiding institutionalization. Fourth, biological markers involving nutrition, metabolism, and the gut microbiota offer promising translational opportunities and could help refine risk stratification and personalized intervention.

At the same time, the Research Topic highlights persistent methodological challenges. Several studies emphasize variability in definitions and endpoints, study designs with a risk of bias (e.g., lack of blinding or insufficient sample size), exclusion of relevant subgroups (e.g., individuals with cognitive impairment), and the scarcity of longitudinal studies that include hard outcomes (mortality, institutionalization). Reproducibility is particularly limited in areas such as dysphagia research, complementary medicine trials, and microbiota-related interventions. Moreover, translating preclinical results (e.g., HIIT in animal models) warrants caution before producing clinical recommendations.

Conclusion

In conclusion, this Research Topic provides a rich and multidimensional view of frailty and age-associated diseases, integrating clinical, biological, and rehabilitative perspectives. The collection highlights both the progress made and the substantial opportunities that remain. Advancing the field will require harmonized methodologies, translational studies linking mechanisms to interventions, and a continued commitment to preserving independence and quality of life in the aging population.

Author contributions

CB: Writing – review and editing. JV: Writing – review and editing. CM-B: Writing – original draft.

Funding

The author(s) declared that financial support was not received for this work and/or its publication.

Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The authors CB, JV, CM-B 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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The author(s) declared that generative AI was used in the creation of this manuscript. It was used to improve the English style.

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Publisher's note

frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 11 December 2024
DOI 10.3389/fmed.2024.1452811

OPEN ACCESS

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RECEIVED 21 June 2024
ACCEPTED 28 November 2024
PUBLISHED 11 December 2024

CITATION
Sun H, Liu J, Tan R, Zhang X, Qian X, Qi C and Qi W (2024) Hand grip strength and all-cause mortality risk in individuals with decreased bone mass: a study from NHANES database. *Front. Med.* 11:1452811.
doi: 10.3389/fmed.2024.1452811

Hand grip strength and all-cause mortality risk in individuals with decreased bone mass: a study from NHANES database

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Objective: Previous studies have demonstrated that grip strength is associated with various health outcomes, including osteoporosis. However, the impact of grip strength on long-term mortality risk among individuals with low bone mass remains unclear. This study aims to investigate the association between grip strength and the risk of all-cause mortality in the population with low bone mass.

Methods: We included 1,343 cases of decreased bone mass from the NHANES database spanning 2013 to 2014. All-cause mortality data were ascertained through linkage with national death index records up to December 31, 2015. Analysis was conducted using the Cox proportional hazards regression model, and we assessed result reliability through various model adjustments and hierarchical analyses, Schoenfeld's global and individual tests are utilized to estimate the time-varying covariance in the Cox proportional hazards regression model's hypothesis.

Results: Throughout an average follow-up period of 69.5 months, 148 deaths were documented. After adjusting for covariates, a significant association between grip strength and the risk of all-cause mortality was observed in individuals with decreased bone mass (HR = 0.9, 95% CI: 0.87–0.93, $p < 0.001$). Individuals with normal grip strength, compared to those with low grip strength, exhibited a 56% lower risk of all-cause mortality (HR = 0.44, 95% CI: 0.29–0.67, $p < 0.001$). Various models consistently demonstrated similar significant trends post-adjustment. Subgroup analysis revealed an interaction between grip strength and coronary heart disease ($p < 0.05$). Schoenfeld's global and individual tests confirmed the reliability of the model ($p > 0.05$).

Conclusion: Our findings indicate that low grip strength is associated with increased all-cause mortality risk in individuals with decreased bone mass. The inclusion of routine monitoring of grip strength in patients with osteopenia and the encouragement of maintaining or improving grip strength in this population may offer a novel approach to health management for these individuals.

KEYWORDS

osteoporosis, mortality risk, grip strength, aging, NHANES

1 Introduction

Osteoporosis is a metabolic bone disease strongly associated with age. As global populations age, the incidence of osteoporosis continues to rise annually, imposing significant burdens on society (1). Osteoporotic fractures represent its most severe complication and are closely linked to patient mortality (2). Effective prevention of these complications is crucial for enhancing osteoporosis management.

Handgrip strength, quantified using a dynamometer, is a crucial indicator of muscle strength (3) and demonstrates a close relationship with osteoporosis. Research has shown that handgrip strength is associated with lumbar (4) and distal radius bone mineral density (BMD) (5). Additionally, low handgrip strength in postmenopausal Japanese women correlates with an increased risk of site-specific fractures over 10–15 years (6). Furthermore, diminished grip strength has been linked to higher mortality rates following hip fractures (7).

Handgrip strength measurement offers objectivity and high repeatability, making it a valuable tool for health and disease prediction research. As a simple, reliable, and inexpensive evaluation tool, handgrip strength assessment has shown significant predictive and diagnostic value in conditions such as sarcopenia (8), osteoporosis, and osteoporotic fractures (9). Previous studies have demonstrated that grip strength can serve as a predictor of total and cardiovascular mortality (10), and may also have a potential predictive role in the risk of all-cause death in elderly women with reduced bone mass (11). Grip strength also plays a pivotal role in osteosarcopenia (12).

While grip strength shows promise as a prognostic indicator for several diseases and correlates closely with BMD, research exploring its impact on long-term outcomes in individuals with decreased bone mass remains limited. Hence, this study investigates the relationship between grip strength and long-term mortality risk among people with osteopenia, aiming to provide evidence-based insights for their health management.

2 Method

2.1 Data source

Data concerning individuals with osteopenia were sourced from the publicly available National Health and Nutrition Examination Survey (NHANES) database. Mortality data were obtained from publicly released datasets by the United States Centers for Disease Control and Prevention (CDC). The NHANES database, managed by the National Center for Health Statistics (NCHS), aims to gather comprehensive health data across all age demographics in the United States. The NHANES protocol underwent evaluation by the NCHS Research Ethics Review Board, ensuring that all participants provided informed consent. We extracted data from the survey year 2013–2014, including BMD measurements, demographic details (age, gender, race, marital status, family income), anthropometric measures (height, weight, BMI, waist circumference), and questionnaire responses covering smoking habits, diabetes history, cardiovascular disease history, stroke history, and blood pressure levels. Detailed descriptions and measurement methodologies for each variable are available on the NHANES website.

2.2 BMD and low bone mass

We collected BMD data from the total femur, femoral neck, trochanter, and intertrochanter regions for the period spanning 2013 to 2014. BMD measurements were conducted using dual-energy X-ray absorptiometry (DEXA). The data were acquired with the Hologic QDR-4500A fan-beam densitometer (Hologic, Inc., Bedford, Massachusetts) equipped with Apex 3.2 software. Prior to each measurement, the densitometer was calibrated to ensure accuracy.

Osteoporosis and osteopenia were characterized by low bone mass. The criteria for these conditions were established according to the World Health Organization (WHO) standards (13). Osteopenia was defined as BMD values ranging from 1 to 2.5 standard deviations (SD) below the mean of young adult male and female reference populations. Osteoporosis was defined as BMD values more than 2.5 SD below the mean of the young reference population. The threshold of BMD for osteopenia and osteoporosis was based on the study of Looker et al. (14). The specific BMD thresholds for males and females can be found in the original study.

2.3 Hand grip strength

Hand grip strength was assessed using a hand grip meter. Each hand was tested three times, and the maximum sum of these readings across both hands was recorded as the comprehensive grip strength. We used half of the comprehensive grip strength as our metric for grip strength data. Given the known disparity in grip strength between males and females, we analyzed and categorized grip strength separately for each gender. We adopt the definition of sarcopenia for the European population as defined by the European Working Group on Sarcopenia in Older Adults (EWGSOP) (15). According to this standard, low grip strength is considered when male grip strength is below 27 kg and female grip strength is below 16 kg.

2.4 Covariates

Through an analysis of previously published studies, we identified factors associated with grip strength, osteoporosis, or mortality risk. These include general demographic characteristics such as age, gender, race, education level, household income poverty ratio (16, 17), marital status (18), body measurements including height (cm), weight (kg), and BMI (<25, 25–30, ≥30) (19). Additionally, we considered blood pressure (mmHg), past medical history including diabetes (yes/no), cardiovascular diseases: congestive heart failure (yes/no), coronary heart disease (yes/no), angina

pectoris (yes/no), heart attack (yes/no), stroke (yes/no) and fracture (yes/no) (20, 21).

2.5 Sources of death data

The death data originates from the CDC and is linked to the NHANES database using a specific Inclusion Number. Further details regarding data conversions and links are available on the corresponding website.

2.6 Statistical analysis

Count data were presented as mean ± standard deviation, while measurement data were expressed as percentages. The analysis utilized a Cox regression model to examine the relationship between grip strength and mortality risk through both univariate and multivariate regression analyses. To assess result robustness, various models were constructed by adjusting covariates. Model 0 remained unadjusted. Model 1 incorporates general demographic characteristics including gender, age, race, marital status, family income, and education level. Model 2 builds upon Model 1 by adjusting for BMI and blood pressure. Model 3 further adjusts for smoking based on Model 2. Model 4 incorporates factors potentially increasing mortality risk, such as congestive heart failure, coronary heart disease, angina pectoris, myocardial infarction, and stroke. To handle missing data, we applied multiple imputation (MI) with 5 replications using the chained equation approach via the R mice package, enhancing statistical power and reducing bias. Five sets of complete data were generated, and their effect values were integrated. Model 5 represents the post-MI integrated effect values based on the fully adjusted model. Interaction and stratified analyses were conducted using subgroup variables. Schoenfeld's global and individual tests were applied to assess the time-varying covariances in the Cox proportional hazards regression analysis.

All analyses were performed using R version 4.22 and FreeStatisticsV1.9.2 software. A significance level of $p < 0.05$ was applied for determining statistical significance.

3 Results

3.1 Baseline characteristics

The demographic profile of the study population is depicted in Table 1. A total of 1,343 individuals with decreased bone mass were enrolled, comprising 54.1% women. The mean age of the cohort was 62.0 ± 11.8 years. Among them, 137 participants exhibited low grip strength, while 1,206 had normal grip strength. By the end of 2015, 148 patients had deceased, with an average follow-up duration of 69.5 ± 13.9 months.

Analysis of baseline data revealed that individuals with higher grip strength were predominantly younger, more educated, and had a higher weight and height. Additionally, this subgroup exhibited lower prevalence of cardiovascular and cerebrovascular diseases.

3.2 Association between grip strength and mortality

Table 2 presents the results of multivariate regression analysis investigating the association between grip strength and the risk of all-cause mortality among individuals with decreased bone mass. The analysis revealed a gradual reduction in the risk of mortality with increasing grip strength as a continuous variable (HR = 0.90, 95% CI: 0.87–0.93, $p < 0.001$). When comparing individuals with low grip strength to those with non-low grip strength, the latter exhibited a 56% lower risk of all-cause mortality (HR = 0.44, 95% CI: 0.29–0.67, $p < 0.001$). This trend remained consistent across various adjustment models, as depicted in Figure 1.

3.3 Subgroup analysis

Figure 2 displays the results of our subgroup analysis. Subgroup analysis results indicated that, although no significant difference was observed, the negative correlation trend of high grip strength on the risk of all-cause mortality among each subgroup remained consistent with the main analysis. Notably, a history of coronary heart disease exhibited a significant interaction with grip strength and the risk of all-cause mortality ($p < 0.05$).

3.4 Cox proportional hazard assumption test

According to the Cox proportional hazards regression model, the hazard ratio of individual variables, such as hand grip strength, remains constant over time. We conducted a Cox proportional hazards model test using Schoenfeld residuals to evaluate the continuous and categorical variables of grip strength, respectively. The results, depicted in Figure 3, demonstrate that Schoenfeld's individual and global tests do not suggest a violation of the proportional hazards assumption ($p > 0.05$).

4 Discussion

Our findings indicate that low grip strength may elevate the risk of all-cause mortality in individuals with decreased bone mass. Specifically, compared to those with higher grip strength, individuals with low grip strength experience a 56% higher risk of all-cause mortality. This trend persists across adjustments in our model and in stratified analyses. Our sensitivity analysis also verifies the reliability of the model.

The association between grip strength and health outcomes has been extensively investigated. Previous studies have consistently linked lower grip strength to increased risks of all-cause mortality, cardiovascular mortality, myocardial infarction, and stroke (22). Additionally, grip strength has been associated with heightened risks of all-cause dementia and mortality (23). Studies have also demonstrated poorer outcomes in patients with type 2 diabetes who exhibit lower grip strength, suggesting the inclusion of grip strength monitoring in their health management (24).

TABLE 1 Basic characteristics of included data.

	Total (n = 1,343)	Low grip strength (Male < 27 Kg Female < 16 Kg) (n = 137)	Non-low grip strength (Male ≥ 27 Kg Female ≥ 16 Kg) (n = 1,206)	p
Gender, n (%)				0.865
Male	617 (45.9)	62 (45.3)	555 (46)	
Female	726 (54.1)	75 (54.7)	651 (54)	
Age	62.0 ± 11.8	71.4 ± 10.1	60.9 ± 11.5	<0.001
Race, n (%)				0.508
Mexican American	152 (11.3)	20 (14.6)	132 (10.9)	
Other Hispanic	110 (8.2)	10 (7.3)	100 (8.3)	
Non-Hispanic White	711 (52.9)	65 (47.4)	646 (53.6)	
Non-Hispanic Black	171 (12.7)	21 (15.3)	150 (12.4)	
Other Race	199 (14.8)	21 (15.3)	178 (14.8)	
Education, n (%)				0.009
Less than high school	295 (22.0)	37 (27)	258 (21.4)	
High school diploma	296 (22.0)	40 (29.2)	256 (21.2)	
More than high school	752 (56.0)	60 (43.8)	692 (57.4)	
Marital status n (%)				0.018
Married	788 (58.7)	65 (47.4)	723 (60)	
Widowed/Divorced/Separated	447 (33.3)	59 (43.1)	388 (32.2)	
Never married	108 (8.0)	13 (9.5)	95 (7.9)	
Household income poverty ratio, n (%)				<0.001
≤1	237 (19.3)	28 (22.8)	209 (18.9)	
1< to ≤3	481 (39.2)	66 (53.7)	415 (37.6)	
>3	508 (41.4)	29 (23.6)	479 (43.4)	
Weight (kg)	73.3 ± 16.4	68.4 ± 13.9	73.8 ± 16.6	<0.001
Height (cm)	164.9 ± 10.0	160.4 ± 9.7	165.5 ± 9.9	<0.001
BMI	26.9 ± 5.2	26.7 ± 5.6	26.9 ± 5.2	0.686
Diabetes, n (%)				0.001
Yes	208 (15.5)	34 (24.8)	174 (14.4)	
No	1,135 (84.5)	103 (75.2)	1,032 (85.6)	
Smoking, n (%)				0.912
Yes	653 (48.6)	66 (48.2)	587 (48.7)	
No	690 (51.4)	71 (51.8)	619 (51.3)	
Congestive heart failure, n (%)				0.008
Yes	52 (3.9)	11 (8)	41 (3.4)	
No	1,291 (96.1)	126 (92)	1,165 (96.6)	
Coronary heart disease, n (%)				0.001
Yes	89 (6.6)	18 (13.1)	71 (5.9)	
No	1,254 (93.4)	119 (86.9)	1,135 (94.1)	
Angina pectoris, n (%)				0.08
Yes	59 (4.4)	10 (7.3)	49 (4.1)	
No	1,284 (95.6)	127 (92.7)	1,157 (95.9)	
Heart attack, n (%)				<0.001
Yes	77 (5.7)	17 (12.4)	60 (5)	

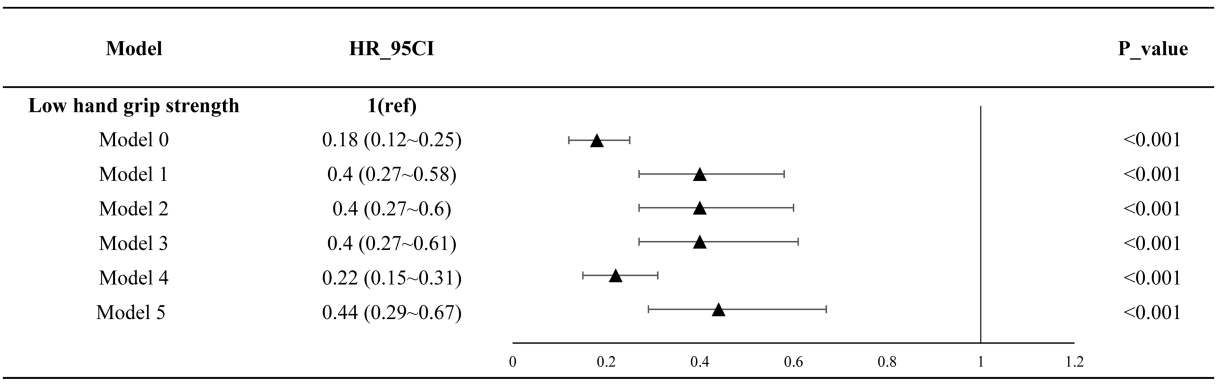
(Continued)

TABLE 1 (Continued)

	Total (*n* = 1,343)	Low grip strength (Male < 27 Kg Female < 16 Kg) (*n* = 137)	Non-low grip strength (Male ≥ 27 Kg Female ≥ 16 Kg) (*n* = 1,206)	*p*
No	1,266 (94.3)	120 (87.6)	1,146 (95)	
Stroke, *n* (%)				<0.001
Yes	72 (5.4)	26 (19)	46 (3.8)	
No	1,271 (94.6)	111 (81)	1,160 (96.2)	
SBP (mmHg)	127.3 ± 18.7	133.2 ± 24.0	126.6 ± 17.9	<0.001
DBP (mmHg)	69.4 ± 13.4	64.9 ± 16.6	69.9 ± 12.9	<0.001
Status, *n* (%)				<0.001
Alive	1,195 (89.0)	86 (62.8)	1,109 (92)	
Deceased	148 (11.0)	51 (37.2)	97 (8)	
Follow-up time (month)	69.5 ± 13.9	58.9 ± 22.5	70.7 ± 12.0	<0.001
Fracture, *n* (%)				0.225
Yes	476 (35.4)	55 (40.1)	421 (34.9)	
No	867 (64.6)	82 (59.9)	785 (65.1)	
BMD, *n* (%)				<0.001
Osteopenia	1,185 (88.2)	98 (71.5)	1,087 (90.1)	
Osteoporosis	158 (11.8)	39 (28.5)	119 (9.9)	

TABLE 2 Cox regression analysis results between grip strength and risk of all-cause mortality after adjusting for covariates.

	n.total	n.event (%)	Follow up time (month)	HR_95CI	*P*_value
Hand strength (kg)	1,343	148 (11)	93,277	0.9 (0.87 ~ 0.93)	<0.001
Low grip strength	137	51 (37.2)	8,067	1(Ref)	
Non-low grip strength	1,206	97 (8)	85,210	0.44 (0.29 ~ 0.67)	<0.001



Model 0, Unadjusted.
Model 1, Adjusted for Age, Gender, Race, Marital status, Education and Income.
Model 2, Adjusted for Mode l + BMI, Blood pressure.
Model 3, Adjusted for Model 2+Smoking.
Model 4, Adjusted for Congestive heart failure, Coronary heart disease, Angina pectoris, Heart attack, Stroke and Fracture.
Model 5, Adjusted all covariates after multiple interpolations.

FIGURE 1
Results after multi-model adjustment (adjusted).

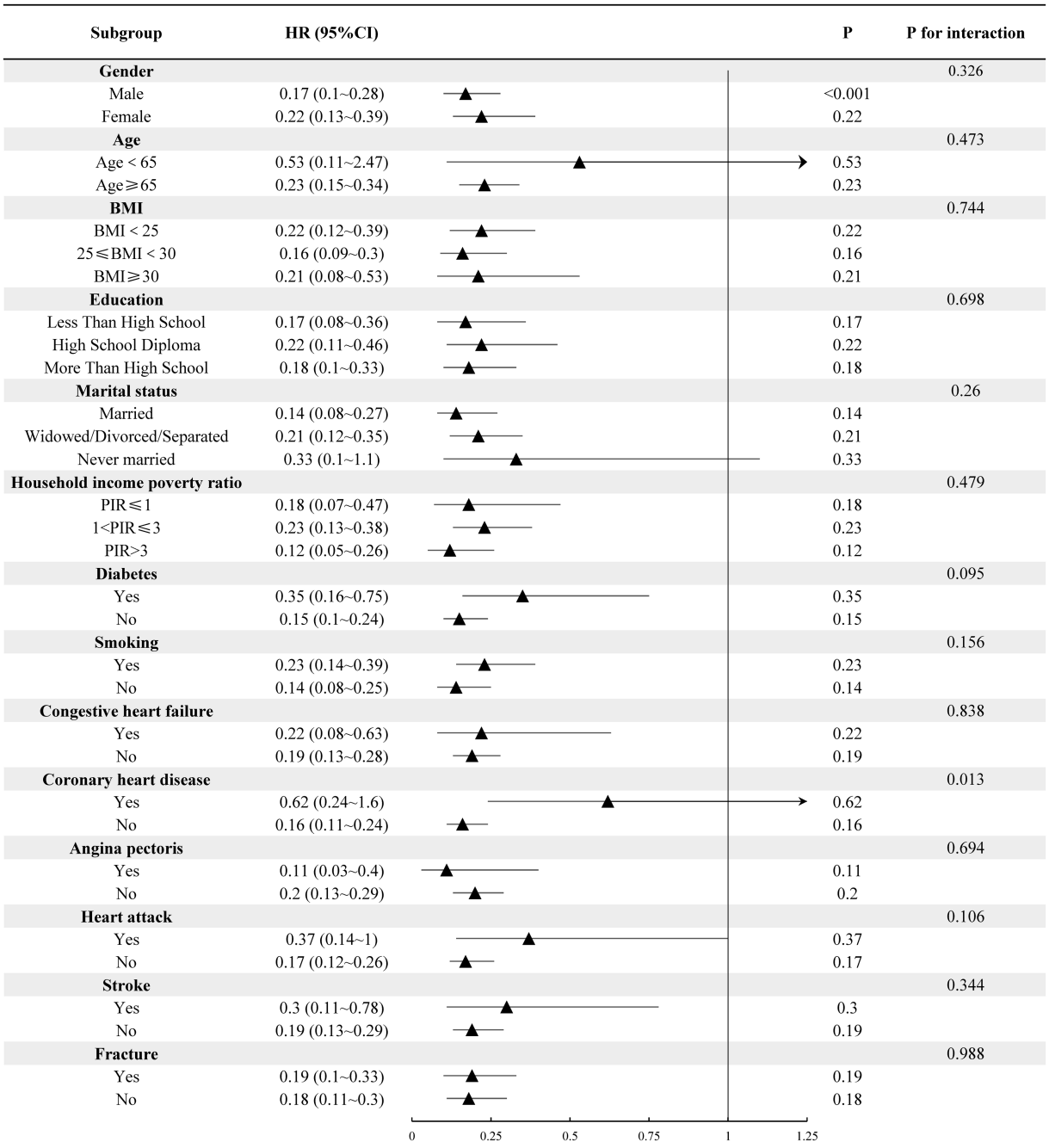


FIGURE 2
Subgroup analysis of hand grip strength and all-cause mortality risk in individuals with decreased bone mass.

Varying perspectives exist on the influence of grip strength on the risk of all-cause mortality among individuals with decreased bone mass. A study reported that decreased bone mass in the distal forearm is associated with an elevated risk of all-cause death, and this association remains unaffected by high grip strength (25). Conversely, a cohort study involving 909 participants in the UK (26) revealed that low grip strength significantly elevates the risk of cardiovascular and all-cause mortality, whereas femoral neck BMD does not correlate with any risk of death. Another investigation, involving 1,032 subjects, indicated that those with muscle weakness or osteopenia face considerably higher mortality risks than those without these conditions (27). Additionally, individuals with reduced muscle mass exhibited notably higher mortality risks. However, the coexistence of osteopenia and osteodystrophy did not significantly augment fracture or mortality risks beyond those linked to each condition independently, emphasizing the distinctions between osteopenia, sarcopenia, and hypodynamia. In contrast, a prospective cohort study of elderly women (11) demonstrated that the potential osteosarcopenia group exhibited a heightened risk of 10-year hip fracture and mortality compared to the normal group or those with isolated low bone mass, aligning with our findings.

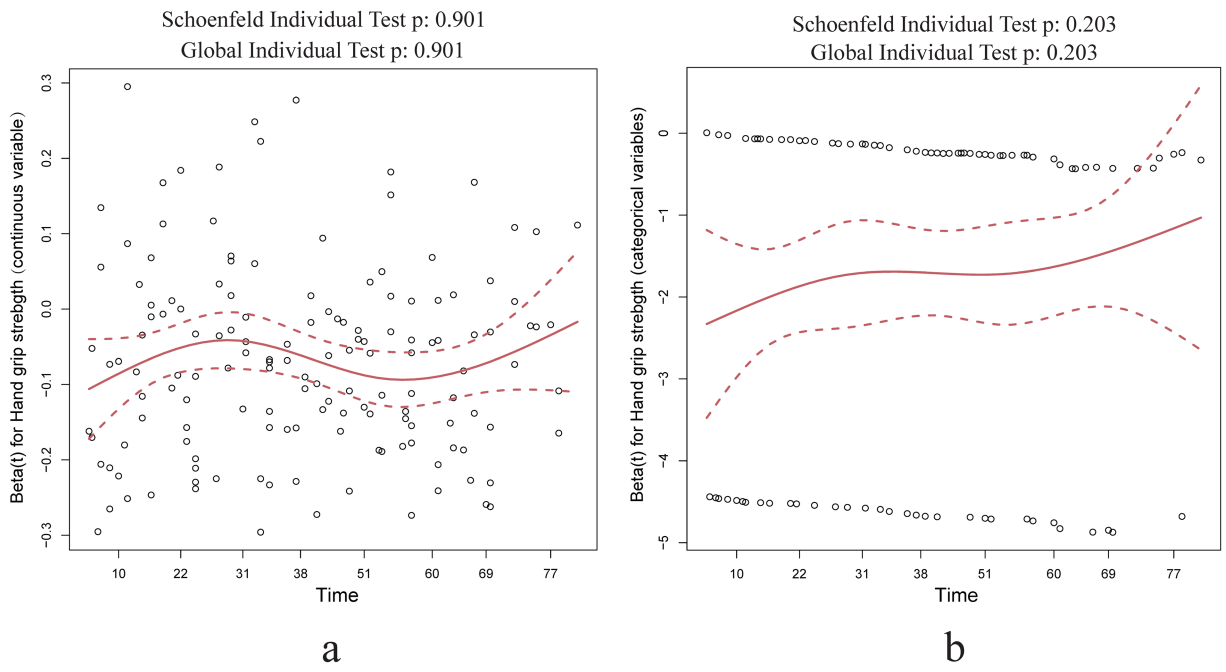


FIGURE 3
Schoenfeld residual test results of hand grip strength in Cox regression analysis. **(a)** Hand grip strength as a continuous variable Schoenfeld residual test results; **(b)** hand grip strength as a categorical variable Schoenfeld residual test results.

Nonetheless, our study presents divergent conclusions from previous research, potentially attributed to variations in definitions of decreased bone mass, sample sizes, and adjustments for confounding variables. The discordant conclusions on this subject may be influenced by several factors, including the lack of unified criteria for defining osteomyopenia, differences in BMD measurement sites, sample size, follow-up duration, data censoring, and other variables. Given the pivotal role of grip strength in predicting adverse risk outcomes and the absence of a consensus on this matter, continued investigation into this topic is necessary.

The impact of grip strength on the risk of all-cause mortality in individuals with decreased bone mass primarily arises from reduced muscle strength, increasing the risk of fractures—a relationship well-documented in previous studies (28–31). Fractures, particularly hip fractures, are significantly linked to elevated mortality risk (32). Additionally, grip strength is viewed as an indicator of nutritional status, with higher grip strength correlating with better physical function (33). Lower grip strength often indicates a higher prevalence of chronic diseases, thereby diminishing the body's resilience to adverse outcomes.

Our study observed the interaction of coronary heart disease in the effect of grip strength on the risk of all-cause death in people with low bone mass. The relationship between CHD and grip strength is bidirectional. Grip strength has demonstrated significant predictive value for the risk of CHD and associated mortality (34–36). Conversely, patients with CHD often exhibit a tendency to reduce grip strength. A prospective Finnish study (37) with a 22-year follow-up period reported a marked decrease in hand grip strength among CHD patients, corroborated by another study (38), indicating that the risk escalates over the course of the disease. CHD is a pivotal determinant of all-cause mortality in patients, a topic extensively covered in previous research. Furthermore, decreased grip strength in CHD patients may exacerbate the risk of all-cause death. However, the specific impact of CHD on grip strength in osteopenia populations remains underexplored and warrants further investigation. Several limitations exist within this study. First, to maintain data integrity, cases with missing information were excluded, thereby reducing the number of included cases to some extent. Second, as the study primarily involves the American population, the generalization of results to other populations remains uncertain. Third, due to its observational design, causal associations cannot be established, and residual confounding factors may not be entirely excluded. Fourth, without weight analysis, the findings may not fully represent the characteristics of the entire NHANES survey population. Finally, the number of deaths involved is relatively small compared to the sample size, which may limit the statistical power of the study. Further verification through studies with larger sample sizes is necessary.

5 Conclusion

Low grip strength is associated with an increased risk of all-course mortality among individuals with decreased bone mass. Integrating routine monitoring of grip strength in patients with osteopenia and promoting the maintenance or enhancement of grip strength in this population may introduce a novel strategy for health management among these individuals.

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 NHANES protocol underwent evaluation by the NCHS Research Ethics Review Board, ensuring that all participants provided informed consent.

Author contributions

HS: Writing – original draft, Writing – review & editing. JL: Conceptualization, Writing – review & editing. RT: Formal analysis, Visualization, Writing – review & editing. XZ: Data curation, Investigation, Writing – review & editing. XQ: Conceptualization, Supervision, Writing – review & editing. CQ: Data curation, Visualization, Writing – review & editing. WQ: Conceptualization, Funding acquisition, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This work was supported by National Natural Science Foundation of China (No. 82074570).

Conflict of interest

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

Publisher's note

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frontiers | Frontiers in Public Health

TYPE Review
PUBLISHED 18 December 2024
DOI 10.3389/fpubh.2024.1424613

OPEN ACCESS

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RECEIVED 29 April 2024
ACCEPTED 15 November 2024
PUBLISHED 18 December 2024

CITATION
Wang X-M, Zhang Y-H, Meng C-C, Fan L, Wei L, Li Y-Y, Liu X-Z and Lv S-C (2024) Scale-based screening and assessment of age-related frailty.
Front. Public Health 12:1424613.
doi: 10.3389/fpubh.2024.1424613

Scale-based screening and assessment of age-related frailty

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As the population ages, the prevalence of age-related frailty increases sharply, which increases the risk of poor health status of older adults, such as disability, falls, hospitalization, and death. Across the globe, frailty is moving toward the forefront of health and medical research. Currently, frailty is believed to be preventable and reversible, so the early identification of frailty is critical. However, there are neither precise biomarkers of frailty nor definitive laboratory tests and corresponding clinical testing techniques and equipment in clinical practice. As a result, the clinical identification of frailty is mainly achieved through the widely used frailty scale, which is an objective, simple, time-saving, effective, economical, and feasible measurement tool. In this narrative review, we summarized and analyzed the various existing frailty scales from different perspectives of screening and evaluation, aiming to provide a reference for clinical researchers and practitioners to judge and manage frail older people accurately.

KEYWORDS

older people, frailty, screening, assessment, scale

1 Introduction

As the life expectancy of the global population gradually increases with the advancement of medical treatment and the improvement of living standards, the problem of population aging is becoming increasingly serious, and how to face population aging positively has become the most important medical and social issue in the world (1). One of the major challenges facing an aging population is the increasing prevalence of age-related frailty, which is a state of reduced ability to cope with stimuli due to age-related declines in the physiological reserve capacity and function of multiple systems and organs (2). Several prospective cohort studies have shown that frailty is strongly associated with poor health and that frail older people are more likely to experience death (3), disability (4–6), falls (7), and hospitalization (2) than non-frail older adults. Although frailty poses a significant risk of adverse health outcomes in older adults, it is a dynamic and reversible disease, which means that it is preventable and controllable and that early recognition and interventions of frailty can halt its progression (2, 8). Early identification and diagnosis of frailty will help to maximize the reversal of its further progression, alleviate or delay underlying symptoms, control adverse clinical health outcomes such as recurrent hospitalization and death, maintain their functional status, and enhance their quality of life. Several studies have shown that timely recognition and intervention of frailty in the clinical setting or daily life can contribute to benefits for older adults (9, 10), and may even delay the onset of death in 3 to 5% of older adults (11). Clinical practice guidelines developed by the International Conference of Frailty and Sarcopenia

Research (ICFSR) also recommend that adults 65 years old and older should be screened for frailty using a simple, validated, and rapid screening tool appropriate for the specific scenario and that all older adults considered to be frail or pre-frail should be further assessed for frailty (12). However, there are no standardized criteria regarding the selection of screening and assessment tools for frailty. Therefore, the development of efficient and practical screening and assessment tools for frailty should be a top priority in the field of frailty research. This paper provides an overview of the current state of research on screening and assessment tools for age-related frailty and the characteristics of commonly used frailty scales, with the aim of helping clinical researchers and practitioners to accurately judge and fine-tune the management of frail older adults.

2 Methodology

The search database was PubMed. The retrieval time node ranged from January 2000 to December 2023. The retrieval strategy was optimized with the use of Boolean logical operators. The retrieval formula is ((“Frailty/diagnosis”[Mesh] OR “Frailty/epidemiology”[Mesh]) OR ((Frailties[Title/Abstract]) OR (Frailness[Title/Abstract])OR (Frailty Syndrome[Title/Abstract]) OR (Debility[Title/Abstract]) OR (Debilities[Title/Abstract]))) AND ((“2000/01/01”[Date - Publication]: “2023/12/31”[Date - Publication])). Then, we imported the transcript of all retrieved literature into Endnote Application. After briefly reading the title and abstract, articles not related to the screening or assessment of frailty were excluded. The specific inclusion criteria were defined as follows: (1) papers covered a population of older adults aged ≥60 years; (2) the paper’s main topic was screening and assessment of frailty; (3) the full text was accessible; (4) paper was presented in English. The exclusion criterion was that the paper was on the pathogenesis or interventions for frailty or its association with other diseases. The process of screening the literature was done independently by two researchers, followed by cross-checking. In case of disagreement between the two researchers, a third person was consulted to assist in the judgment. Next, we read the remaining literature and used an Excel sheet to record the screening or assessment scales addressed in each paper, selecting those that appeared ≥150 times. Finally, we read the literature pertaining to the above scales carefully and used another Excel sheet to document the content, focus, measurement patterns, and application scenarios of each scale for subsequent categorization and summarization.

3 Current status of research on screening and assessment tools for frailty

At present, studies on screening and assessment tools for frailty have mostly focused on two areas: frailty-related biological markers and frailty-related scales. The development of frailty involves multiple complex pathophysiological processes such as chronic inflammatory responses, imbalances in energy metabolism, nutritional deficiencies, immune disorders, oxidative stress, and so on (13). In older frail patients, the levels of biological factors involved in these pathophysiologic processes are altered accordingly and can be biomarkers of frailty. To date, biomarkers of age-related frailty can be categorized as inflammatory response-related biomarkers (C-reactive protein, interleukin-6, tumor necrosis factor) (14–17), metabolism-related biomarkers (muscle growth inhibitor, 25-hydroxyvitamin D, insulin-like growth factor 1) (18–21), immune-related biomarkers (neutrophils/lymphocytes ratio, platelet/lymphocyte ratio and systemic immune-inflammatory index) (22), Oxidative stress-related biomarkers (8-dihydro-2′-eoxyguanosine, reactive oxygen species, and superoxide dismutase) (23, 24), and nutrient-related biomarkers (docosahexaenoic acid and vitamin B12) (25, 26). However, biomarkers are susceptible to a variety of factors, making these indicators potentially less stable. For example, the circulating level of insulin-like growth factor 1 can be affected by nutritional levels and genetic factors, and the ratio of neutrophil/lymphocyte is susceptible to factors such as acute illnesses and infections. In addition, some frailty biomarkers have gender specificity, such as C-reactive protein, interleukin-6, and muscle growth inhibitors, which makes it necessary to take gender into account when selecting biomarkers. Therefore, although the changes in biomarkers precede the appearance of the organism’s phenotype, and the objectivity and sensitivity of biomarkers are superior, their specificity, precision, stability, and reliability are weaker than those of frailty-related scales (27). In fact, due to the lack of definitive laboratory tests and appropriate clinical testing techniques and equipment (28), the frailty-related scales have become the most commonly used clinical tool for the identification and assessment of frailty (29).

The frailty scales are mostly based on the three conceptual models of frailty and are established by incorporating the clinical symptoms, signs and subjective feelings of the patient, which have the advantages of simplicity, time-saving, validity, economy and feasibility, such as: Fried Frailty Phenotype (FFP), Frailty Index (FI), Groningen Frailty Indicator (GFI), and so on. Three of the conceptual models described above are the Biological Phenotype, the Cumulative Health Deficit Model, and the Frailty Integral Model. In 2001, Fried et al. (30) proposed the concept of the Fried Frailty Phenotype (FFP) based on the theory of the Biological Phenotype, stating that frailty is a syndrome that meets three or more of the five phenotypic criteria, which is mostly centered on physical deterioration, together with a decrease in physical performance and muscular strength. The Cumulative Health Deficit Model suggests that the more health deficits are accumulated, the more severe the degree of frailty. Based on the Cumulative Health Deficit Model, Rockwood et al. (31) proposed the concept of the Frailty Index (FI) in 2005, which considered frailty as a complex unity of physiological, psychological, and social functioning, and a risk condition that develops as a result of the accumulation of multiple disorders due to multiple factors. The above two models are commonly used in existing studies and have been generally confirmed. Based on these two models, Gobbens et al. (32) proposed the Integral Model of Frailty (IMF), which further defines the operational definition of frailty as a dynamic and continuous process that includes somatic, psychological, and social aspects. Recently, WHO has proposed a new concept of “intrinsic capacity” based on healthy aging, which emphasizes the physiological and psychological dimensions of the individual, and is a longitudinal assessment that follows a trajectory rather than the traditional assessment of frailty at a cross-section or cut-off point. In a sense, intrinsic capacity evolves from frailty, and frailty is one of the components of the decline trajectory of intrinsic capacity (33).

Another hybrid concept analysis of frailty described frailty as a dynamic and fluctuating inability to manage biopsychosocial and environmental stimuli that involves a decline in functioning and life changes, leading to a loss of autonomy and motivation, or poor health outcomes (34). Based on the above concepts, the frailty scales should address multiple dimensions such as somatic, psychological as well as social conditions. Frailty scales can be categorized as screening scales and assessment scales, and the two are often conflated in clinical practice. In fact, screening tools are not identical to assessment tools, and the emphasis of the two is not the same. The frailty screening scales focus on their operationalization, efficiency, and high sensitivity in order to screen older patients at risk of frailty or in a stage of frailty in a very short period of time, while the frailty assessment scales is more complex, focusing on high precision and support by reasonable biological indicators in order to determine more precisely the stage of frailty in which they are placed, and then to develop different treatment plannings according to their stages and risks (35).

Besides, the different screening and assessment tools count the different prevalence rates of frailty (36). A Meta-analysis showed that the prevalence of frailty within the same group was 12% using the FFP versus 24% using the FI (37). Another cross-sectional study among older Brazilians showed that the prevalence of frailty was 0.3% when assessed only in the physical domain of the Tilburg Frailty Indicator (TFI), 2.9% when assessed in both the physical and social domains, and 52% when assessed in a combination of all three domains: physical, social and psychological (38). Although a variety of geriatric frailty scales have been developed, there is still no recognized gold scale for assessing geriatric frailty, and translation from research to clinical practice remains a challenge in the future (39).Next, this article summarizes and analyzes the existing commonly used frailty scales in terms of their screening and assessment roles, and classifies each scale according to its content, focus, measurement mode, and application scenarios, so that clinicians or researchers can use the most appropriate frailty scales according to their characteristics, thus achieving the goal of early screening, early assessment, and early intervention of frailty, and reducing a series of adverse outcomes.

4 Screening scales for age-related frailty

The purpose of frailty screening is primarily to make a quick diagnosis, which is performed in all groups of older people, to identify those who are at high risk of frailty or already in a state of frailty through the use of simple tests. Here, we summarize and generalize the advantages and disadvantages of some commonly used screening scales for age-related frailty.

4.1 Frail scale (FS)

The FS is a clinically applicable self-screening scale for frail older adults proposed by the experts of the International Academy on Nutrition and Aging (IANA) (40). FS is a simple patient self-reported questionnaire containing only 5 items as follows: fatigue, increased sense of resistance, decreased activity, multimorbidity co-morbidity, and weight loss. It quickly categorizes the state of an older person into 3 types, among which those who meet 3 or more items are frail, those who meet 1 to 2 items are pre-frail, and those who do not have any of the 1 items are in a healthy state (41). FS can be easily mastered by healthcare professionals and has a high degree of maneuverability and screening efficacy, which has been translated into many languages and widely used worldwide (42–44). In addition, FS has high specificity and sensitivity. A survey of the Chinese version of the adaptation of FS among 1,235 Chinese community-dwelling older adults showed that the sensitivity of FS was as high as 86.96% while the specificity was as high as 85.64% (42). Another study, which conducted on 308 Chinese older patients aged 60 years and above, showed that FS had a sensitivity of 85.9% and a specificity of 72.5%, and noted that FS was convenient and time-saving, which could be used for the initial screening of frail patients to improve work efficiency (45). A cross-sectional study conducted by Aprahamian et al. (46) in a geriatric outpatient clinic showed that the sensitivity of FS was 54% and the specificity was 73% and suggested that FS could be selected as a screening tool for frailty because of its significant time and cost benefits. FS can be used not only to screen for frailty but also to predict adverse outcomes in older adults. FS is a valid predictor of mortality in older adults over 10 years, according to a cohort study among older adults aged 65 years and older (47). In a longitudinal study of women's health in middle age in Australia, FS predicted the incidence of disability in women from middle age to old age over the next 15 years (48).

FS is entirely self-reported, without any objective measures, and can even be completed by telephone without face-to-face inspection, which makes it simple and easy to administer (49). The simplicity and ease of FS increases the convenience and completion rate of frailty screening, reduces the cost of screening, helps to carry out the development of frailty review, and is worthy of clinical application. However, FS suffers from a certain amount of information bias due to its complete reliance on patient self-reported outcomes, and special attention should be paid to this point in clinical applications.

4.2 Clinical Frailty scale (CFS)

The CFS is a frailty screening tool developed in 2005 by Rockwood et al. (31) for use in the Canadian Health and Aging Study. The original CFS contained 4 dimensions: physical activity, mobility, physical function, and energy status, which categorized older adults' health status into 7 levels. With further research on geriatric frailty, the scope of CFS was expanded to co-morbidities, functional status, and cognitive ability domains, increasing the classification to 9 (50). The specific levels of CFS are as follows: Very Fit, Fit, Managing Well, Living with Very Mild Frailty, Living with Mild Frailty, Living with Moderate Frailty, Living with Severe Frailty, Living with Very Severe Frailty, and Terminally Ill, wherein levels 5 and above are defined exactly as a frailty state. A follow-up study of 210 acutely hospitalized older patients with adverse health outcomes found that both CFS and FS could identify older adults at risk for hospitalized adverse health outcomes and could be used as an easy screening tool for frailty; however, CFS demonstrated higher sensitivity than FS (89.6% vs. 54.6%) (51). Another cross-sectional study conducted in China also confirmed that the sensitivity of CFS was superior to FS as a screening tool for age-related frailty, both in all patients (94.1% vs. 63.0%) and in patients from different wards (91.8–98.5% vs. 58.0–65.7%) (52). In their study of the association between CFS and in-hospital mortality

in patients with Corona Virus Disease 2019 (COVID-19), Sablerolles et al. (53) found that the in-hospital mortality was significantly higher in frailty patients (CFS 6–9) than in healthy patients (CFS 1–3) and that the grade of CFS was negatively correlated with the health status of the patient. A meta-analysis indicated that CFS could predict in-hospital mortality in acutely ill older patients and is a reliable predictor of short-term mortality in older patients presenting to the emergency department (54).

CFS combines clinical judgment with objective measures and can be used not only to predict the need for institutional care or the incidence of death, but also to assess specific domains including co-morbidities, functioning, and cognition, making it a widely used screening tool for frailty (55). Because of its simplicity, rapidity, and accurate ability to predict adverse outcomes, CFS is often considered the most desirable tool for geriatric frailty screening in emergency medicine (56). In addition, CFS is highly sensitive to symptoms associated with frailty syndrome, which makes it also useful for assessing and stratifying the management of frailty (57). However, the completion of CFS needs to be based on clinical diagnosis combined with the interpretation of clinical parameters, which requires that the user should be a medical staff with a certain medical knowledge base, which limits the popularization and application of CFS to a certain extent.

4.3 Edmonton Frailty scale (EFS)

The EFS is a multidimensional screening scale for frailty developed by ROLFSON et al. (58) for non-specialists without specialized training in geriatrics based on the traditional frailty phenotype. The EFS consists of 9 dimensions and 11 entries as follows: (1) Cognitive function (unable to complete the clock drawing test successfully); (2) Functional performance (needing help from others in daily activities); (3) General health (self-assessment of health and the number of hospitalizations in the last year); (4) Independence (unable to complete manual labor alone, unable to walk 2 flights of stairs or walk 1,000 m); (5) Social support (unable to seek outside support successfully when encountering problems); (6) Medication status (being on 5 or more prescription medications at the same time, forgetting to take medication); (7) Mental status (depression); (8) Nutritional aspects (unintentional and significant weight loss recently); (9) Self-control (urinary and fecal incontinence). The EFS has a maximum score of 17, with a score of 0 to 4 indicating no frailty, 5 to 6 indicating sensitive individuals prone to frailty, 7 to 8 indicating mild frailty, 9 to 10 indicating moderate frailty, and 11 or more indicating severe frailty. EFS covers all domains of frailty and is highly correlated with other frailty scales (59). A study of the differences in the prevalence of frailty calculated by five frailty screening tools showed that the prevalence of frailty screened by the EFS was 25.2%, which was most similar to the prevalence of frailty of 27.6% after integrating the five frailty screening tools mentioned above, suggesting that the accuracy of EFS screening was high (52). In addition, the above study found that the EFS had the highest specificity for the assessment of frailty in surgical wards at 98.1%. EFS is commonly used in the identification of geriatric frailty prior to surgery and helps to stratify the risks and identify potentially modifying factors, which makes it have a higher feasibility rating in the surgical setting (60). A prospective study in people aged 70 years and older undergoing major abdominal surgery showed that the EFS has good reliability and validity and can be used as a preoperative assessment tool to predict the risk of surgical complications in older adults (61). In a study conducted by McIsaac et al. (62), it was found that although the accuracy of assessments of postoperative risks using the modified Fried Index (mFI) and the EFS was similar, the EFS had the advantage of a shorter time-consuming and greater patient acceptance, and should be recommended for clinical use.

EFS can be completed within 5 min, with high acceptance by both investigators and respondents. It is easy to operate and can be used by professionals or even non-professionals in multiple departments. It has a wide range of applications venues, which can be used in medical settings such as emergency, outpatient, and hospital wards, as well as in non-medical settings such as the community and the home, making it a reliable screening tool for geriatric frailty (63). However, EFS uses only one question to assess the specifics of the social support domain, disputing the comprehensiveness of the social frailty screen.

4.4 Fried Frailty phenotype (FFP)

FFP is a phenotype derived by Fried et al. (30) from observing and tracking the follow-up to validate adverse outcomes in 5317 older adults aged 65 years or older who participated in the U.S. Longitudinal Cardiovascular Health Study, which explains why FFP was also called the Cardiovascular Health Study Index (CHS). The entries of FFP consist of 5 self-reported symptoms combined with biologically measured signs. The details of its entries are as follows: significant loss of body mass (unintentional weight loss of more than 4.5 kg or more in the past 1 year), weakness (low grip strength in both hands), fatigue (self-reported to be more easily fatigued in the last 6 months), slowness of the body (significant slowing of the walking speed), and physical inactivity (sedentary and physically inactive). Among them, those who fulfill 3 or more are defined as frail, those who have 1 or 2 are defined as pre-frail, and those who do not have any of the above 5 are defined as non-frail. FFP can not only measure the physical frailty status of older adults but also reflect the mental health status of the older adults and obtain more objective and accurate data, which is the most popular and widely used frailty measurement tool in the clinic (12). Results of a survey conducted among cancer patients showed that FFP had a sensitivity of 92% and a specificity of 41% for screening for frailty (64). FFP is widely applicable and its reliability and validity have been validated many times (65). FFP has now been shown to have predictive value for adverse health outcomes in a diverse range of older adults, including hospitalized and general older adults (66).

FFP is excellent for initial stratification for risks of the older population based on different characteristics (i.e., robust, pre-frail, and frail), without the need for an initial clinical assessment, and can be applied at the first patient contact (67). However, FFP focuses on the physiological level of assessment, lacks social, psychological, environmental, and multiple disease factors, and the implementation of some items (e.g., grip strength, step speed, etc.) requires trained personnel and specialized tools (68). The characteristics of FFP described above make it inappropriate for older adults with cognitive impairment, psychiatric disorders, impaired functioning, or in the acute phase of illness, which also make its applicability limited to

hospitals, communities, and nursing facilities. In addition, the 5 phenotypic criteria of frailty allow for different ways of measuring them, and many previous studies have adapted their measurements, which have been confirmed to lead to differences in measurement effects (69). Therefore, future studies should report all the details about how the phenotypic criteria of frailty are measured in order to facilitate the interpretation of the results.

4.5 Other common screening scales for frailty

In recent years, more and more frailty screening tools have been developed as a result of the progress of frailty research. For example, in 2007 Ensrud et al. (70) found that data collected using the Study of Osteoporotic Fractures (SOF) Index was independently associated with FFP-predicted frailty-related adverse health outcomes, and subsequently, the SOF index became one of the screening tools for frailty; the Kihon Checklist (KCL) was proposed by the Japanese government for the implementation of the long-term care insurance system (71); and the Simple Self-Assessment Screening Tool—the Vulnerable Elders Survey-13 (VES-13) was created by Saliba et al. (72). The characteristics of common frailty screening scales are summarized in Table 1 and compared from nine perspectives, including entries, time required, content, and so on (30, 31, 40, 58, 70–76).

5 Assessment scales for age-related frailty

Rapid screening should be followed by further precise assessment of all older adults in pre-frail and frail states. An accurate assessment to evaluate which state of frailty a frail older adult is in can help to predict poor health outcomes better and facilitate the development of individualized treatment and management plans for frailty patients. Recently, there have been a large number of studies devoted to the development of objective quantitative frailty assessment tools (77). Since these assessment tools are not limited to questionnaires and there are differences in the consistency of the assessment tools, places of application, populations administered, and dimensions assessed, the results of the assessment of frailty cannot yet be judged uniformly. Therefore, we will next summarize the characteristics of the commonly used assessment scales for age-related frailty.

5.1 Frailty index (FI)

FI is a classic tool for assessing frailty in older adults developed by Mitnitski et al. (78) based on the cumulative deficit model. It covers multiple dimensions such as physical, psychology, cognition, and social functioning, and contains 30 to 70 evaluation items, the specific content of which is variable. Since there are no standardized criteria for the content of its items, researchers can choose their own entries according to their own research purposes. Although FI lacks specific variables that are uniformly standardized, the stability of FI is supported by the fact that FI consisting of different numbers and types of deficient items yields similar assessment results in different populations or research settings. Generally speaking, when FI $\geq$ 0.25, it implies frailty; when FI < 0.12, it implies non-frailty; when FI is between 0.12 and 0.25, it implies that the older adults are in the pre-frail stage (79). The sensitivity and specificity of FI in identifying frailty was 94.8 and 87.0% in all patients, 96.4 and 88.8% in patients on the cardiology ward, 95.9 and 81.1% in patients on the non-surgical ward and were 89.6 and 89.5% on the surgical ward (52). FI can be used not only for the screening of debilitation but also for the assessment of debilitation. FI is the first tool to successfully quantify the frailty state of older adults and has been widely used in several countries due to its good reliability and validity (80). FI is strongly associated with negative health-related outcomes (including mortality) and with deterioration in disease-specific health status, which makes it a good predictor of clinical prognosis (81, 82). It has been found that FI can be utilized to evaluate the role of musculoskeletal disorders on frailty, rather than just being a categorical variable (83). In addition, FI has important applications in reflecting health service needs, public health management, and interventions. During the period of the COVID-19 pandemic, the use of an electronic version of the FI to assess frailty helped clinicians make decisions by identifying patients most likely to require ICU (intensive care unit) admission and those with a poor prognosis (84).

By focusing on the cumulative number of individual health deficits and integrating multiple complex health information into a single indicator, FI breaks through the limitation of a single variable describing the functional status, and can better assess the overall health status of older adults. With its advantages of multidimensionality, continuity, and objectivity, FI is suitable for frailty assessment in almost all environments. However, the establishment of FI requires a large amount of clinical information, while obtaining a large amount of clinical information is laborious, extremely cumbersome, and time-consuming, which is a major challenge in the use of FI for the assessment of frailty.

5.2 Comprehensive geriatric assessment (CGA)

CGA was conceptualized for the development of a scientific rehabilitation training program for older adults in the 1940s by Marjory Warren (85). As the population ages, the application of CGA continues to extend and becomes a common method of assessing and treating older patients with frailty or loss of function (86). CGA focuses on comprehensive assessments of somatic function, cognitive function, psychology, and social/environmental factors in older adults, thereby identifying and quantifying the degree of frailty, and providing the basis for subsequent frailty intervention strategies and comprehensive care, which is conducive to the early reversal of frailty, the slowing down of the deterioration process of frailty, and the improvement of health outcomes (87). A systematic evaluation that included 22 studies involving 10,315 patients showed that patients in the group that took interventions based on CGA had a lower likelihood of death or worsening of their condition and a higher likelihood of cognitive improvement compared to the group that took conventional medical care (88). Lee et al. (87) found that a CGA-based intervention program for a frail population could potentially promote healthy aging in community-dwelling older adults, with sustained health benefits of up to 1 year for them. Mazya et al. (89) conducted a trial of dynamic geriatric assessment-frailty

TABLE 1 Overview and comparison of screening scales for age-related frailty.

Scale	Year	Country	Items	Time	Contents	Diagnostic criteria	Characteristics	Measure methods	Application site
FS (40)	2008	America	5	15–30s	Fatigue, resistance, ambulation, illness, Loss of weight	Satisfying: ≥3 items	(i) Simple and time-saving. (ii) One-dimensional, only focusing on the physical aspect. (iii) Subjective.	Self-screening	Hospital, community
CFS (31)	2005	Canada	9	<5 min	The illustrated entries assessing the physical activity, mobility, physical functioning, energy status, co-morbidities, and cognition	Satisfying: ≥ levels 5	(i) Fast. (ii) Accurate prediction of adverse outcomes. (iii) Professional medical knowledge is required.	Doctor's clinical judgment	Hospital, community
EFS (58)	2006	Canada	9	<5 min	Cognition, basic health status, independence, social support, drug use, nutrition, emotion, function, incontinence	Satisfying: ≥ 7 scores	(i) Simple and fast. (ii) Strong predictive validity of surgical risk. (iii) Easy to be accepted. (iv) Poor comprehensiveness because it only has one indicator assessing areas of social support.	Clinician, non-professionals' judgment	Hospital
FFP (30)	2001	America	5	<10 min	Weight loss, slow pace, decreased grip strength, low physical activity, fatigue	Satisfying: ≥ 3 items	(i) Objective and accurate. (ii) Tedious and time-consuming. (iii) Professional measuring tools are required. (iv) One-dimensional, only focusing on the physical aspect.	Doctor's clinical observation	Hospital, sanatorium, community
SOF Index (70)	2007	America	3	<5 min	Weight loss, exhaustion, and unable to rise from chair 5 times	Satisfying: ≥2 items	(i) Simple to operate. (ii) Poor comprehensiveness, because it only includes the physical level. (iii) Poor specificity.	Self-screening, assessment	Community
KCL (71)	2007	Japan	25	<15 min	7 areas: physical function, nutrition, feeding, social activity, memory, mood, and lifestyle	Satisfying: >0.25	(i) Strong specificity with a separate frailty critical value in each dimension. (ii) Accurate. (iii) Time-consuming.	Self-screening	Community
VES-13 (72)	2001	America	13	<5 min	4 areas: activities of daily living, physical function, self-rated health, and one question on age	Satisfying: ≥ 3 scores	(i) Simple and time-saving. (ii) Strong predictive validity of disability and death. (iii) Widely used in older patients with tumors.	Self-screening	Community
MFST-HP (73)	2016	Netherland	15	-	3 areas: physical function, psychological items, and social items. (the higher the score, the more serious the degree of frailty)	Satisfying: ≥ 6 scores	(i) Good reliability. (ii) Better performance for excluding non-frail states. (iii) Poor ability to predict adverse health outcomes.	Doctor's clinical judgment	Hospital
PRISMA-7 (74)	2008	Canada	7	<10 min	3 areas: basic demographic characteristics, social support, and activities of daily living	Satisfying: ≥3 scores	(i) High sensitivity. (ii) Poor specificity. (iii) Poor ability to predict adverse health outcomes.	Self-screening	Community, outpatient department, emergency department
GFST (75)	2012	France	6	<5 min	2 areas: doctors' clinical judgment and self-reported decline in physical function, such as living alone, weight loss, fatigue, mobility difficulties, memory loss, and slow pace	Doctors identify frailty based on questionnaires	(i) Time-saving. (ii) Helpful for general practitioners to make clinical decisions. (iii) Subjective because it depends on the clinical decision of the general practitioners.	Doctor's clinical judgment	Community
SPPB (76)	1994	America	3	-	Walking speed test, repeated chair stands test, and balance test	Satisfying: ≤ 6 scores	(i) Simple to operate. (ii) Poor specificity. Poor comprehensiveness, because it only includes the physical level.	Doctor's clinical judgment, non-professionals' judgment	Community, outpatient departmen

CFS: Clinical Frailty Scale; EFS: Edmonton Frailty Scale; FFP: Fried Frailty Phenotype; FS: FRAIL Scale; GFST: the Gérontopôle Frailty Screening Tool; KCL: Kihon Checklist; MFST-HP: the Maastricht Frailty Screening Tool; PRISMA-7: the Program of Research to Integrate the Services for the Maintenance of Autonomy-7; SOF Index: Study of Osteoporotic Fractures Index; SPPB: the Short Physical Performance Battery; VES-13: Vulnerable Elders Survey-13.

10.3389/fpubh.2024.1424613

intervention, in which the control group of the study received conventional treatment and humanistic care while the intervention group received dynamic assessment by CGA and multidisciplinary team interventions (including medication adjustments, exercise, and dietary advice, etc.) in addition to conventional care. After the 24-month intervention, the proportion of patients in the intervention group who were pre-frail was significantly higher than in the control group, suggesting that more patients with chronic diseases or co-morbidities in the intervention group moved from frailty to pre-frailty or strong than that in the control group. With the help of CGA, a comprehensive and scientific assessment of frailty can be made and a personalized medical intervention plan for the older adults can be developed to slow down the process of frailty by healthcare professionals.

CGA can accurately judge the health status of older adults, assess the degree or stage of frailty, identify its causes or triggers, and provide suggestions for its preventive or therapeutic measures, which can help in making risk stratification and clinical decisions for frailty. However, as the CGA is a multidimensional and interdisciplinary diagnostic and therapeutic process that emphasizes a multidimensional and comprehensive risk factor exploration and assessment, it requires a large amount of manpower, energy, and time, which is inconvenient in practice and is only applicable to the hospital healthcare environment (90). Furthermore, despite the fact that many studies have shown a large advantage of CGA for the assessment of frailty, most of these studies were conducted on small samples of older adults within a single institution or region, resulting in poor accuracy of the results of these studies, which still need to be further validated (91).

5.3 Groningen Frailty Indicator (GFI)

GFI is a widely used frailty screening tool developed by Steverink et al. (92) in 2001. The GFI consists of the physical dimension (mobility, multiple health problems, physical fatigue, vision and hearing), the psychological dimension (depressed mood and anxiety), the cognitive dimension (cognitive dysfunction), and the social dimension (emotional isolation), with a total of 15 entries. The 15 entries of the GFI are all dichotomous questions, with each score set at 0 or 1. Higher scores on the GFI indicate more severe frailty, with those scoring ≥4 diagnosed as moderately or severe frailty (93). A study comparing the ability of four frailty screening tools to predict frailty-related adverse outcomes showed that the sensitivity of the GFI in predicting the frailsty adverse outcomes of death and hospitalization was 76.2 and 63.9%, respectively, and the specificity was 42.1 and 50.3%, which suggests that the GFI has a higher sensitivity and a poorer specificity (94). When the Chinese version of the GFI was used to screen for pre-frailty and frailty in 350 Chinese community-dwelling older adults, it demonstrated good internal consistency, with a Cronbach's alpha coefficient of 0.87, a re-test reliability of 0.87, and the concurrent validity between the GFI and the Fried frailty phenotype of 0.76. suggesting that the GFI is a reliable and valid tool for pre-frailty and frailty screening in community-dwelling older adults (95). In addition, GFI can accurately predict total healthcare costs for the following year and can help healthcare professionals allocate healthcare resources (96).

GFI has been widely used in many countries such as Germany, Italy, France, and so on, and it is suitable for use in different assessment environments, such as communities, nursing homes, and healthcare facilities (97). However, compared with other scales, GFI focuses more on physical indicators such as physical strength, functioning, and health status, and does not adequately take into account psychological, cognitive, and social aspects, which may make the results of the GFI assessment slightly less integrated and comprehensive.

5.4 Other common assessment scales for frailty

As the prevalence of frailty increases, more and more frailty assessment tools are being developed to make individualized and precise interventions for frail patients. For example, the Comprehensive Frailty Assessment Instrument (CFAI), which was first included in environmental assessment, was developed (98) and the Rapid Geriatric Assessment (RGA), which improves on the cumbersome assessment process of the CGA, was also created (99). A comparison of various common frailty assessment scales is shown in Table 2 (78, 86, 92, 98–101).

6 Conclusion

Frailty is an emerging global health burden with significant implications for clinical practice and public health. With the rapid growth of an aging population, the prevalence of frailty increases year by year. Frailty is a dynamically changing clinical state, with the pre-frailty phase showing potential reversibility. The early recognition of frailty and appropriate interventions for it can help slow or even reverse the process of it and reduce the risk of adverse outcomes. In order to achieve "healthy aging" centered on wellness, we need to improve the rate of the early identification of frailty for its early precise intervention. Although there are approximately 67 screening and assessment tools for frailty internationally and and there is a trend toward an increase in the number of such tools (77), different screening and assessment tools have more significant differences in conceptual basis, clinical utility, program content, and place of application. As a result, there is still considerable debate as to what is the best scale for screening and assessing frailty.

Strictly speaking, frailty screening scales and assessment scales have different requirements and should not be confused. Screening scales need to be simple, quick, and highly sensitive to frailty, which allows clinicians to recognize frailty quickly. Assessment scales require high accuracy, utility, and support of sound biological theories, which allows clinicians to identify the stages of frailty in older adults accurately and predict the occurrence of adverse health events in frail older adults, such as falls, cognitive deficits, loss of mobility, and death. Through reading a large amount of literature, we have differentiated and reviewed the most common frailty scales for screening and assessment in order to help researchers as well as healthcare professionals to select the most appropriate frailty scales for its identification and assessment. Based on our summaries and

TABLE 2 Overview and comparison of assessment scales for age-related frailty.

Scale	Year	Country	Dimension	Item	Time (min)	Contents	Assessment criteria	Characteristics	Measuremethod	Application site
FI (78)	2001	Canada	4	30–70	20–30	Physical functions, psychological aspects, cognitive ability, and social functions	Non-frailty: FI: < 0.12. Pre-frailty: FI: 0.12–0.25. Frailty: FI ≥ 0.25.	(i) A broad scope focusing on overall health assessment. (ii) Strong predictive validity. (iii) Tedious and time-consuming.	Doctor's clinical observation	Hospital, community
CGA (86)	1989	America	6	30+	<15	General medical assessment, physical function, psychological status, social behavior ability, environmental health, and other assessment such as: diet health	A continuous score. Frailty: scores >0.25. The higher the score, the more severe the frailty.	(i) Focusing on the older inpatients. (ii) Widely recognized and applied. (iii) Complex content without an uniform standard.	Doctor's clinical observation	Hospital
GFI (92)	2001	Netherland	4	15	<15	Physical functions, psychological aspects, cognitive ability, and social functions	Frailty: scores ≥4. The higher the score, the more severe the frailty.	(i) Simple. (ii) Uncertain predictive ability for adverse health outcomes.	Self -assessment	Community
CFAI (98)	2013	Belgium	4	23	<15	Physical functions, psychological aspects (mood and emotion), social functions (social relations and social support), environment	Mild frailty: scores: 20–40. Moderate frailty: scores: 41–50. Severe frailty: scores: 51–97.	(i) Simple to operate. (ii) Uncertain assessment of social functions.	Self -assessment	Community
RGA (99)	2015	America	4	18	<5	Degree of frailty, nutritional status, degree of anorexia and cognitive impairment	It includes 4 scales: the FS, the SARC-F, the SNAQ, and the RCS. Each scale is scored separately.	(i) Time-saving. (ii) High degree of reliability. Several entries are difficult to understand and memorize.	Doctor's clinical observation	Hospital
TFI (100)	2010	Netherland	3	15	<15	Physical functions, psychological aspects, and social functions	Frailty: scores ≥5. The higher the score, the more severe the frailty.	(i) Simple. (ii) Comprehensive. (iii) Subjective.	Self -assessment	Hospital, sanatorium, community
FRAIL-NH (101)	2015	America	4	7	<10	Physical functions, nutritional condition, co-morbidities, and self-care ability	The higher the score, the more severe the frailty.	(i) Simple. (ii) Time-saving. (iii) Good predictive validity for adverse health outcomes.	Doctor's clinical observation	Hospital, sanatorium

CFAI: Comprehensive Frailty Assessment Instrument; CGA: Comprehensive Geriatric Assessment; FI: Frailty Index; FRAIL-NH: Fatigue, Resistance, Ambulation, Incontinence/Illness, Loss of weight, Nutritional approach, and help with dressing; FS: FRAIL Scale; GFI: Groningen Frailty Indicator; RCS: Rapid Cognitive Screen; RGA: Rapid Geriatric Assessment; SARC-F: the Simple Five item Scoring Scale for Sarcopenia; SNAQ: Simplified Nutritional Appetite Questionnaire; TFI: Tilbury Frailty Indicator.

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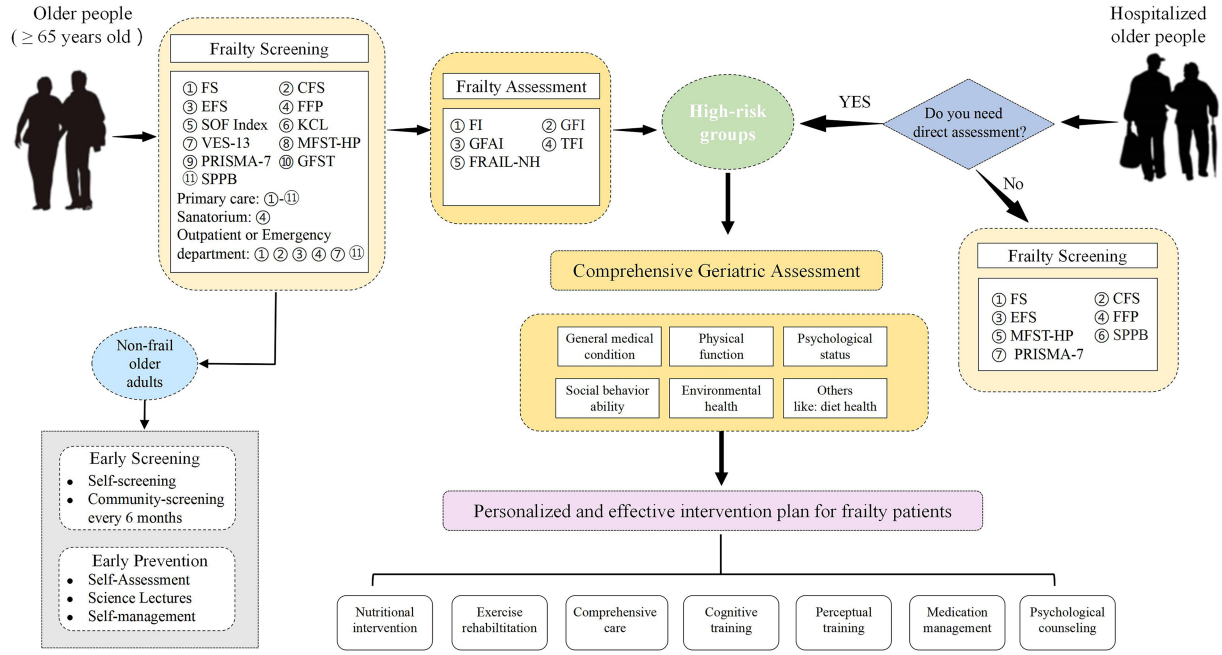

FIGURE 1
The process of screening and assessment for the frailty in different types of older people. The development of frailty can be slowed or even reversed by the early recognition, accurate assessment, and timely interventions for frailty, which will reduce the strain of frailty on health care systems around the world and promote healthy aging of the global population. In the future, we still need to explore objective, simple, time-saving, effective, economical, and feasible scales that can accurately identify and assess frailty in clinical practice.

generalizations, we roughly design the process of screening and assessment for the frailty in different types of older people, which is shown in Figure 1. The high-risk groups and older people without frailty symptoms are screened out through a rapid screening scale, and the high-risk groups should go to the hospital for treatment. Older people without frailty symptoms should adopt self-screening and regular community screening once every 6 months to prevent the emergence of frailty. For older hospitalized patients, high-risk groups are screened out through the doctor's simple judgment (whether it needs to be evaluated directly), and then a detailed and comprehensive evaluation can make them quickly benefit from the follow-up personalized intervention treatment.

The development of frailty can be slowed or even reversed by early recognition, accurate assessment, and timely interventions for frailty, which will reduce the strain of frailty on healthcare systems around the world and promote healthy aging of the global population. Although we have provided insights into potential solutions for early identification and assessment of frailty by reviewing a large body of literature, however, there are some limitations to our study. Firstly, we searched only one database and limited our search to one language, which may have led to the omission of relevant articles. Secondly, our review lacked a critical assessment of the included articles, which resulted in the variable quality of the articles we included. Finally, we only summarized scales that have been studied frequently and are relatively well-established, which is somewhat one-sided. In the future, we still need to explore objective, simple, time-saving, effective, economical, and feasible scales that can accurately identify and assess frailty in clinical practice.

Author contributions

X-MW: Writing – original draft. Y-HZ: Writing – original draft. C-CM: Conceptualization, Writing – review & editing. LF: Conceptualization, Writing – review & editing. LW: Conceptualization, Writing – review & editing. Y-YL: Formal analysis, Writing – review & editing. X-ZL: Funding acquisition, Supervision, Writing – review & editing. S-CL: Supervision, Visualization, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This work was supported, at least in part, by the Science & Technology Development Fund of Tianjin Education Commission for Higher Education (2022ZD044).

Acknowledgments

We thank our reviewers and editor for critical feedback that enhanced this work.

Conflict of interest

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

Publisher's note

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frontiers | Frontiers in Medicine

TYPE Systematic Review
PUBLISHED 12 February 2025
DOI 10.3389/fmed.2025.1537240

OPEN ACCESS

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RECEIVED 30 November 2024
ACCEPTED 30 January 2025
PUBLISHED 12 February 2025

CITATION
Liu J, Wu Y, Long Z, Zhang S and Wu S (2025) The association between cognitive frailty and the risk of fall occurrence in older adults: a meta-analysis of cohort studies.
Front. Med. 12:1537240.
doi: 10.3389/fmed.2025.1537240

The association between cognitive frailty and the risk of fall occurrence in older adults: a meta-analysis of cohort studies

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Background: Cognitive frailty increases the risk of fall occurrence. However, previous studies have shown inconsistent correlations between cognitive frailty and the risk of fall occurrence.

Objective: To systematically review studies and explore the association between cognitive frailty and the risk of fall occurrence.

Methods: Databases were systematically searched. Meta-analysis was performed using RevMan 5.4 software after evaluation of the quality of the included studies by 2 researchers.

Results: A total of five studies including 16,962 patients were included. The results of Meta-analysis showed that the cognitive frailty group increased the risk of occurrence of falls in older adults [OR = 1.38, 95% CI (1.09, 1.73), p = 0.006]. Subgroup analyses showed that cognitive frailty in older adults increased the risk of fall occurrence using different cognitive frailty assessment tools, study participants from the community, different regions, and different sample sizes.

Conclusion: The results of this study suggest that cognitive frailty in older adults is an independent risk factor for the occurrence of falls, and it is recommended that caregivers strengthen the assessment of cognitive aspects of older adults admitted to the hospital.

KEYWORDS

cognitive frailty, falls, meta-analysis, older adults, systematic review

Highlights

- In this systematic review and meta-analysis, we considered for the first time the possible relationship between cognitive frailty and the occurrence of falls in a cohort study. The results of this study suggest that cognitive frailty in older adults is an independent risk factor for the occurrence of falls.
- It is recommended that caregivers strengthen the assessment of cognitive aspects of older adults admitted to the hospital so that they can accurately identify those who are at high risk for falls.
- Different CF assessment tools were used in the included studies and there was a certain recall bias in the assessment of falls, which had an impact on the result.

Introduction

A fall is usually defined as an event in which an individual falls to the ground or other lower plane as a result of an unintended fall (1). The incidence of falls increases with age, and preventing and managing falls has become a challenge for society. According to the World Health Organization, the percentage of older adults who have experienced at least one fall in a year is 30% (2). Falls in older adults can lead to fractures, joint dislocations and disability, which can lead to increased dependency and decreased quality of life and even death (3). Early identification of fall-related risks in older adults and intervention is crucial for caregivers. In 2013, the International Association of Gerontology first proposed the new concept of Cognitive Frailty (CF), which refers to the combination of frailty and mild cognitive impairment (MCI) in the exclusion of neurodegenerative disorders such as dementia (4). A Meta-analysis showed that frailty was significantly associated with a high risk of falls occurring (5). Another Meta-analysis of 27 studies found that community-dwelling older adults with MCI had more than twice the risk of fall occurrence than cognitively normal older adults (6). The introduction of the concept of cognitive frailty combines the two, emphasizing the co-occurrence of frailty and MCI, which, at a theoretical level, would significantly increase the occurrence of falls in older adults. A Meta-analysis showed that CF not only increases the risk of dementia, but also increases the risk of adverse outcomes such as death (7). However, in various current studies, the findings are not entirely consistent (8–10).

In current clinical care, falls assessment has become a routine item in the admission assessment. The Morse Falls Risk Assessment Scale is the most commonly used in clinical practice and is currently considered the best predictive tool. The scale has six entries, but four of the scale's entries focus on frailty aspects of the older adult's characteristics, less on cognitive aspects, and only one question in the last entry asks about good mental status. In addition, assessments of cognition are rare in current admission routine nursing assessments. As mentioned earlier, the impact of MCI on falls has become prominent and there is a need to strengthen the assessment of cognition in the nursing assessment of older adults on admission. Therefore, this study will systematically evaluate the relationship between CF and the risk of fall occurrence in older adults with the aim of determining whether CF is an independent risk factor for falls, thereby drawing attention to the cognitive aspect of clinical care. The assessment of CF may provide intervenable targets for clinical caregivers to reduce the risk of fall occurrence in older adults.

Methods

Design

A systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statements.

Search strategy

The system searched Cochrane Library, PubMed, Embase, Medline, CINAHL, Scopus, Proquest Central, Web of Science, SinoMed, CNKI, VIP and Wan fang Databases. The search period was from the establishment of the database to December 2023, and databases were searched by "cognitive frailty/cognitive dysfunction/cognitive impairment/cognitive decline/cognit*" "frailty/frail*/frailty syndrome/frail elderly" "accidental falls/fall*/falling/slip" as search terms. Using PubMed as an example, its specific search strategy is shown in Figure 1.

Eligibility criteria

Literature Inclusion Criteria: (1) Study population: older adults aged ≥60 years; (2) Exposure factors: CF was assessed using the 2013 International Consensus Panel (4), which proposes the co-existence of frailty and MCI in the exclusion of neurodegenerative diseases such as dementia. Among them, frailty was assessed using the current frailty assessment tools for the older adults that are used more at home and abroad, such as the Fried Frailty Phenotype Scale and the FRAIL Frailty Scale, etc. MCI was assessed using commonly used cognitive assessment scales, such as the Mini-mental State Examination (MMSE), cognitive tests or self-reports, Montreal Cognitive Assessment (MoCA), etc.; (3) Outcome indicator: occurrence of falls; (4) Study type: prospective cohort study on the relationship between CF and the risk of falls occurrence in older adults.

Literature exclusion criteria: (1) Data in the original study could not be converted and applied; (2) Data could not be extracted and duplicated literature.

Literature screening and data extraction

Data from the selected studies were extracted from Excel spreadsheets by 2 researchers each. Any disagreements were resolved

#1 cognitive dysfunction[MeSH]
#2 cognitive frailty[Title/Abstract] OR cognitive dysfunction [Title/Abstract] OR cognitive impairment[Title/Abstract] OR cognitive decline[Title/Abstract] OR cognit*[Title/Abstract]
#3 frailty[MeSH]
#4 frail elderly[MeSH]
#5 frailty[Title/Abstract] OR frail*[Title/Abstract] OR frailty syndrome[Title/Abstract]ORfrail elderly[Title/Abstract]
#6 accidental falls[MeSH]
#7 fall*[Title/Abstract] OR falling[Title/Abstract] OR slip[Title/Abstract]
#8 #1 OR #2
#9 #3 OR #4 OR #5
#10 #6 OR #7
#11 #8 AND #9 AND #10

FIGURE 1
PubMed search strategy.

by consensus with the 3rd researcher. Basic information was extracted and cross-checked for the included literature, which included: first author and year of publication, region of investigation, source of study population, sample size, duration of follow-up, age, survey instrument for CF, fall survey instrument, OR and 95% CI, and adjustment factors.

Literature quality evaluation

For accuracy, 2 researchers independently completed the data extraction process. Any data discrepancies could be resolved by referring to the original articles. Literature quality was evaluated using the Newcastle-Ottawa Quality Assessment Scale (NOS) (11), which includes three dimensions: study population selection, comparability, and outcome measures, with a total of 8 entries and a total score of 9. Articles with a score of 6 or higher were of high quality.

Statistical analysis

This study used EndNote X9 software for literature management, extracted data using Excel sheets, and applied RevMan 5.4 software for Meta-analysis. The ending index was the occurrence of falls, and the combined effect size was expressed as the ratio (OR) and 95% CI, and the combined data were tested for heterogeneity and combined with I^2 to evaluate the magnitude of heterogeneity. If $p > 0.10$ and $I^2 \leq 50\%$, there was homogeneity among studies, and a fixed-effects model was selected for Meta-analysis; if $p \leq 0.10$ and $I^2 > 50\%$, there was heterogeneity among studies, and a random-effects model was selected for Meta-analysis. Subgroup analysis was performed according to the basic characteristics of the included studies to explore and reduce heterogeneity, and sensitivity analysis was used to evaluate the stability of the results. Differences were considered statistically significant at $p < 0.05$.

Results

Study characteristics

According to the established search plan, a total of 3,041 studies (2,911 in English and 130 in Chinese) were obtained from the initial examination, and after screening according to the criteria, five (8, 9, 12–14) studies were finally included, all of which were in English. The literature screening process is shown in Figure 2.

Basic characteristics of the included studies

Five (8, 9, 12–14) studies were included as prospective cohort studies with a total of 16,962 patients. 2 (9, 14) studies used the Fried Frailty Phenotypic Scale and the MMSE Scale as the assessment tools for CF; 1 (8) study used the Fried Frailty Phenotypic Scale and the Hasegawa Dementia Scale to assess CF; 1 (12) study used the FRAIL Frailty Scale and the Mini-Cog Scale to assess CF; and 1 (13) study assessed CF using the Fried Frailty Phenotype Scale and cognitive tests or self/proxy reports. Falls were assessed using a single entry asking about the occurrence of falls, which ranged from 10.6 to 47.6% (see Table 1).

Evaluation of the quality of included studies

The included studies were evaluated for quality on the NOS scale and scored 7–9, indicating that the included studies were all high-quality literature, with one study (8) scoring a perfect score (see Table 2).

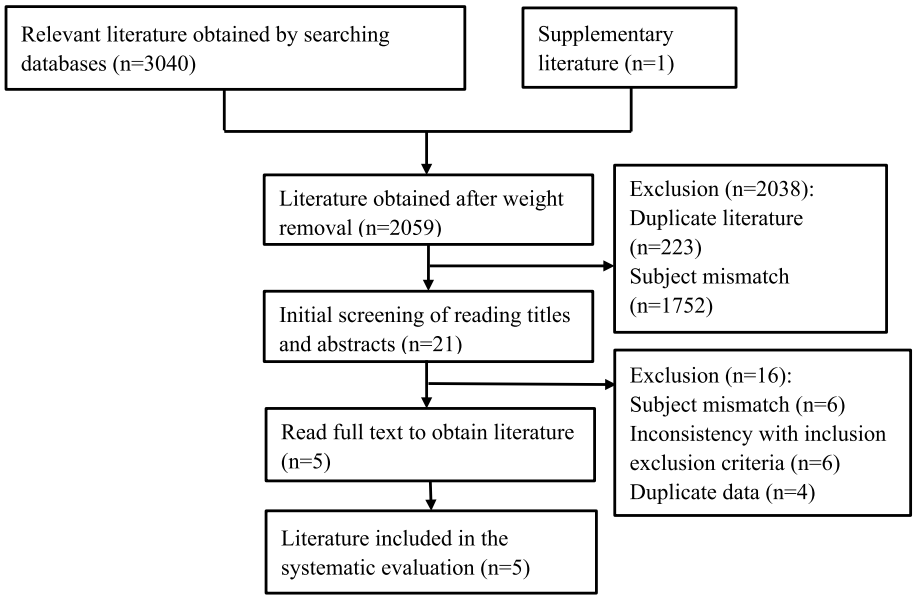

FIGURE 2
PRISMA flowchart.

TABLE 1 Basic characteristics of included studies.

First author and year of publication	Area of investigation	Source of study population	Sample size	Duration of follow-up	Age	Cognitive frailty instrument		Falls instrument	OR (95% CI)	Adjustment factors
						Physical frailty	Mild cognitive impairment			
Ma (8), 2021	China	Community	965	3 years	74.9 ± 3.7	Fried Frailty Phenotype Scale	Hasegawa Dementia Scale	Single-entry issues	3.11 (1.06, 9.15)	Gender, age, education level, occupation, marital status, BMI, smoking and alcohol history, health status, depression, diabetes, hypertension
Zhang (12), 2021	China	hospital	9,192	30 days	72.4 ± 5.7	FRAIL Frailty Scale	Mini-Cog Scale	Single-entry issues	3.00 (1.32, 6.83)	Age, gender, education level, depression, ward aggregation effects
Ge (13), 2021	United States of America	hospital	6,000	6 years	≥65	Fried Frailty Phenotype Scale	Cognitive testing or self/proxy reports	Single-entry issues	1.28 (1.17, 1.40)	Age, gender, race, education level, living alone, obesity, co-morbidities, mobility impairments
Rivan (14), 2021	Malaysia	Community	400	5 years	69.0 ± 6.2	Fried Frailty Phenotype Scale	MMSE Scale	Single-entry issues	2.98 (1.78, 4.99)	Age, gender, education level, waist circumference, loneliness status
Brigola (9), 2020	Brazilian	Community	405	4 years	70.6 ± 7.1	Fried Frailty Phenotype Scale	MMSE Scale	Single-entry issues	1.44 (0.51, 4.05)	Gender, age, education level, BMI

TABLE 2 Quality assessment of included studies.

Inclusion in the study	Selection of study participants				Comparability between groups	Outcome measures total score			Score
	Representativeness of the exposed group	Representativeness of the non-exposed group	Exposure factors determined	Exposure factors determined no outcome measures to observe at the time of the study		Whether outcome evaluations were independent	Whether follow-up was long enough	Follow-up completeness	
Ma (8)	1	1	1	1	2	1	1	1	9
Zhang (12)	1	1	1	0	2	1	0	1	7
Ge (13)	1	1	1	0	2	1	1	1	8
Rivan (14)	1	1	1	0	2	1	1	0	7
Brigola (9)	1	1	1	0	2	1	1	0	7

10.3389/fmed.2025.1537240

Relationship between CF and the occurrence of falls

There was heterogeneity among the included studies ($p = 0.003$, I^2=75%), so a random effects model was chosen for Meta-analysis. The results showed that the CF group increased the risk of fall occurrence compared to the non-CF group [OR = 1.38, 95% CI (1.09, 1.73), $p = 0.006$], and the difference was statistically significant (see Figure 3).

Subgroup analysis

In order to further identify the reasons for heterogeneity, this study explored the relationship between CF and the risk of fall occurrence in older adults in 4 aspects (CF assessment tool, source of study participants, region, and sample size) based on the basic characteristics of the included studies. (1) CF assessment tools: 2 studies (9, 14) CF was assessed using the Fried Frailty Phenotype Scale and the MMSE Scale, and the rest of the studies used the more commonly used CF assessment tools. Meta-analysis showed that the use of the Fried Frailty Phenotype Scale and the MMSE Scale, as well as the other combinations of the assessment tools, indicated that older adults with CF were at increased risk of falls. (2) Source of study population: three (8, 9, 14) studies were community-sourced and two (12, 13) were hospital-sourced. Meta-analysis showed that hospital-sourced CF in older adults did not increase the risk of falls [OR = 1.28, 95% CI (0.90, 1.82), $p = 0.17$], and community-sourced CF in older adults was associated with an increased risk of falls. Associated with an increased risk of falls. (3) Region: 3 studies (8, 12, 14) were in Asia, and 2 studies (9, 13) were in the Americas. Meta-analysis of the results showed that CF in older adults in different regions increased the risk of fall occurrence. (4) Sample size: 2 studies (9, 14) had a sample size of less than 900, and 3 studies (8, 12, 13) had a sample size of more than 900. Meta-analysis of the results showed that sample size did not affect the correlation between CF in older adults and an increased risk of fall occurrence (see Table 3).

Sensitivity analysis and publication bias

Sensitivity analyses were performed after excluding each of the five prospective cohort studies whose outcome indicator was the occurrence of falls, and the results showed no significant change in the amount of the combined effect, indicating that the results of the Meta-analysis of this study were essentially stable. Publication bias was not analyzed because the number of included studies was small and did not meet the minimum number of documents for making a funnel plot.

Discussion

A total of 5 prospective cohort studies were finally included in this study, and the scores of the included literature were rated from 7 to 9 after standardized evaluation, of which, 2 studies (8, 13) scored 8–9, suggesting that the overall quality of the included literature was high. The included studies all used the more commonly used current CF and falls assessment tools, and each study controlled for the influence of confounding factors on the results, and the results also showed that the results of this study were relatively stable after the exclusion of each study. Based on this, the results of the Meta-analysis of this study have high reliability. However, because all of the fall assessments in this study were single-entry inquiries about falls and relied on patient self-reporting, there was some recall bias and the effect of the remaining confounders, and the results of this study need to be viewed with caution.

A cross-sectional study (10) showed that CF was associated with falls in community-dwelling Japanese older adults. However, Brigola et al. (9) did not find an association between CF and falls after a 4-year follow-up of 405 older adults. The results of this study showed that patients in the CF group had a 1.38-fold increased risk of falls compared with patients in the non-CF group, suggesting that CF is a risk factor for the occurrence of falls in older adults.

The mechanisms underlying the association between CF and falls in older adults are complex: slow gait speed, a key feature of frailty, is associated with cognitive deficits in processing speed, attention, and executive function (15), and cognitive deficits and resulting declines in cognitive reserve may make it difficult to ameliorate frailty (16); another study (17) found that both frailty and MCI are associated with higher levels of inflammatory markers, and that CF significantly elevated inflammatory markers in older adults may trigger the onset of falls by accelerating muscle loss and impairing muscle tissue regeneration; and research (18) suggests that older adults with CF often experience reduced nutrients or visual impairment, and are less responsive when

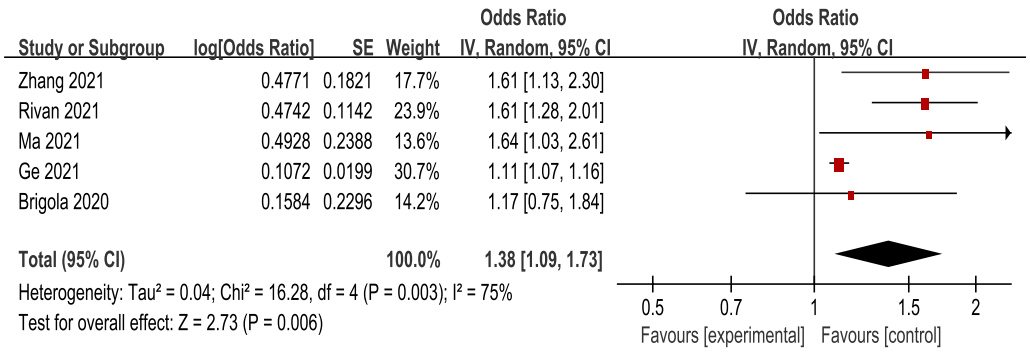

FIGURE 3
Association between CF and the occurrence of falls.

TABLE 3 Subgroup analyses of the association between CF and the risk of fall occurrence.

Criteria for grouping	Number of studies included	Confluence effect size		Heterogeneity test	
		p	OR (95% CI)	*p*	I^2 (%)
Cognitive frailty assessment tool					
Fried Frailty Phenotype Scale + MMSE Scale	2	<0.001	1.71 (1.24, 1.84)	0.22	34
Fried Frailty Phenotype Scale + Cognitive performance tests or self/proxy reports	1	<0.001	1.11 (1.07, 1.16)	-	-
Fried Frailty Phenotype Scale + Hasegawa Dementia Scale	1	0.04	1.64 (1.03, 2.61)	-	
FRAIL Frailty Scale + Mini-Cog Scale	1	0.009	1.61 (1.13, 2.30)	-	-
Source of research subjects					
Hospitals	2	0.17	1.28 (0.90, 1.82)	0.04	75
Community	3	<0.001	1.53 (1.27, 1.84)	0.45	0
Region					
Asia	3	<0.001	1.61 (1.35, 1.92)	1.00	0
Americas	2	<0.001	1.11 (1.07, 1.16)	0.82	0
Sample size					
<900	2	<0.001	1.71 (1.24, 1.84)	0.22	34
≥900	3	<0.001	1.35 (1.00, 1.83)	0.04	70

presented with a new environment, making them susceptible to falls. These results suggest that geriatric syndromes such as frailty and MCI may represent common pathways that modulate the association between individual risk factors and falls, presenting a synergistic effect on falls. Therefore, when older adults have these two geriatric syndromes, they are more susceptible to falls, early screening for CF may help to prevent falls, and the assessment and management of CF should be emphasized among clinical caregivers.

Subgroup analyses in this study showed that older adults assessed as having CF using the Fried Frailty Phenotype Scale and the MMSE Scale assessment tools were at higher risk for falls; that community-dwelling older adults with CF had a significantly increased risk for falls compared to those in hospital settings; and that neither the size of the sample from different regions nor the size of the sample from different studies affected the relevance of the increased risk for falls in older adults with CF.

The Fried Frailty Phenotype Scale was proposed by Fried et al. (19) in 2001 based on the theory of the cycle of frailty, including five assessment indicators such as unconscious weight loss, and the Asia-Pacific Clinical Practice Guidelines for the Management of Frailty in the Older stated that the use of this scale is effective in predicting the risk of falls in older adults, and it is one of the internationally recognized tools for the assessment of frailty. The MMSE Scale was developed by Folstein et al. (20) in 1975, and several studies have used this combined scale for CF assessment. Kim et al. (21) screened 1,248 community-dwelling older adults using this combined scale and found a correlation between CF and falls. The results of the subgroup analysis in this study found that community-dwelling older adults with CF had a significantly increased risk of falls compared to those in the hospital setting, possibly due to the higher prevalence of CF among older adults in the community (7), which, combined with the greater range of motion of older adults in the community setting, puts them at increased risk of falls.

The present study has different findings from previous studies after subgroup analysis of the source of the study population. The results of this study showed a nonsignificant relationship of increased risk of fall occurrence in older adults with CF in the hospital setting, which we consider to be a meaningful finding due to the paucity of current research on this outcome. It is hypothesized that the possible reasons for this are that in the hospital setting, clinical staff are more timely in assessing and teaching falls; secondly, falls are recognized as a major event affecting the safety of older adults admitted to the hospital, and nurses, as the main promoters of patient safety, will enhance care for falls; finally, older adults admitted to the hospital are usually in relatively serious condition, and they may have a limited ability to get out of bed, which may also reduce the incidence of falls to some extent. In other words, this also proves that CF is very significantly related to the occurrence of falls, and that CF is a strong predictor of falls, and timely intervention can reduce the incidence of fall events. Both Zhang (12) and Ge (13) et al. demonstrated that elderly patients with CF are at a higher risk of falling compared to those healthy hospitalized elderly patients, which suggests that screening for CF is important for the prevention of falls in hospitalized elderly patients. Therefore, the assessment of CF and management of falls in both community and hospitalized older adults should be strengthened.

Implications of this study for clinical practice and future research

Based on the results of this study, CF in older adults significantly increases the risk of falls, and CF in older adults increases the risk of falls using different CF assessment tools, different sources of study participants (other than hospitals), different regions, and different sample sizes. This implies that clinical caregivers need to assess CF and

implement appropriate interventions to enhance early warning awareness, prevention, and management when older adults are admitted to the hospital. There are fewer and limited quality studies related to CF interventions, and one study found that physical activity moderated the relationship between CF and falls (22), and activity participation can be considered as an effective way to improve CF. In addition, studies have shown that intervention programs including exercise training, nutrition programs, and memory training can reverse debilitation and cognitive impairment (13). Therefore, appropriate exercise training and nutritional interventions need to be considered in conjunction with inpatient fall-related education at discharge to reduce the incidence of falls.

Limitations of this study

Only Chinese and English literature was included in this study, which may have language bias; fewer studies were included and the sample size for subgroup analysis was smaller; different CF assessment tools were used in the included studies and there was a certain recall bias in the assessment of falls, which had an impact on the results.

Conclusion

The present study is based on a Meta-analysis of prospective cohort studies, and the results show that CF in older adults is an independent risk factor for the occurrence of falls. This suggests that nursing assessment of cognitive aspects should be strengthened at the time of hospital admission in older adults, and attention should be paid to the cumulative risk of cognitive emergence in debilitating situations, thus reducing the incidence of falls and improving the quality of care.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: the data that support the findings of this study are available from the corresponding author on reasonable request.

Author contributions

JL: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. YW: Conceptualization, Data curation, Formal analysis, Supervision, Writing – review & editing. ZL: Data curation, Methodology, Resources, Validation, Visualization, Writing – review & editing. SZ: Data curation, Investigation, Project administration, Software, Writing – review & editing. SW: Conceptualization, Funding acquisition, Resources, Software, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

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

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frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 26 February 2025
DOI 10.3389/fmed.2025.1540050

OPEN ACCESS

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RECEIVED 05 December 2024
ACCEPTED 03 February 2025
PUBLISHED 26 February 2025

CITATION
Merchant RA, Dong YQ, Kumari S and Murphy D (2025) Frailty, malnutrition, healthcare utilization, and mortality in patients with dementia and cognitive impairment obtained from hospital administrative data.
Front. Med. 12:1540050.
doi: 10.3389/fmed.2025.1540050

Frailty, malnutrition, healthcare utilization, and mortality in patients with dementia and cognitive impairment obtained from hospital administrative data

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Introduction: With aging populations, the prevalence of dementia, frailty and malnutrition will increase. The aim of this study is twofold (a) to determine the demographic data, including frailty and malnutrition prevalence in older patients with diagnosis of dementia and/or cognitive impairment and (b) to determine its impact on outcomes such as length of stay (LOS), readmission and mortality stratified by frailty status.

Methods: Retrospective single-center cohort study conducted using hospital database on older patients ≥65 yrs. admitted to a tertiary hospital between March 2022 and Dec 2023 and discharged with either primary or secondary diagnosis of dementia or cognitive impairment. Data on age, gender, ethnicity, comorbidities, discharge diagnoses, Hospital Frailty Risk Score (HFRS), Clinical Frailty Scale (CFS), activity of daily living (ADL), 3-Minute Nutrition Screening and outcomes such as LOS, readmission, mortality and cost of hospitalization were extracted. Those aged between 65 to 74 years old were categorized as "young-old," and ≥75 years old as "old-old."

Results: Dementia or cognitive impairment diagnosis was prevalent in 8.6% (3090) older patients, and 33.7% were malnourished. 54.5% were female with a mean age of 82.0 years. Almost one fourth were dependent on ADL. Based on frailty defined by (i) HFRS—26.0% had intermediate and 18.2% high frailty (ii) CFS—41.0% were mild/moderately frail, and 32.2% severely frail. Median LOS was 8 days. 30 and 90-days readmission rates were 23.2 and 35.4%, respectively. In-hospital mortality was 7.8% and 30-day mortality 14.0%. High HFRS (aOR 1.511, 95% CI: 1.089–2.097; $p = 0.013$), severe frailty (aOR 4.325, 95% CI: 0.960–2.684; $p < 0.001$) and terminal frailty (aOR 39.762, 95% CI: 18.311–86.344; $p < 0.001$) were significantly associated with inpatient mortality. Intermediate HFRS (aOR 1.682, 95% CI: 1.380–2.050; $p < 0.001$), mild/moderate frailty (1.609, 95% CI: 1.254–2.065; $p < 0.01$), high HFRS (aOR 2.178, 95% CI: 1.756–2.702; $p < 0.001$) and severe frailty (2.333, 95% CI: 1.804–3.017; $p < 0.01$) were significantly associated with 30-days readmission. The impact of malnutrition on healthcare utilization was highest in the old-old with high HFRS and severe frailty.

Conclusion: Frailty and malnutrition have significant impact on healthcare utilization, readmission rates, and mortality among older adults with dementia and/or cognitive impairment.

KEYWORDS
dementia, cost, length of stay, readmission, mortality, malnutrition

Introduction

With aging populations, the prevalence of dementia, frailty and associated disability will increase, putting strain on finite resources. Dementia encompasses a spectrum of neurological disorders characterized by progressive cognitive decline, impairment in activities of daily living, and mortality. The progression of dementia typically follows a gradual trajectory, starting with mild cognitive impairment and advancing to severe disability (1). This disease progression is intricately linked with frailty, a syndrome marked by decreased physiological reserve and increased vulnerability to stressors and malnutrition which is a risk factor for both frailty and dementia (2–4). Frailty is categorized into physical, social and cognitive frailty, and significantly increases risk of cognitive impairment and dementia (2, 5). The coexistence of dementia and frailty accelerates cognitive and physical decline, leading to increased healthcare utilization, disability, and mortality (6). Both prevention of dementia and frailty are global health priorities, and many countries are adopting population wide initiatives to delay the onset, reverse or delay the progression of these conditions (7, 8).

Singapore, one of the fastest-aging countries globally, projects that one in four of its population will be 65 years old and above by 2030, and nearly one in two by 2050 (9). A recent publication, studying the healthcare burden of cognitive impairment in the Singapore Chinese population, showed that these patients incurred 17.0% increased costs annually, mainly from emergency department visits and unplanned admissions (10). Data from the United Kingdom showed that the number of persons living with dementia (PLWD) who were hospitalized have increased by 93.0% between 2011 and 2017 (11). Similarly, the cost of their care during the same time period had doubled from £1.2bn to £2.7bn and costs due to emergency admissions were 30.0% higher than those with no dementia. This increase in admissions may be due to increased awareness and access to diagnostic facilities, longer life expectancies, increased multimorbidity, suboptimal integrated care or community resources at discharge, lack of caregiver availability and social isolation (9). Hospitalization is often harmful and distressing for older adults, more so for PLWD. The risks of functional decline, delirium, malnutrition, incontinence, nosocomial infections, falls, unnecessary tests and adverse drug events with prolonged length of stay (LOS) and readmissions are increased in this group of individuals (12, 13). Hospitalization has been associated with 1.7 to 3.3-fold increased decline in cognitive trajectory (14).

PLWD are at increased risk of malnutrition and prevalence varies depending on setting, stage of dementia and population being studied. Malnutrition rates may be as high as 47.8% in community dwelling to 75.6% in institutionalized PLWD with a pooled prevalence of 26.98% (15). This may be due to changes in taste and smell affecting appetite, poor oral health, physical limitation, forgetting to eat, psychosocial and behavioral factors and increase energy expenditure from wandering (16). Malnutrition is associated with poor quality of life, sarcopenia, falls, accelerated decline in cognition and frailty trajectory, hospitalization, and mortality (17). Hospitalization poses additional risks for PLWD such as delirium, prolonged bed rest, and nil by mouth orders (18, 19). The combined effects of dementia, frailty, and malnutrition create a vicious cycle that accelerates decline and increased mortality.

Previous studies have demonstrated that PLWD experience higher healthcare utilization and costs. However, there is a paucity of research on the impact of frailty and malnutrition in patients with dementia and/or cognitive impairment and its association with healthcare utilization, readmissions, mortality, and cost. Therefore, the aim of this study was twofold. Firstly, to determine the demographic data, including frailty status and malnutrition prevalence, in patients with diagnosis of dementia and/or cognitive impairment admitted to an academic hospital and secondly, to determine its impact on outcomes such as length of stay, readmission and mortality on this cohort, stratified by frailty status.

Methodology

All patients over the age of 65 yrs (35,930 patients), admitted to a tertiary hospital from March 2022 to Dec 2023 were reviewed using the institution's administrative database for diagnosis of dementia or cognitive impairment. Existing, de-identified data was extracted by executives from the Value Driven Outcome Department. Dementia or cognitive impairment diagnosis was based on either primary or secondary diagnosis. In addition, older patients were also included in the analysis if they were on any of the acetylcholinesterase inhibitors or memantine as a surrogate for diagnosis of dementia (Supplementary Table S1).

Demographic data

Data on age, gender, ethnicity, underlying comorbidities, discharge diagnoses, age adjusted Charlson Comorbidity Index, Hospital Frailty Risk Score (HFRS), Clinical Frailty Scale (CFS) and activity of daily living (ADL) 2 weeks prior to admission and malnutrition was obtained from hospital administrative database. Those aged between 65 to 74 years old were categorized as young-old, and ≥ 75 years old as old-old.

Common discharge diagnoses were based on previous publications were such as delirium, pneumonia, urinary tract infection, constipation, hyponatremia, ischemic stroke, intracranial hemorrhage, acute myocardial infarction, congestive cardiac failure, orthostatic hypotension, osteoporotic fracture, Parkinson's Disease, and sepsis (20). Malnutrition was defined using 3-Minute Nutrition Screening (3-MinNS) tool (score range between 0 and 9) (21). A score of ≥3 was used to diagnose malnutrition. ADL data was obtained 2 weeks prior to admission and accessed from nursing notes.

Information on premorbid CFS 2 weeks before admission was collected at the triage area in the emergency department for patients ≥65 years. CFS 1–4 were categorized under robust/vulnerable, 5–6 mild/moderate, 7–8 as severe frailty and 9 as terminally ill. HFRS scoring was computed using the ICD-10 codes and was initially described in 2018 by Gilbert et al. (22). It has since been validated in

many continents and is associated with adverse outcomes such as mortality, and length of stay (23, 24). HFRS is classified into low <5, intermediate 5–15 and high >15. The Age-adjusted Charlson comorbidity index was initially validated to predict mortality is a constitute of weighted index of age, number and seriousness of comorbid disease (25).

Outcome

Outcomes data such as LOS, readmission (within 30 and 90 days after discharge), in-hospital and 30-day mortality, and the cost of hospitalization was obtained from the hospital database. Cost was defined as the total cost of hospitalization to care provider per patient per episode during our observation window. Cost data was further categorized into laboratory, medication, radiology, occupational therapy, and physiotherapy cost.

Statistical analysis

All data analysis was conducted on STATA Version 15. Frequencies and percentages were used to summarize the categorical variables. Continuous variables were presented with mean, standard deviation, median, and interquartile range (IQR). We adopted the t-test for continuous variables and the Pearson's χ^2 test for categorical variables to compare the statistical significance between young-old and old-old groups.

We stratified the patients into different groups according to their HFRS, CFS and malnutrition. Medians of the total cost and rates of readmission and in-hospital mortality were calculated for each group to compare the outcomes and costs across groups.

Logistic regressions were performed to estimate the odds ratio of HFRS and CFS on 30 and 90-day readmission, and in-hospital mortality. Multivariate linear regressions were conducted to estimate the effects of HFRS and CFS on total cost of hospitalization. The logarithm transformation was performed for the cost for normalization of the skewed distribution and proportional interpretation of results. We adjusted for both the demographics, including age, gender, ethnicity, and multimorbidity, in the regression analysis. The low frailty or robust/vulnerable group were used as reference groups.

Ethics

The study was reviewed and approved by NUHS Research Office NUH-RNR-2024-0034. As anonymous data was obtained from the database, informed consent was not required.

Results

Demographics and prevalence of common comorbidities

There was a total of 3,090 older adults (≥65 years) diagnosed with dementia and/or cognitive impairment with 4,238 in-hospital admissions in this hospital between March 2022 and December 2023. Dementia or cognitive impairment diagnosis was prevalent in 8.6% of all older adults who were hospitalized, 54.5% were female with a mean age of 82.0 ± 8.0 years (Table 1). The top 3 diagnoses prevalent in almost one third of the patients were delirium (31.5%), pneumonia (33.3%), and UTI (32.5%). For comorbidity prevalence, hypertension (56.4%) was highest followed by diabetes mellitus (40.7%) and hyperlipidemia (40.5%). Based on frailty status defined by HFRS, 55.8% were classified as low, 26.0% as intermediate and 18.2% as high. Based on CFS, 25.1% were either robust or vulnerable, 41% had mild or moderate frailty, and 32.2% severe frailty. The prevalence of malnutrition was 33.7%.

There were significant differences in the demographics between the young-old compared with the old-old. There was higher prevalence of female in the old-old group (57.3% vs. 43.6%) and Chinese ethnic group (84.1% vs. 70.6%). With regards to discharge diagnoses, delirium (34.1%), pneumonia (34.7%) and UTI (33.7%) was more prevalent in the old-old. Similarly, other diagnoses more prevalent in the old-old include hyponatremia (21.5% vs. 13.4%), acute myocardial infarction (12.7% vs. 9.8%), and osteoporotic fracture (7.6% vs. 3.1%). The prevalence of ischemic stroke, diabetes mellitus and hyperlipidemia were lower in the old-old. Almost half of the young-old had underlying diabetes mellitus compared to one third of the old-old. Figure 1 shows that 15–20% of older patients with cognitive impairment were dependent on various activities of daily living prior to admission. Only one fourth were independent in ambulation. In the old-old compared to young-old, the prevalence of severe frailty based on CFS was almost double (35.6% vs. 19.5%) and high HFRS 25% higher (19.2% vs. 14.5%). Malnutrition was significantly higher in the old-old (37.2%) compared to young-old (20.7%). Half of those with severe frailty and more than two thirds of those with terminal frailty had underlying malnutrition (Figure 2). The prevalence was similarly high in those with high HFRS.

Outcomes

The overall median LOS was 8.0 days (IQR 8.0–16.0). Thirty-day and ninety-day readmission rates were 23.2 and 35.4%, respectively. In hospital mortality was 7.8% and 30-days mortality was 14.0%. Both the mean and median LOS were shorter in the old-old group. Indices for in-hospital mortality (8.5% vs. 5.2%), and 30 days mortality (15.4% vs. 8.2%) were significantly higher in the old-old compared with young-old. Breakdown of cost by frailty status is shown in Figure 3. Patients with severe frailty incurred higher costs in the laboratory, radiology, and/or medication category and high HFRS in the medication and laboratory category. Those terminally ill also incurred higher costs in the laboratory and radiology category. Median costs were significantly lower (by 25%) in the old-old than in the young-old across all frailty categories except those with high HFRS, severe frailty and malnutrition (Figure 4).

Tables 2, 3 shows outcomes by different frailty criteria with/without malnutrition in the young-old, and old-old. The results show that outcomes vary significantly with frailty levels, frailty screening tools or the presence of malnutrition. In the young-old group, the 90 days readmission rates among those with high HFRS, severe frailty, high HFRS + severe frailty, and high HFRS + severe frailty + malnutrition were 60.2, 44.3, 65.4 and

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TABLE 1 Demographics and outcome of dementia or cognitive impairment.

	All	65–74 years	≥ 75 years	*p*-Value
	3,090	643 (20.8)	2,447 (79.2)	
Demographics				
Gender				**<0.001**
Male	1,407 (45.5)	363 (56.5)	1,044 (42.7)	
Female	1,683 (54.5)	280 (43.6)	1,403 (57.3)	
Age (years)	82.0 ± 8.0	70.4 ± 2.7	85.1 ± 6.0	**<0.001**
Ethnicity				**<0.001**
Chinese	2,512 (81.3)	454 (70.6)	2058 (84.1)	
Malay	225 (7.3)	82 (12.8)	143 (5.8)	
Indian	181 (5.9)	54 (8.4)	127 (5.2)	
Others	172 (5.6)	53 (8.2)	119 (4.9)	
Discharge Diagnosis				
Delirium	973 (31.5)	138 (21.5)	835 (34.1)	**<0.001**
Pneumonia	1,028 (33.3)	177 (27.5)	851 (34.8)	**0.001**
UTI	1,004 (32.5)	180 (28.0)	824 (33.7)	**0.006**
Constipation	232 (7.5)	39 (6.1)	193 (7.9)	0.119
Hyponatremia	612 (19.8)	86 (13.4)	526 (21.5)	**<0.001**
Ischaemic Stroke	302 (9.8)	82 (12.8)	220 (9.0)	**0.004**
Intracranial Bleed	152 (4.9)	38 (5.9)	114 (4.7)	0.192
Acute Myocardial Infarction	373 (12.1)	63 (9.8)	310 (12.7)	**0.047**
Diabetes Mellitus	1,257 (40.7)	319 (49.6)	938 (38.3)	**<0.001**
Hypertension	1743 (56.4)	379 (58.9)	1,364 (55.7)	0.145
Hyperlipidaemia	1,252 (40.5)	307 (47.7)	945 (38.6)	**<0.001**
Heart failure	244 (7.9)	51 (7.9)	193 (7.9)	0.970
Orthostatic hypotension	263 (8.5)	57 (8.9)	206 (8.4)	0.718
Osteoporosis fractures	207 (6.7)	20 (3.1)	187 (7.6)	**<0.001**
Parkinson's Disease	162 (5.2)	36 (5.6)	126 (5.2)	0.649
Sepsis	437 (14.1)	101 (15.7)	336 (13.7)	0.201
Hospital Frailty Risk Score				
Low	1721 (55.8)	375 (58.5)	1,346 (55.1)	**0.023**
Intermediate	801 (26.0)	173 (27.0)	628 (25.7)	
High	562 (18.2)	93 (14.5)	469 (19.2)	
Clinical Frailty Score*				**<0.001**
Robust (CFS 1–3)	321 (12.4)	115 (21.2)	206 (10.1)	
Vulnerable (CFS 4)	330 (12.7)	96 (17.7)	234 (11.4)	
Mild (CFS 5)	443 (17.1)	94 (17.3)	349 (17.1)	
Mod (CFS 6)	620 (23.9)	130 (23.9)	490 (23.9)	
Severe (CFS 7–8)	835 (32.2)	106 (19.5)	729 (35.6)	
Terminally ill (CFS 9)	41 (1.6)	2 (0.4)	39 (1.9)	
Age adjusted Charlson's Comorbidity Index, median (IQR)	6 (IQR 4–7)	6 (IQR 4–7)	6 (IQR 4–8)	0.252
Malnutrition^	895 (33.7)	116 (20.7)	779 (37.2)	**<0.001**
Outcomes				
In-hospital Mortality	240 (7.8)	33 (5.1)	207 (8.5)	**0.005**
30-days Mortality	430 (13.9)	53 (8.2)	377 (15.4)	**<0.001**

(Continued)

TABLE 1 (Continued)

	All	65–74 years	≥ 75 years	*p*-Value
	3,090	643 (20.8)	2,447 (79.2)	
30-days Readmission	718 (23.2)	148 (23.0)	570 (23.3)	0.883
90-days Readmission	1,093 (35.4)	229 (35.6)	864 (35.3)	0.885
Length of Stay since Admission (day)				
Mean	12.7 ± 15.2	15.9 ± 18.9	11.9 ± 14.0	**<0.001**
Median (IQR)	8 (IQR 4–16)	8 (IQR 5–19)	8 (IQR 4–15)	

n(%); *n* ± SD; malnutrition defined by 3 min Nutrition Screening score ≥ 3.
*Missing data *n* = 500.
^Missing data for 441.
Bold values indicate statistically significant differences between groups ($p < 0.05$).

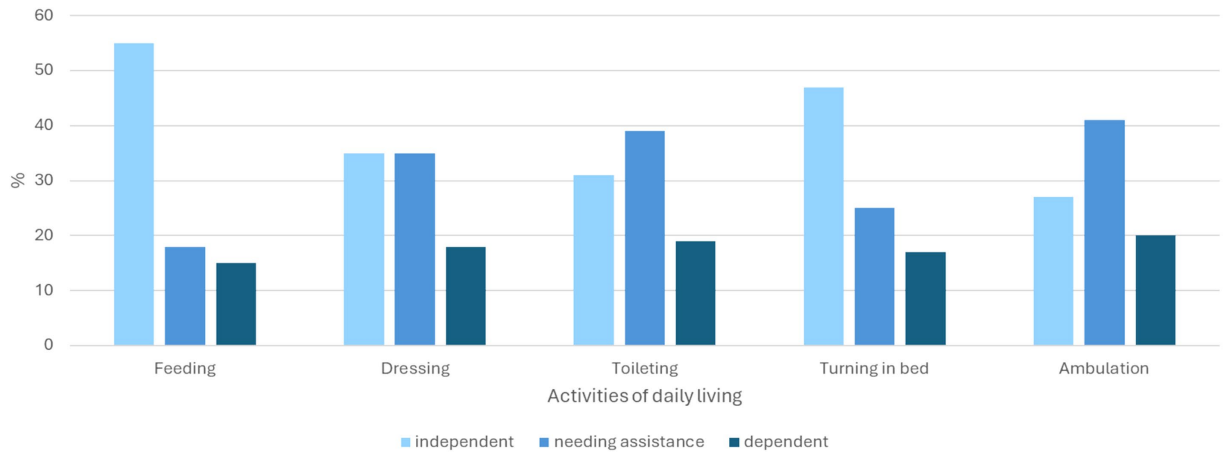

FIGURE 1
Activity of daily living 2 weeks prior to admission.

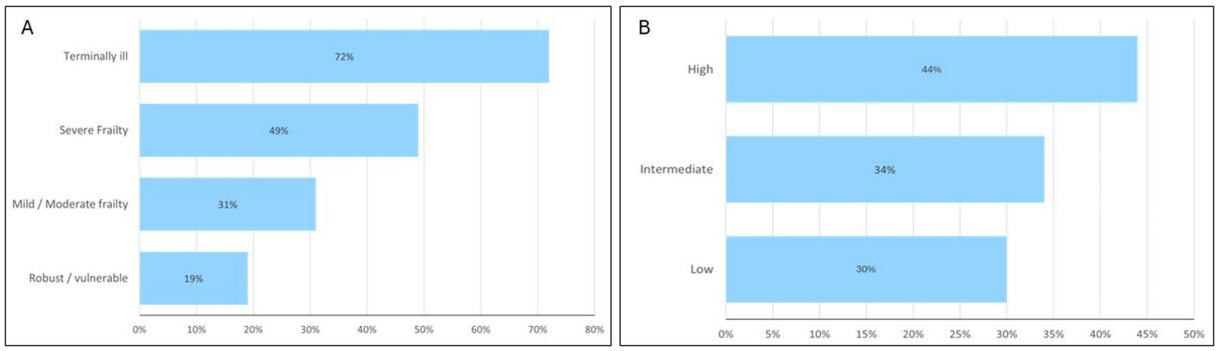

FIGURE 2
Prevalence of malnutrition across frailty groups defined by clinical frailty score **(A)** and hospital frailty risk score **(B)**.

60.0%, respectively, (Table 2). In the old-old group, the 90 days readmission rates among those with high HFRS, severe frailty, high HFRS + severe frailty, and high HFRS + severe frailty + malnutrition were 48.6, 44.3, 55.7 and 61.7%, respectively. Patients classified as moderately frail + high HFRS similarly had high 90-days readmission rates (65.4% in the young-old and 58.3% in the old-old). Amongst those with malnutrition, 30- and 90-days' readmission rates were between 41.8 and 43.9%. In the old-old terminally frail patients, the inpatient mortality rate was highest at 61.5%, followed by 17.5% amongst those with severe frailty + malnutrition (Table 3).

Table 4 shows the association between different frailty screening tools (HFRS: Table 4A, CFS: Table 4B) and mortality, readmission, cost and LOS. Patients with higher or more severe frailty had considerably worse health outcomes compared with low frailty or robust/vulnerable group. High HFRS (aOR 1.511, 95% CI:

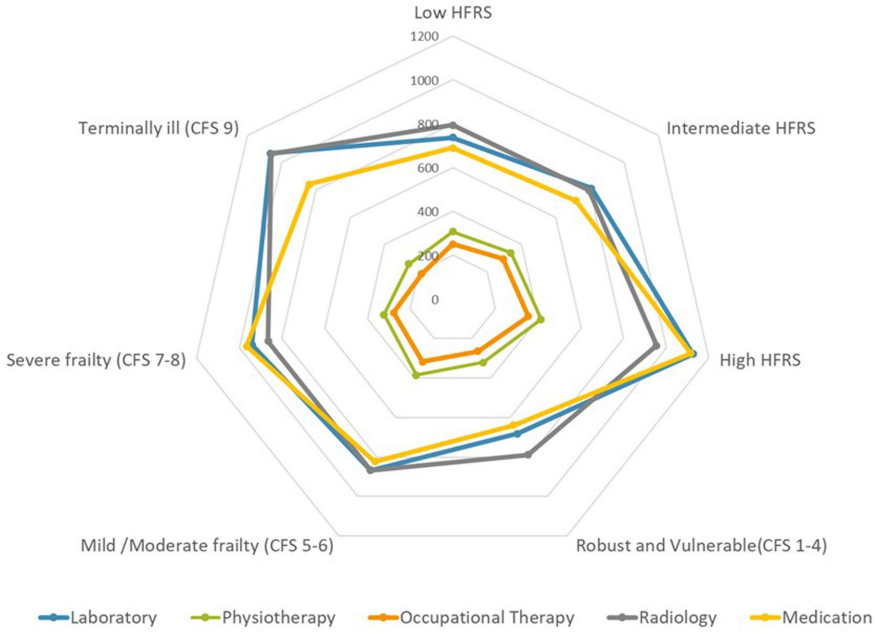

FIGURE 3
Categorical cost by hospital frailty risk score (HFRS) and clinical frailty scale (CFS).

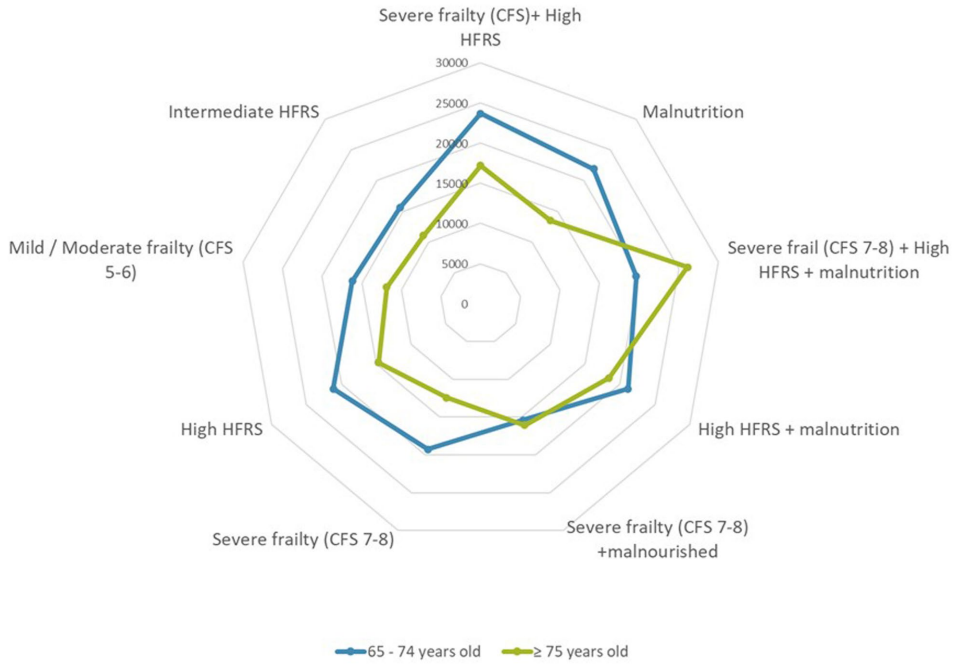

FIGURE 4
Cost breakdown by frailty status defined by hospital frailty risk score and/or clinical frailty scale in the presence or absence of malnutrition.

1.089–2.097; $p = 0.013$), severe frailty (aOR 4.325, 95% CI: 0.960–2.684; $p < 0.001$) and terminal frailty (aOR 39.762, 95% CI: 18.311–86.344; $p < 0.001$) were significantly associated with in-patient mortality. Intermediate HFRS (aOR 1.682, 95% CI: 1.380–2.050; $p < 0.001$), mild/moderate frailty (1.609, 95% CI: 1.254–2.065; $p < 0.01$), high HFRS (aOR 2.178, 95% CI: 1.756–2.702; $p < 0.001$) and severe frailty (2.333, 95% CI: 1.804–3.017; $p < 0.01$) were significantly associated with 30-days readmission. Similar findings were observed for readmissions within 90 days.

The cost of care for patients with intermediate HFRS was 12.2% ($p = 0.003$) and high HFRS 39.8% ($p < 0.01$) higher than those without frailty (Table 4A). Patients with intermediate HFRS had 16.2% ($p < 0.001$) longer length of stay while those with high HFRS had 47% ($p < 0.001$) longer length of stay (Table 4A). The findings

TABLE 2 Malnutrition, hospital frailty risk score, clinical frailty score, and readmission (30- and 90-day) in the young-old, and old-old.

	Number of patients (*n*)		Readmission (30D) *n*(%)		Readmission (90D) *n* (%)	
Age groups (years)	65–74	≥75	65–74	≥75	65–74	≥75
Hospital frailty risk score (HFRS)—based on ICD-10 Codes						
Intermediate	173	628	41 (23.7)	178 (28.3)	71 (41.0)	264 (42.0)
High	93	469	34 (36.6)	150 (32.0)	56 (60.2)	228 (48.6)
Clinical frailty scale (CFS)—based on mobility, balance, and activities of daily living						
Mild/Moderate frailty	224	839	62 (27.7)	198 (23.6)	92 (41.1)	315 (37.5)
Severe frailty	106	729	30 (28.3)	236 (32.4)	47 (44.3)	323 (44.3)
Terminal frailty	2	39	0 (0)	5 (12.8)	1 (50)	7 (18.0)
Hospital frailty risk score (HFRS) and clinical frailty score (CFS)						
Mild/Moderate frailty (CFS) + High HFRS	45	156	16 (35.6)	54 (34.6)	27 (60.0)	91 (58.3)
Severe frailty (CFS) + High HFRS	26	183	10 (38.5)	74 (40.4)	17 (65.4)	102 (55.7)
Mild/Moderate frailty (CFS) + Intermediate HFRS	59	217	17 (28.8)	63 (29.0)	25 (42.4)	90 (41.5)
Severe frailty (CFS) + Intermediate HFRS	28	193	7 (25.0)	71 (36.8)	11 (39.3)	98 (50.8)
Malnutrition, hospital frailty risk score and clinical frailty score						
Malnutrition	116	779	51 (43.9)	326 (41.8)	51 (43.9)	326 (41.8)
Severe frailty (CFS) + High HFRS + malnutrition	10	94	6 (60.0)	41 (43.6)	6 (60.0)	58 (61.7)
High HFRS + malnutrition	23	198	11 (47.8)	76 (38.4)	13 (56.5)	111 (56.1)
Severe frailty (CFS) + malnutrition	33	316	16 (48.5)	121 (38.3)	19 (57.6)	159 (50.5)

Malnutrition defined by 3 min Nutrition Screening score ≥ 3. Severe frailty: CFS score 7–8; Mild/Moderate frailty: CFS 5–6.

TABLE 3 Malnutrition, hospital frailty risk score, clinical frailty score, and in-hospital mortality in the young-old, and old-old.

	Number of patients (*n*)		In-hospital mortality *n* (%)	
Age groups (years)	65–74	≥75	65–74	≥75
Hospital frailty risk score (HFRS)—based on ICD-10 Codes				
Intermediate	173	628	6 (3.5)	52 (8.3)
High	93	469	10 (10.8)	51 (12.4)
Clinical frailty scale (CFS)—based on mobility, balance, and activities of daily living				
Mild/Moderate frailty	224	839	10 (4.5)	44 (5.2)
Severe frailty	106	729	13 (12.3)	105 (14.4)
Terminal frailty	2	39	1 (50)	24 (61.5)
Hospital frailty risk score (HFRS) and clinical frailty score (CFS)				
Mild/Moderate frailty (CFS) + High HFRS	45	156	4 (8.9)	11 (7.1)
Severe frailty (CFS) + High HFRS	26	183	4 (15.4)	25 (13.7)
Mild/Moderate frailty (CFS) + Intermediate HFRS	59	217	1 (1.7)	6 (2.8)
Severe frailty (CFS) + Intermediate HFRS	28	193	3 (10.7)	29 (15.0)
Malnutrition, hospital frailty risk score and clinical frailty score				
Malnutrition	116	779	9 (7.8)	104 (13.3)
Severe frailty (CFS) + High HFRS + malnutrition	10	94	0 (0)	13 (13.8)
High HFRS + malnutrition	23	198	2 (8.7)	29 (14.6)
Severe frailty (CFS) + malnutrition	33	316	3 (9.1)	55 (17.4)

Malnutrition defined by 3 min Nutrition Screening score ≥ 3. Severe frailty: CFS score 7–8; Mild/Moderate frailty: CFS 5–6.

were similar for frailty based on CFS scores where patients with mild/moderate frailty incurred 26.6% ($p < 0.001$) and severe frailty 36.8% ($p < 0.001$) more cost than the robust/vulnerable group. Patients with mild/moderate frailty and severe frailty had 29.7% ($p < 0.001$) and 43.3% longer length of stay, respectively, compared to the robust/vulnerable frailty group (Table 4B).

Table 5 shows association of high HFRS, severe frailty and malnutrition in combination with readmission (30 and 90-days),

TABLE 4 Association of hospital frailty risk score (HFRS) (A), clinical frailty scale (CFS) (B) with readmission (30 and 90-days), in-hospital mortality, cost and length of stay.

A.			
Outcomes	Hospital Frailty Risk Score (Low HFRS as reference group)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
		p value	*p* value
In-hospital mortality	Intermediate	1.036 (0.749–1.433)	1.049 (0.756–1.455)
		0.831	0.776
	High	**1.616 (1.169–2.233)**	**1.511 (1.089–2.097)**
		0.004	**0.013**
Readmission within 30 days	Intermediate	**1.687 (1.384–2.055)**	**1.682 (1.380–2.050)**
		<0.001	**<0.001**
	High	**2.182 (1.761–2.704)**	**2.178 (1.756–2.702)**
		<0.001	**<0.001**
Readmission within 90 days	Intermediate	**1.900 (1.594–2.265)**	**1.892 (1.586–2.256)**
		<0.001	**<0.001**
	High	**2.700 (2.219–3.280)**	**2.709 (2.224–3.300)**
		<0.001	**<0.001**
		Coef. (95% CI)	Coef. (95% CI)
*Cost (Log transformation)	Intermediate	**0.135 (0.054–0.215)**	**0.122 (0.043–0.202)**
		0.001	**0.003**
	High	**0.370 (0.279–0.461)**	**0.398 (0.308–0.488)**
		<0.001	**<0.001**
*LOS (Log transformation)	Intermediate	**0.173 (0.091–0.255)**	**0.162 (0.081–0.243)**
		<0.001	**<0.001**
	High	**0.449 (0.356–0.543)**	**0.470 (0.377–0.562)**
		<0.001	**<0.001**

B.			
Outcomes	Clinical Frailty Scale (Robust/vulnerable as reference group)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
		p value	*p* value
In-hospital mortality	Mild/Moderate (CFS 5–6)	1.606 (0.960–2.684)	1.550 (0.925–2.599)
		0.071	0.096
	Severe (CFS 7–8)	**4.937 (3.066–7.950)**	**4.325 (2.666–7.016)**
		<0.001	**<0.001**
	Terminal (CFS 9)	**46.875 (21.848–100.573)**	**39.762 (18.311–86.344)**
		<0.001	**<0.001**
Readmission within 30 days	Mild/Moderate (CFS 5–6)	**1.558 (1.217–1.995)**	**1.609 (1.254–2.065)**
		<0.001	**<0.001**
	Severe (CFS 7–8)	**2.250 (1.752–2.889)**	**2.333 (1.804–3.017)**
		<0.001	**<0.001**
	Terminal (CFS 9)	0.668 (0.257–1.741)	0.688 (0.263–1.799)
		0.409	0.445

(Continued)

10.3389/fmed.2025.1540050

TABLE 4 (Continued)

B.			
Outcomes	Clinical Frailty Scale (Robust/vulnerable as reference group)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
		p value	*p* value
Readmission within 90 days	Mild/Moderate (CFS 5–6)	**1.551 (1.257–1.914)**	**1.583 (1.280–1.958)**
		<0.001	**<0.001**
	Severe (CFS 7–8)	**1.989 (1.599–2.474)**	**2.051 (1.639–2.567)**
		<0.001	**<0.001**
	Terminal (CFS 9)	0.606 (0.275–1.337)	0.620 (0.280–1.372)
		0.215	0.238
		Coef. (95% CI)	Coef. (95% CI)
*Total Cost (Log transformation)	Mild/Moderate (CFS 5–6)	**0.210 (0.117–0.304)**	**0.266 (0.173–0.358)**
		<0.001	**<0.001**
	Severe (CFS 7–8)	**0.266 (0.168–0.365)**	**0.368 (0.269–0.467)**
		<0.001	**<0.001**
	Terminal (CFS 9)	0.117 (−0.186–0.420)	0.230 (−0.068–0.529)
		0.450	0.131
*LOS (Log transformation)	Mild/Moderate (CFS 5–6)	**0.247 (0.152–0.343)**	**0.297 (0.202–0.392)**
		<0.001	**<0.001**
	Severe (CFS 7–8)	**0.345 (0.245–0.445)**	**0.433 (0.332–0.534)**
		<0.001	**<0.001**
	Terminal (CFS 9)	0.167 (−0.141–0.476)	0.262 (−0.043–0.568)
		0.287	0.092

Adjusted for age, gender, and ethnicity.
*Multivariate linear regression using logarithm transformation.
Bold values indicate statistically significant differences between groups ($p < 0.05$).

in-hospital mortality, cost and LOS. Reference was made to the absence of malnutrition. High HFRS, severe frailty + malnutrition incurred 47.3% ($p = 0.001$) higher cost and 51.3% longer LOS. High HFRS+ malnutrition and severe frailty+malnutrition were associated with increased inpatient mortality (aOR 1.906, 95% CI: 1.070–3.394; $p = 0.029$ and aOR 2.149, 95% CI: 1.391–3.322; $p = 0.001$ respectively).

Figure 5 (A: HFRS, B: CFS) shows the number of inpatient and outpatient visits by different frailty categories. Patients with high HFRS had an average of 11, terminally ill 9 and severe frailty 6 annual outpatient visits. Patients with high HFRS, severe frailty or terminally ill had an average of 2.5 annual inpatient admissions (Figure 5).

Discussion

Patients with dementia and/or cognitive impairment constitute a heterogeneous group. They are at higher risk of hospitalization hazards, increased healthcare utilization and mortality (26). However, studies on the impact of frailty and malnutrition in this population are limited. Our results demonstrated that frailty, irrespective of the screening tools used, was significantly associated with a higher likelihood of in-patient mortality, 30-day or 90-day readmission, and increased healthcare utilization, including LOS and costs, among patients with cognitive impairment and/or dementia. Although there was no significant difference in the 30- and 90-day readmissions between young-old and old-old, the former incurred higher costs and exhibited longer LOS. Inpatient, and 30-days mortality was significantly higher in the old-old. The presence of malnutrition further exacerbated these outcomes, highlighting the compounded negative impact of both malnutrition and frailty on healthcare utilization and prognosis. Malnutrition in patients with severe frailty or high HFRS was associated with increased in-patient mortality. In patients who had both high HFRS and severe frailty, malnutrition was associated with increased cost and LOS.

The prevalence of dementia and/or cognitive impairment was 8.6%, and almost 80% were ≥75 years old. The prevalence of dementia and cognitive impairment is known to increase with age and is often underdiagnosed. Depending on age groups and specialty, more than one third of older patients ≥70 years old may have underlying dementia but diagnosis in the acute setting is often complicated by concurrent presence of delirium where many of these patients may also have underlying dementia (27, 28). Despite including both cognitive impairment and/or dementia, the prevalence in our study population was relatively low. Other surrogates for cognitive impairment such as impairment in ADL could serve as a useful surrogate for frailty and cognitive impairment (29). However, another study using hospital database similarly found prevalence of dementia in 7.5% of hospitalized older patients (30). The top three discharge diagnoses were delirium, pneumonia and urinary tract infection. Pneumonia incidence is more frequent in patients with dementia, and accounts for 25% of hospitalization (30, 31). These patients are at an increased

TABLE 5 Association of high Hospital Frailty Risk Score (HFRS), severe frailty and malnutrition with readmission (30 and 90-days), in-hospital mortality, cost and length of stay.

	Outcome	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
		p value	*p* value
Severe frailty (CFS) + High HFRS + malnutrition (reference: severe frailty + high HFRS)*	In-hospital mortality	0.795 (0.361–1.747)	0.725 (0.323–1.630)
		0.568	0.436
	Readmission within 30 days	1.515 (0.869–2.643)	1.618 (0.916–2.858)
		0.143	0.097
	Readmission within 90 days	1.455 (0.839–2.522)	1.513 (0.865–2.645)
		0.182	0.147
		Coef. (95% CI)	Coef. (95% CI)
	*Total Cost (Log transformation)	**0.441 (0.169–0.713)**	**0.473 (0.204–0.742)**
		0.002	**0.001**
	*LOS (Log transformation)	**0.486 (0.201–0.770)**	**0.513 (0.232–0.795)**
		0.001	**0.000**
High HFRS + malnutrition (reference: high HFRS)	In-hospital mortality	**2.142 (1.220–3.760)**	**1.906 (1.070–3.394)**
		0.008	**0.029**
	Readmission within 30 days	1.269 (0.891–1.808)	1.390 (0.963–2.007)
		0.186	0.079
	Readmission within 90 days	0.985 (0.708–1.371)	1.078 (0.765–1.520)
		0.929	0.666
		Coef. (95% CI)	Coef. (95% CI)
	*Total Cost (Log transformation)	−0.023 (−0.187–0.142)	0.068 (−0.095–0.232)
		0.785	0.413
	*LOS (Log transformation)	0.018 (−0.152–0.187)	0.105 (−0.065–0.274)
		0.839	0.226
Severe frailty (CFS) + malnutrition [reference: severe frail (CFS)]	In-hospital mortality	**2.209 (1.440–3.389)**	**2.149 (1.391–3.322)**
		0.000	**0.001**
	Readmission within 30 days	1.341 (0.997–1.804)	1.326 (0.981–1.791)
		0.053	0.066
	Readmission within 90 days	1.132 (0.860–1.492)	1.137 (0.858–1.505)
		0.377	0.371
		Coef. (95% CI)	Coef. (95% CI)
	*Total Cost (Log transformation)	−0.110 (−0.244–0.023)	−0.048 (−0.181–0.085)
		0.105	0.478
	*LOS (Log transformation)	−0.102 (−0.239–0.035)	−0.048 (−0.185–0.089)
		0.144	0.493

Adjusted for age, gender, and ethnicity.
*Multivariate linear regression using logarithm transformation.
Bold values indicate statistically significant differences between groups ($p < 0.05$).

risk of recurrent pneumonia and increased mortality (30, 31). One third of our old-old participants had a discharge diagnosis of delirium. Previous studies showed that delirium may be prevalent in almost half of hospitalized older patients with dementia (32).

One third of the patients had severe frailty defined by CFS but only one fifth had high HFRS. HFRS is derived from ICD-10 codes whereas CFS better reflects function, ADL and mobility (22, 33). The combination of both screening tools which measured different aspects with malnutrition in our study population was associated with increased LOS and cost, but either one with malnutrition, only with inpatient mortality. At least mild/moderate frailty based on CFS was prevalent in three quarters of hospitalized patients with dementia and/or cognitive

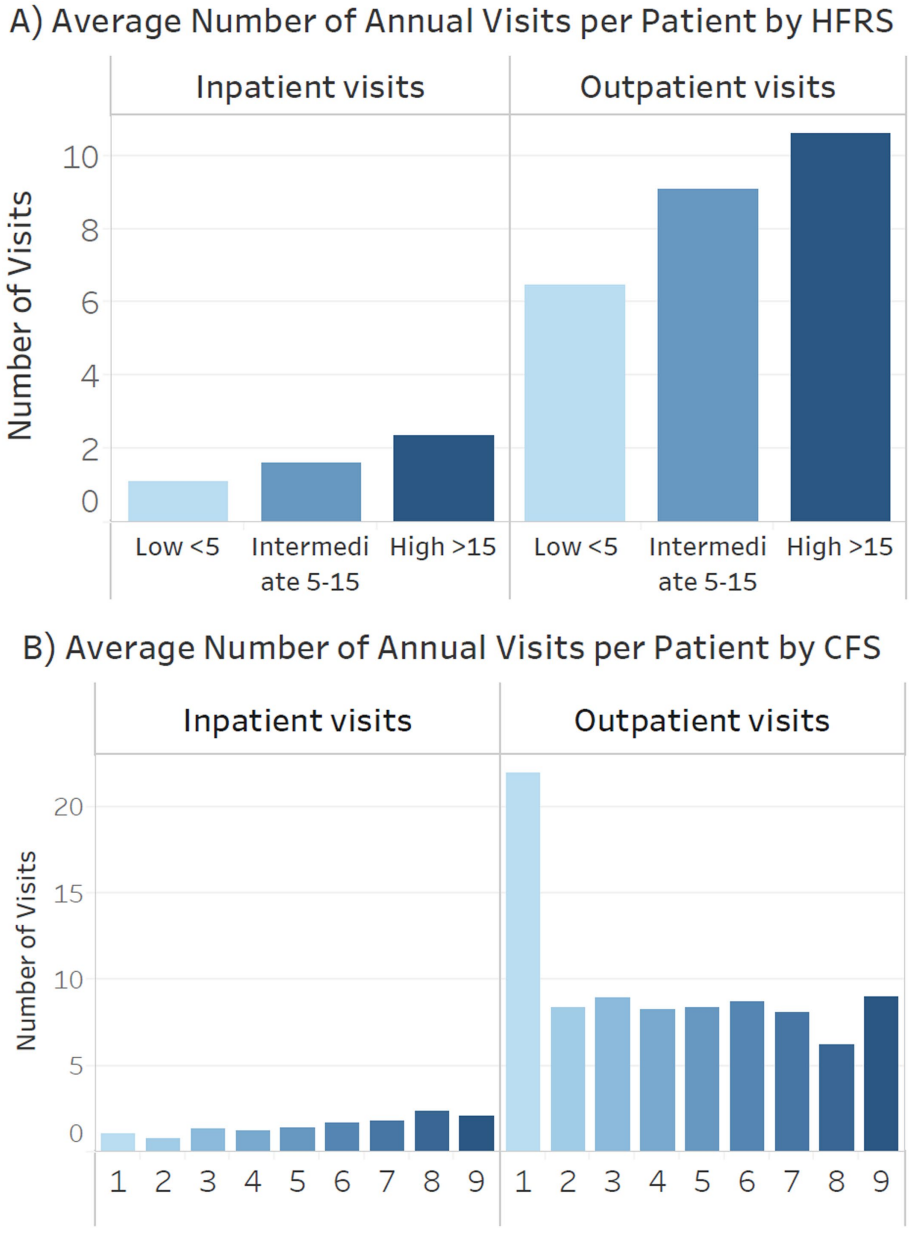

FIGURE 5
Annual inpatient admissions and outpatient visits by **(A)** Hospital Frailty Risk Score (HFRS) **(B)** clinical frailty scale (CFS).

impairment. The prevalence of frailty in patients with dementia in the acute care setting is reported to be between 50.8 and 91.8% (34). The cost and LOS were significantly higher in the frail patients. Unlike other studies which showed that old age was associated with greater healthcare utilization, our study showed that young-old cohort with intermediate or mild/moderate and high or severe frailty incurred higher costs and longer LOS (35, 36). Besides increased inpatient and 30-days mortality in the old-old, other reasons for shorter LOS and lower cost may be that a large proportion of patients aged 75 years or older in this institution are cared for by geriatricians. A prior study showed that patients under geriatricians' care had lower LOS and incurred reduced costs (20). An observational study from US acute hospitals, where the mean age of study participants was 82.5 years, reported a significant association of patients with a comorbid diagnosis of dementia with longer LOS, higher mortality, but lower costs and fewer procedures (37). This was attributed to communication issues, less intense care and administrative delays.

More than one third of the old-old in our study population were malnourished. Hospitalized patients are usually complex with high morbidity. In addition, PLWD often experience difficulties in meal preparation, have higher prevalence of anorexia of aging, swallowing difficulties, polypharmacy, mobility issues or access to food (38). Our findings are similar to a recent meta-analysis by Arifin et al. which reported a prevalence of 32.52% and a further 46.80% at risk of malnutrition (4). Borda et al. similarly reported a prevalence of 28.7% amongst those with mild dementia, and greater functional decline over 5 years in those who were malnourished (3). Malnutrition is a well-recognized modifiable risk factor for dementia, frailty, disability and mortality. It is associated with reduced quality of life, sarcopenia,

increased morbidity, and accelerated decline in both cognition and frailty (3, 17, 39, 40). While most older adults get screened for malnutrition in the hospital and long-term care setting (16), they may not be routinely screened in primary care or memory clinic. Good practice guidelines on dementia should incorporate nutrition screening in older patients at every healthcare encounter (16). The 2024 ESPEN guideline on nutrition and hydration in dementia recommends routine screening for malnutrition and dehydration, elimination of potential causes, oral nutritional supplement to improve nutrition status, and adequate social support (38).

Diagnosis of dementia is associated with double the risk of mortality (30). The prevalence of inpatient mortality in patients with dementia and/or cognitive impairment was 7.8%, which was significantly lower than other studies which showed prevalence as high as 24.3% (30). However, the old-old patients in our study with terminal illness had an in-patient mortality rate of 61.5, and 17.4% in those with severe frailty and malnutrition. Patients with severe frailty had four times higher odds, and those with terminal illness had forty times higher odds for in-patient mortality. The presence of malnutrition in those with high HFRS or severe frailty was associated with a 2-fold increase in the odds of in-patient mortality compared with those without malnutrition.

The readmissions rates, especially in the mild/moderate to severe frailty and/or high HFRS and malnourished old-old group were increased where up to two-thirds were readmitted at 90 days and slightly more than one third at 30 days. Both high HFRS and severe frailty were associated with more than double the risk of 30- and 90-days readmission, with high HFRS showing the greatest risk of 90 days readmission. The association was also significant for mild/moderate or intermediate frailty. Almost three quarters of our study population were assisted or dependent on ambulation, feeding and toileting prior to hospital admission. Our findings are in keeping with a systematic review by Ma et al. comprising of 19 studies which showed 30-day readmission rates were between 7 to 35% in persons living with dementia (41). Management of patients with dementia and/or cognitive impairment is complex due to concurrent presence of multimorbidity, functional consequences, behavioral problems, polypharmacy, food refusal and increasing dementia severity (36, 42–44). In addition, this group of patients are particularly susceptible to delays in diagnosis and management, hazards of hospitalization and possible even ageism (45). PLWD who are hospitalized may often feel isolated, may be subjected to repetitive monitoring and endless tests, barrier in communication or sensory impairment may lead to emotional trauma, lack of sleep and restraints may further accelerate functional decline and delirium risk (12).

Although we know that 'Less is More' in patients with advanced dementia or frail, the medications, laboratory and radiology cost were higher in the high HFRS, and severe frailty group (33, 46). With increasing severity of frailty, outpatient visits did not reduce and those with terminal illness still had 9 visits/year. The young-old incurred higher costs. Another study from the same institution showed that healthcare utilization was significantly higher in the young-old group in the last 12 months of their life (47). Yorganci et al. showed that both rates and LOS of unplanned hospital admissions are higher in the last 12 months of their life (48). Documentation of advanced dementia in the clinical notes has also shown to be associated with shorter LOS, lower use of intensive care unit and 30-day mortality (49). Other good practices include improving the uptake of advanced care planning and deprescribing drugs with lowest benefit to harm ratio through STOPP&START or Beers criteria (50, 51).

Studies have shown that despite initiatives to improve healthcare professionals' knowledge and other healthcare initiatives in managing patients with dementia, barriers to optimal care delivery in this group persists due to competing priorities and emphasis on managing chronic diseases, social isolation, lack of adequate care transition including caregiver education and handover, fragmentation of care and lack of multidisciplinary collaboration (52, 53). In multi-ethnic countries like Singapore, language barrier, social determinant of health and cultural differences may also have an impact on healthcare utilization. A recent narrative review by Browne et al. which included 16 studies from the USA, Taiwan, Australia, Canada, Sweden, Japan, Denmark and The Netherlands showed that factors such as reduced mobility, increased numbers of chronic conditions, inadequate discharge panning and interdisciplinary collaboration, socio-economic inequalities amongst different ethnic groups and behavioral symptoms increased readmission rates (54). It is believed that 20–40% of these admissions could be avoided.

While the strength of our study includes a robust database, with comprehensive data on nutrition, healthcare utilization and frailty, there are several limitations which warrants mention. First, the accuracy of data obtained is subject to accuracy of diagnosis, documentation and coding. The prevalence of dementia and/or cognitive impairment was much lower in our study population. However, this may not undermine our findings on the association of frailty with increased healthcare utilization, and mortality. Second, we had no information on other factors which may impact healthcare utilization and mortality such as severity of illness, advance care planning (ACP), social determinants of health, caregiver education, discharge destination and community resources. ACP has been associated with reduced healthcare utilization and LOS (55). In addition, while we had no information on staging of dementia, but dependent in ADL and frailty could serve as a surrogate measure. One third of these patients were classified under severe frailty category who may be approaching end of life, where discussion on goal-directed care and appropriate care could have an impact on overall outcome. Third, we have no information on intervention and compliance with nutritional supplements which could have had an impact on the outcome. Last, CFS is based on records obtained at the emergency department triage. While emergency department healthcare professionals have been trained to record premorbid CFS 2 weeks prior to admission, there may be a recall bias in the setting of acute illness or there may not be any caregivers available. CFS is able to measure the dynamic nature of frailty whereas HFRS is a measure of comorbidities and may not change with change in functional status. Combining both with malnutrition was associated with worst outcomes in patients with dementia and/or cognitive impairment.

Our study highlights that health administration data is a crucial resource for determining healthcare quality and outcomes. This study provides essential insights for policymakers and healthcare providers responsible for establishing standards for future care of patients with dementia and cognitive impairment, frailty and malnutrition. Implementing health system approaches like the Age-Friendly Health System's 4 M's (What Matters, Mobility, Medication, and Mentation) (35), including enhancing health care professionals knowledge on person centered care for dementia and conducive environment design should be a priority in every healthcare institution (53). Integration of

frailty and nutrition assessments in healthcare encounters, alongside comprehensive geriatric assessment and consideration of social determinants of health, discharge destinations, caregiver education, and seamless care transitions, is vital for managing readmissions, healthcare utilization, and mortality rates (56, 57). By adopting a goal-directed care approach, we can better address the needs of this vulnerable population and improve their overall health outcomes, indirectly enhancing healthcare utilization.

Assessment and management of patients with dementia require a multifaceted approach which includes early detection of frailty, malnutrition and other geriatric syndromes, and these individuals will benefit from comprehensive geriatric assessment and targeted interventions. Future research should focus on exploring the impact of advanced care planning, social determinants of health, malnutrition intervention such as oral nutrition solution, caregiver education, discharge planning, and care transition on readmission, healthcare utilization, and mortality in these patients. This will further clarify the factors influencing these outcomes and inform strategies to better manage care for individuals with dementia and cognitive impairment.

Conclusion

This study underscores the significant impact of frailty, and malnutrition in patients with dementia and/or cognitive impairment on healthcare utilization, readmission rates, and mortality. These findings highlight the essential need for healthcare providers to prioritize assessments of frailty and nutrition in patients with dementia or cognitive impairment to better manage their health outcomes. Given the severe vulnerability of this population segment, addressing these issues through regular frailty assessments and integrating data from administrative records can lead to more informed care decisions and resource allocation.

Data availability statement

The datasets presented in this article are not readily available because data on cost will not be available for sharing. Requests to access the datasets should be directed to mdcram@nus.edu.sg.

Ethics statement

The studies involving humans were approved by NUHS Research Office NUH-RNR-2024-0034. As anonymous data was obtained from the database, informed consent was not required.

Author contributions

RM: Conceptualization, Data curation, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. YD: Formal analysis, Methodology, Software, Writing – original draft, Writing – review & editing. SK: Conceptualization, Data curation, Methodology, Project administration, Writing – original draft, Writing – review & editing. DM: Methodology, Project administration, Resources, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

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.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2025.1540050/full#supplementary-material

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frontiers | Frontiers in Medicine

TYPE Review
PUBLISHED 26 February 2025
DOI 10.3389/fmed.2025.1494645

OPEN ACCESS

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RECEIVED 11 September 2024
ACCEPTED 20 January 2025
PUBLISHED 26 February 2025

CITATION
Wang Z, Shi R and Moreira P (2025) Post-stroke dysphagia: identifying the evidence missing. *Front. Med.* 12:1494645. doi: 10.3389/fmed.2025.1494645

Post-stroke dysphagia: identifying the evidence missing

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Dysphagia is a high-profile dysfunction that often occurs after a stroke, with a prevalence of 50%–80%. Post-stroke dysphagia (PSD) often leads to serious complications such as pneumonia and malnutrition, reducing the quality of life and leading to poor prognosis or even death. PSD causes these adverse physical and psychological impairments to patients, which becomes a challenge for both patients and physicians. This review intends to contribute to the international debate on evidence-based options on Stroke Rehabilitation and to better understand the need for further research on PSD and summarizing evidence on some of the most relevant topics and clarifying its clinical practice value for Neurology, stroke rehabilitation experts, rehabilitation and nursing staff, as well as patients. The article identifies and discusses the gaps in knowledge on PSD and elaborates on current evidence concerning the selection of subjects, examination methods, patient data extraction and analysis, classification of stroke lesions, details of dysphagia, significance of results, and neuromodulation of dysphagia, from the perspective of rehabilitation physicians. The review identified a set of 10 points and parameters for the international debate on PSD, namely: stroke onset, cognitive impairment, feeding method, contrast medium, swallowing reflex delay, swallowing evaluation form, division of brainstem, multiple stroke sites, basal ganglia lesions and neuromodulation techniques. The article explores available evidence on factors associated with dysphagia and stroke site. Although there is plenty of evidence exploring the correlation between stroke site and swallowing disorders, the pathophysiological mechanisms between the two are complex, and expert interpretations of the evidence and clinical opinions vary on which swallowing abnormalities occur. The study generates evidence on current evidence-based options on Stroke Rehabilitation and a better understanding of the need for further research on Post-Stroke Dysphagia. Taking a patient-centric approach, the ultimate goal is to generate on how can available evidence influence policy or practice or research or clinical education. The article provides a structured discussion clarifying key points on the relationship between stroke lesions and swallowing dysfunctions and contributes to clarifying the gaps in evidence to further improve the quality of life of the patients suffering from Post-Stroke Dysphagia.

KEYWORDS

dysphagia, stroke, rehabilitation, healthcare management, geriatrics, elderly

Introduction

Dysphagia is a high-profile dysfunction that often occurs after a stroke, with a prevalence of 50%—80% (1). Post-stroke dysphagia (PSD) can lead to serious complications such as pneumonia and malnutrition, reducing the quality of life and leading to poor prognosis or even death. PSD causes these adverse physical and psychological impairments to patients, which becomes a challenge for both patients and physicians; there is plenty of evidence (2–5) exploring the correlation between stroke site and swallowing disorders. However, the pathophysiological mechanisms between the two are complex, and expert interpretations of the evidence and clinical opinions vary on which swallowing abnormalities occur (6).

Understanding the relationship between stroke site and dysphagia is crucial for developing targeted rehabilitation strategies, improving patient outcomes, and guiding clinical decision-making.

This commentary intends to contribute to the international debate on evidence-based options on Topics in Stroke Rehabilitation and to better understand the need for further research on PSD. We discuss this by summarizing data on some of the most relevant topics and clarifying its clinical practice value for Neurology, stroke rehabilitation experts, rehabilitation and nursing staff, as well as patients. From the perspective of rehabilitation physicians, we will elaborate our views on the selection of subjects, examination methods, data extraction, and analysis, classification of stroke lesions, details of dysphagia and the significance of the result.

We organize our discussion in a set of 10 points briefly introduced in Table 1 and expanded below.

TABLE 1 Factors associated with dysphagia and stroke site.

Parameter	
Stroke onset	Within 1 month (5, 7–9)
	Months (2, 10)
Cognitive impairment	Exclusion (5, 7, 37)
	Inclusion (9)
Feeding method	Oral feeding (5, 11, 12)
	Alternative feeding (9, 13–16)
Contrast medium	Semisolid 4 mL bolus (4), 3 mL of water (5)
	2 mL of thin liquid, 5 mL of thin liquid, and 5 mL of curd-type yogurand (12)
	Five types substances (water, puree, banana, soft diet, and cookies) (11)
	5 mL of food puree A and liquid B (3)
Swallowing reflex delay	Delayed if the food was kept inside the mouth for a long period (50)
	Triggered after the bolus reached the pyriform sinuses (5, 54)
	Triggered after the bolus reached the valleculae (55)
Swallowing evaluation form	FOIS (17–19)
	MBSImp (7, 8, 20, 21)
	FEES (75, 76)
Division of brainstem	Brainstem and non-brainstem (22–24)
	Pontine, midbrain, medulla oblongata (8, 25)
	Dorsolateral and medial medulla oblongata (26–28)
Multiple stroke sites	Exclusion (4, 5, 11)
	Inclusion (7, 12, 21, 64)
Basal ganglia lesions	Prolonged pharyngeal bolus transit time (29)
	Severe dysphagia (30, 31)
	Controlled swallowing movements (7)
	prolonged oral transit time (32, 33)
Neuromodulation techniques	5 Hz rTMS (77), 10 Hz rTMS (79)
	5 Hz PES (78)

Methods

The authors performed a narrative review approach and analysis applying the Scale for the Assessment of Narrative Review Articles–SANRA. The PUBMED, EMBASE and COCHRANE databases were searched for English-language articles, with search terms described as stroke, lesion, dysphagia, swallowing disorders, relationship. Reviews, clinical studies, and case reports were used to contextualize the findings. Articles should meet any of the following criteria:

- Patients with CT/MRI-confirmed stroke;
- Swallowing assessment was completed;
- Stroke sites were categorized;
- The relationship between stroke and swallowing was statistically analyzed;
- Articles involving studies in children (age <18 years) or animals were excluded.

The selection of the period and database is ensured to be relevant to the current clinical practice and research standards. After reviewing the selected topics, two reviewers independently read the abstracts and selected relevant articles for full-text review. Data that met the inclusion criteria were extracted, tabulated, and analyzed. Finally, 81 articles were analyzed. At least two researchers read the selected articles. The researchers arranged the article by topic and created a table for analysis. These articles helped to explain the background of the findings.

Post-stroke dysphagia is a major concern for patients and medical personnel, directly impacting the patient's life and quality of life. Although researchers have conducted studies on this topic, swallowing is a highly delicate and complex motor process, making it challenging to explore the relationship between stroke and swallowing. Therefore, this paper aims to analyze previous articles, refine their findings, exclude studies with inadequate research methods, and suggest more standardized and suitable research methods for future studies.

Results

The analysis of the included articles exploring factors that may influence the relationship between stroke and dysphagia, as well as the diversity of relationships between the two. Is reflected in the following 10 points:

Point 1. The subjects included in stroke onset studies are usually selected from patients with acute stroke, that is, within 1 month (5, 7–9, 30, 34) after the onset of the stroke. Some acute stroke patients can spontaneously recover the swallowing function in a relatively short period of time; despite this tendency to recover, many stroke patients continue to have swallowing dysfunctions 1 month after stroke (35). Thus, we believe Future studies should take a broader perspective and include patients with acute stroke, and stroke patients who were also in the recovery period (2 weeks to 6 months after the onset). The recovery period is also critical for patients' rehabilitation (36), which will become more relevant for an increasing number of stroke patients. A 2020 retrospective study (2) included patients with a median stroke onset time of 2.5 month s(IQR 0.7–11.0). Significantly, this study indicates that inconsistencies in the length of stroke onset may have had an impact on the results of the study. Thus, additional research is necessary to further analyze the effect of time of onset on swallowing function using multiple regression analysis (5, 34), which seems to be a key idea to be further discussed amongst practitioners worldwide.

Point 2. Cognitive impairment and dysphagia

Most studies on dysphagia exclude patients with cognitive impairment, potentially overlooking the role of cognitive function in post-stroke dysphagia (5, 7, 37). Recent evidence (25, 33) elucidated the clinical features and lesions that contribute to delayed swallowing: lip, tongue and oropharynx correlate with the degree of cognitive impairment, and cognitive function is significantly lower in patients with delayed oral transit time. In addition, lesions in the left frontal lobe were associated with a delayed oral phase. It follows, thus, that consideration of these patients will give additional insights into the factors associated with post-stroke dysphagia and enrich symptomatic diagnosis and treatment.

A study (38) suggested that cognition is better to be considered as a mediator along with physical aspects of dysphagia. Post-stroke dementia or post-stroke cognitive impairment (PSCI) may affect up to one-third of stroke survivors (39). PSCI is closely related to swallowing dysfunctions. The normal ingestion-swallowing process is divided into the anticipatory stage (cognitive stage), oral preparation stage, oral transport stage, pharyngeal stage, and esophageal stage. The anticipatory stage is a prerequisite for oral preparation by recognizing the food's consistency, volume, temperature, and taste to predict the oral handling and routine ingestion procedures. Oral preparation refers to the stage from the intake of food to the completion of mastication, mainly the ingestion and processing of food. These two periods can be controlled at will and stopped at any time. Additional evidence (40) reported that during the anticipatory stage of swallowing, sensory stimuli related to food play an important role in the behavioral and neurophysiological aspects of swallowing. The primary sensorimotor cortex (S1M1) is an important area for executing swallowing as well as integrating sensorimotor information related to swallowing preparation. Cognitive function influences the intake and delivery of bolus during the oral preparation and oral phases. Previous studies have reported that the worse the cognitive function, the higher the prevalence of swallowing dysfunction in stroke patients, and the better the cognitive function, the greater the probability of patients achieving oral feeding (41, 42). Therefore, although available evidence already suggests that PSCI should be prioritized for swallowing assessment and rehabilitation and may be crucial for developing targeted interventions and rehabilitation strategies (43), further evidence is necessary.

Point 3. Inclusion of nasogastric tube-fed patients

Similarly, in a large number of studies on PSD, some patients who have not yet ingested orally are excluded (5, 11, 12); We believe that stroke patients fed by nasogastric tubes should be included, especially to obtain a mechanism for the inability to feed via mouth at different stroke lesions, making the results more valuable for clinical practice. Several studies have included patients requiring tube feeding, considered impaired oral intake and tube feeding as specific signs of dysphagia, and analyzed the site of brain lesions associated with them (9, 13–16). A study in particular (42) identified that 73% of patients who died had alternative alimentation. Therefore, for the patients with PSD who had alternative feeding methods, evidence allows to arugue that clinical intervention should actively implement intervention measures as soon as possible. Those who have not yet eaten orally are not unable to do so but are unable to do so safely. Hence the need for additional evidence on when to add to clinical procedures followed by Rehabilitation professionals on when to perform VFSS on these patients to assess their safety in eating and formulate a rehabilitation plan for when and how to begin oral intake assuming the best swallowing treatment is swallowing.

Point 4. Consistency and volume of swallowing contrast solvents

In this point we want to contribute to the international debate by pointing out that there is evidence to sustain the argument that consistency and volume of the swallowing contrast solvent are not the same; hence, the possibility that this may contribute to the different findings between stroke site and VFSS findings, which may be more one-sided for some studies using only one solvent (4, 5). For example, a particular study (12) used the three substances: 2 mL of thin liquid, 5 mL of thin liquid, and 5 mL of curd-type yogurand to patients swallow, suggesting that increasing the bolus viscosity may reduce the aspiration severity. Another study (11) used five types substances (water, puree, banana, soft diet, and cookies) to test the relationship between stroke lesions and aspiration. On other study (3) took 5 mL of food puree A and liquid B as the solvents for VFSS, and no correlation was observed between the pharyngeal response time (PRT) and lateralization of brain lesion. We believe that Future studies should include liquids with different volumes, such as 7 mL, 10 mL, or with different viscosity of thin liquids or thickened liquids, thus providing details of what properties cause swallowing disorders at different stroke areas, or what kind of swallowing disorders occur at the same stroke area with different properties, thus making new available evidence for practice more comprehensive.

Hence, the decision of using iodine contrast medium liquids is usually determined based on the results of clinical evaluation (44–47). In principle, the amount of liquids is from less to more, from thick to thin, as thin liquids or water may delay the swallowing reflex in patients. Sensory feedback plays an important role in the oral stage, for patients with bucco-facial apraxia after stroke, the sensory pathway of the oral proprioceptor and tactile mechanoreceptor into the central nervous system (CNS) is damaged and the signal transmission is delayed, while effective coordination of these jaw and tongue movements depends on the integration of information from a dense array of sensory receptors in the oral (48), thus leading swallowing uncoordinated and prone to aspiration as water is easily deformable and flowable. Some studies advocated that thickened liquids have a shorter laryngeal vestibule closure time than thin liquids and that thickened liquids do not increase pharyngeal residue and are safer for patients (46, 49–51). Thus, to what extent examining the different properties of the liquids may refine the association between stroke lesions and swallowing dysfunctions details and may provide guidance for the development of a swallowing dysfunction diet? This is another topic we humbly suggest for further international debate and additional generation of evidence. When it comes to the accuracy of dysphagia assessment, it is important to mention flexible endoscopic evaluation of swallowing (FEES), it is only considered the other gold standard (next to VFSS). The sensitivity of the FEES to aspiration and pharyngeal residue was higher than that of the VFSS as derived from the Giraldo (75) study. The sensitivity of the two tests to detect premature pharyngeal spillage was similar. However, it should be taken into account that the FEES may be more uncomfortable for the patient to use, as well as the 'white screen' at the moment of swallowing, not being able to see the video during swallowing is also a disadvantage of the FEES. The Espitalier (76) study demonstrated that the VFSS allows better quantification of pharyngeal residues. The VFSS is relatively more commonly used in the clinic, and objective evaluation of the observation form becomes crucial.

Point 5. Interpretation of VFSS and swallowing reflex delay

The interpretation of VFSS varies significantly, the more controversial point being the determination of the swallowing reflex delay. Some studies do not have a clear definition of swallowing reflex delay. For example, one study (52) considers the food kept inside the mouth for a long period as a delay, whereas in other study (53) patients with a latency time >3 s were defined as having a delayed swallowing reflex. Additional International evidence reports different definitions of delayed swallowing reflex. Two relevant studies (5, 54) defined it as liquid remaining in the pyriform sinuses for more than 0.1 s (3 frames) before swallowing. Another study (55) generates evidence to argue that the delayed swallowing reflex is triggered 1 s after the bolus reached the valleculae. However, the hyoid elevation is often used as a marker for the initiation of the swallowing reflex under VFSS. Hence, two other studies (56, 57) define the starting point of pharyngeal swallowing as the head of the bolus reaching the lower edge of the mandibular branch; the end point is the last video frame from the head of the bolus to the vallecular sinus, until the hyoid bone is raised. Thus, further research is required to clarify how the swallowing reflex delay may need to be unified through the frame by frame analysis of VFSS to reduce the risk of misjudgment.

Point 6. Patterns of PSD abnormalities

There are a variety of patterns of PSD abnormalities, with most studies including aspiration and laryngeal penetration, clearance or prevalence of oral cavity residue, vallecular residue, pharyngeal residue after one swallow, and swallowing reflex delay (2, 4, 11, 12). However, generation of evidence could be more comprehensive. Several studies (7, 8, 20, 21) applied the Modified Barium Swallow Study Impairment Profile (MBSImP) to analyze the relationship between brain lesion location and 17 physiological aspects of swallowing. The results of these studies suggest that laryngeal elevation, anterior hyoid excursion, laryngeal vestibular closure, and pharyngeal residue can be associated with lesioned voxels or regions of interests. It seems like when the VFSS videos were analyzed using the MBSImP, the results were more accurate and could include more details of swallowing dysfunctions. As a standardized scale, MBSImP (58) information gained from the examination is critical for identifying and distinguishing the type and severity of swallowing impairment, determining the safety of oral intake, testing the effect of evidence-based frontline interventions, and formulating oral intake recommendations and treatment planning. The swallowing movement is one of the most complex and unique movements of the body, involving sequential activation and deactivation of the oropharyngeal muscles. It involves the contraction of the submental muscle groups, the upward and forward movement of the hyoid bone, the epiglottis folding back, the contraction of the pharyngeal constrictor muscles, the opening of the cricopharyngeal muscle and other important steps to ensure the closure of the airway and the opening of the esophagus.

MBSImP includes 17 important physiological elements of the swallowing process. We purpose therefore, for the international debate on the matter, that Future studies should undertake scoring details within the MBSImp (59–61), such as lip closure, soft palate elevation, and laryngeal elevation can all be used to enrich the system for the relationship between stroke lesions and swallowing dysfunction patterns. Laryngeal elevation plays two important roles: one is to achieve airway protection; the other is to pull the cricopharyngeal muscle forward and promote its opening. Once the laryngeal elevation is abnormal in time or degree, it will cause bolus to enter the airway through the throat, resulting in aspiration. Therefore, we can argue that each step of swallowing deserves special specific attention in Future research.

Point 7. Brainstem stroke and dysphagia

There are several studies on the relationship between brainstem stroke and dysphagia. However, the division of brainstem sites varies, with some divided into brainstem and non-brainstem (22–24), others into pontine, midbrain, medulla oblongata (8, 25), and others into dorsolateral and medial medulla oblongata (26–28). In this context, we argue that we need more international evidence to allow for a better understanding of the implications when we divide brainstem into the midbrain, pons, medial medulla, and lateral medulla. The brainstem, as a vital center containing various important reflex centers, is connected to the III-XII cranial nerves and is a relay station for the superior and inferior afferent pathways. The brainstem swallowing center is located in the medulla

oblongata, called the medullary central pattern generator (CPG) (62), and when it is damaged, the nucleus tract solitaries-dorsal swallowing group (NTS-DSG) is unable to synthesize the afferent information and affects the initiation of swallowing patterns; the medulla-ventral swallowing group (VLM-VSG) fails to distribute swallowing drive to the various motor nerve pools associated with swallowing, affecting the motor drive of cranial nerves V, VII, IX, X, and XII; excessive salivation; difficulty in laryngeal elevation; retention of food in the vallecula sinus; aspiration; or even in severe cases, not knowing how to swallow; and cricopharyngeal achalasia. On study (10) concluded that the medullary region governs the rhythmic pattern of pharyngeal swallowing; whereas the pontine region transmits the received peripheral information upwards to the CNS. Furthermore, another study (63) uncovered the importance of the primary motor cortex-parabrachial nuclei and nucleus tractus solitary (M1-PBN-NTS) neural circuit in driving the protective effect of electroacupuncture (EA) stimulation at the CV23 acupoint (EA-CV23) against swallowing dysfunction and thus reveal a potential strategy for dysphagia intervention. Therefore, evidence on best approaches to achieve more precise analysis of swallowing dysfunction seems necessary. Hence, new appropriate therapeutic approaches could be subsequently applied to the stroke lesions.

Point 8. Multi-site stroke and swallowing outcomes

Some studies (4, 5, 11) have excluded multiple stroke site (2 or more). While other studies (7, 12, 64) incorporate multi-site stroke cases, summarizing that lesions located in supratentorial and infratentorial regions (i.e., multiple sites) were predictive of poor swallowing outcomes, mainly including primarily the sensorimotor integration areas and their corresponding white matter tracts. We believe that stroke patients with multiple lesions should be included in Future studies, as multiple lesions may exacerbate swallowing disorders. One study (21) suggested that the combination of lesioned regions might also determine the recovery of swallowing function. For example, combined strokes in insular and frontal regions are independent predictors of prolonged dysphagia course. More evidence on this point is required. Including such patients in Future studies may provide more mechanisms for CNS control of swallowing, as well as diverse clinical manifestations of swallowing disorders in patients, for timely detection and treatment.

Point 9. Basal ganglia lesions and silent aspiration

Different views on the characteristics of PSD caused by basal ganglia lesions have been studied (7, 9, 29–33). Basal ganglia lesions are significant independent factors for swallowing reflex delay. One other study (65) has reported that basal ganglia infarction leads to impaired dopamine metabolism and decreased production of substance P (SP), decreased SP concentration in the pharynx and tracheal mucosa, and decreased pharyngeal and cough reflexes, making it very easy for aspiration to occur. More importantly, it is a silent aspiration (especially when it occurs during sleep, without coughing), which leads to aspiration pneumonia. The swallowing and coughing reflexes are the defense mechanisms that prevent the inhalation of pharyngeal contents into the lower respiratory tract. It has also been reported (66) that the basal ganglia infarction is associated with attention deficit and bucco-facial apraxia. Therefore, disuse is also one of the important features of basal ganglia lesions, and damage to the basal ganglia area not only has a delayed pharyngeal transmission time but may also trigger dangerous silence aspiration. Silence aspiration is extremely harmful to patients and deserves our attention for further investigation in Future studies as also proposed in recent studies (67–70) and following recent trends in healthcare research (71–74).

Point 10. Neuromodulation techniques for dysphagia

Neuromodulation techniques for dysphagia are commonly used, such as pharyngeal electrical stimulation (PES), repetitive transcranial magnetic stimulation (rTMS), etc. For the site and intensity of stimulation is the focus of experts' research. Twelve patients with dysphagia were randomly divided into 5 Hz rTMS, 1 Hz rTMS, or PES for neuromodulatory technology intervention (77). The patients were assessed by VFSS before and 60 min after the intervention to calculate the penetration aspiration scores (PAS). In the 5 Hz rTMS and PES intervention groups were shown to stimulate cortical excitation within the swallowing motor system, 1 Hz transcranial magnetic stimulation resulted in cortical inhibition, and the 5 Hz frequency stimulates the motor function of the pharyngeal mucosa, which led to a better induction of excitability in the cerebral swallowing motor cortex. Due to the small number of patients, it was not possible to compare the effectiveness between the different interventions. And PAS, which is not a perfect assessment of swallowing function. Future larger studies are needed to further explore the efficacy of these neuromodulatory treatments for dysphagia. Suntrup-krueger (78) found that PES could improve swallowing function by promoting increased secretion of neuropeptide substance P in saliva and enhancing the swallowing reflex by studying 20 healthy volunteers who underwent PES for 10 min 5 Hz. However, the experiment did not perform VFSS in patients with dysphagia as a means of demonstrating that PES improves swallowing function. Du's study concluded that 10 Hz rTMS is effective in the treatment of PSD, and that the C3 (left the central) area [86] may be a target for rTMS in the treatment of PSD. However, the assessment of swallowing function was missing the esophageal phase, as well as there was no detailed explanation for the C3 region. Therefore, larger and precise studies on the neuromodulation of dysphagia are needed in the future to explore innovative therapeutic targets to improve efficacy.

Conclusions

This literature review contributes to the international debate on evidence-based practice for recognizing the relationship between stroke and dysphagia. The review identified ten key points and parameters related to PSD, including stroke onset, cognitive impairment, feeding method, contrast medium, swallowing reflex delay, swallowing evaluation form, division of brainstem, multiple stroke sites, basal ganglia lesions, and neuromodulation techniques. The main findings emphasize the need to standardize the assessment of dysphagia using VFSS, improve the classification of stroke lesions, and refine the relationship between stroke and dysphagia to guide treatment.

Regarding evidence-based practice in identifying the relationship between stroke and dysphagia. Summarized with the following:

- Standardize the process of assessing dysphagia with the VFSS;
- Make the classification of stroke lesions more complete;

- Refine the relationship between stroke and dysphagia to make the results more informative and thus guide treatment.

For clinical practice, it provides a comprehensive framework for evaluating and managing post-stroke dysphagia. By identifying key points and parameters related to PSD, it equips clinicians with a more nuanced understanding of the condition, enabling them to tailor treatment plans to individual patient needs. Furthermore, the emphasis on standardizing the assessment process with VFSS and refining the relationship between stroke and dysphagia can lead to more effective interventions, reducing complications and improving patient outcomes. Ultimately, this study contributes to enhancing the overall quality of stroke care and rehabilitation, fostering a more patient-centered and evidence-based approach to managing post-stroke dysphagia.

This article also has some limitations, firstly, the article only analyzed patients whose primary disease was stroke, and did not analyze swallowing dysfunction caused by other diseases, a wider range of diseases can be included in the next step; secondly, the article only discussed the specific matters of the VFSS assessment of swallowing dysfunctions, with the development of swallowing assessment tools, the laryngoscopy, high-density surface EMG, and other instrumental assessments should be studied as well; lastly, our article only analyzed the treatments of swallowing dysfunctions of Neuromodulation techniques, and in the future, more treatments can be included in the analysis. Another limitation was that limited results are described for neuromodulation techniques, although numerous studies have been carried out in recent years, and this is because the focus of the study was set on other techniques; the number of patients described in the present review is very limited and transcranial direct current stimulation (tDCS) was not considered.

Future studies may tackle the Limitations points identified and based on clinical and imaging factors, including the selection of the study population, the distribution of stroke types, and the assessment of the details of dysphagia, and we emphasize the importance of these factors as prognostic factors. Clinicians and rehabilitation professionals should further consider the broad spectrum of mechanisms of recovery and prognosis of PSD to support the development of neuroanatomical models of PSD physiology and therapeutic approaches that address the neurophysiologic basis of PSD as well as neuromodulation techniques.

Author contributions

ZW: Conceptualization, Data curation, Investigation, Methodology, Writing – original draft. RS: Supervision, Validation, Writing – review & editing. PM: Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by Shandong Province Key Discipline of Traditional Chinese Medicine - Chinese Medicine Rehabilitation Project and Qilu Medical School Traditional Chinese Medicine Academic Heritage Project in 2023 (Grant No. 2022-JS03).

Conflict of interest

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

Publisher's note

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frontiers | Frontiers in Medicine

TYPE Systematic Review
PUBLISHED 11 March 2025
DOI 10.3389/fmed.2025.1529218

OPEN ACCESS

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RECEIVED 16 November 2024
ACCEPTED 26 February 2025
PUBLISHED 11 March 2025

CITATION
Xu Z, Zhou R, Zhou X, Zhang Z, Li Q and Wang G (2025) The current state and development trends of frailty research in diabetic patients: a bibliometric analysis. *Front. Med.* 12:1529218.
doi: 10.3389/fmed.2025.1529218

The current state and development trends of frailty research in diabetic patients: a bibliometric analysis

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Background: Diabetes mellitus is a global public health issue, often leading to organ damage, complications, and disabilities. Frailty is an age-related syndrome characterized by reduced physiological reserve and increased vulnerability to stressors, significantly affecting the prognosis of older diabetic patients. The prevalence of frailty is notably higher in older adults with diabetes than in those without. Therefore, a bibliometric analysis of research on diabetes-related frailty can provide deeper insights into the current state of this field and inform future research directions.

Methods: This study retrieved English-language publications on diabetes-related frailty from the Web of Science Core Collection (WOS) database, covering the period from 2005 to 2023. A total of 403 articles were included in the analysis. Statistical analysis and data visualization were conducted using Microsoft Excel, R Studio, VOS viewer, and Cite Space 6.3.R1. The analysis emphasized journals, authors, keywords, country collaborations, institutional collaborations, and references to elucidate trends and knowledge structures within the field of diabetes-related frailty research.

Results: The number of publications on diabetes-related frailty has been steadily increasing each year, with research predominantly focused in developed countries, particularly the United States and Europe. The University of London has emerged as the institution with the highest volume of publications, while Alan J. Sinclair has been recognized as a significant contributor to this field. Key research hotspots include the complications associated with diabetes-related frailty, epidemiology, and quality of life. Additionally, a timeline analysis of references suggests that diabetic nephropathy is currently at the forefront of research in this area.

Conclusion: This comprehensive bibliometric analysis of diabetes-related frailty research underscores the necessity for improved international collaboration to further investigate the mechanisms underlying diabetes-related frailty and to devise more effective prevention and treatment strategies. Future research should emphasize the relationship between diabetic nephropathy and frailty, as well as the development of personalized intervention programs tailored for frail diabetic patients.

KEYWORDS

bibliometrics, diabetes, frailty, Cite Space, VOS viewer

1 Introduction

Diabetes represents a significant public health challenge that poses a serious threat to human health globally, resulting in considerable socioeconomic burdens worldwide (1). It is projected that by 2045, the number of individuals living with diabetes will reach 629 million worldwide (2). Diabetes is a metabolic disorder with multiple etiologies, characterized by chronic hyperglycemia stemming from defects in insulin secretion, insulin action, or both, which leads to disturbances in carbohydrate, fat, and protein metabolism (3). Prolonged hyperglycemia can result in chronic damage and functional impairment in various organs and tissues, including the eyes, kidneys, heart, blood vessels, and nerves, thereby severely impacting patients' quality of life (4). Studies have shown that diabetes is associated with complications, disability, and frailty syndrome (5).

Frailty is a syndrome characterized by a decline in physiological function, primarily resulting from decreased physiological reserves. This decline leads to increased susceptibility to diseases, heightened vulnerability, and a diminished capacity to withstand stress, presenting as a nonspecific state (6). Currently, the concept of frailty is increasingly recognized as a multidimensional health condition, including physical frailty, cognitive frailty, psychological frailty, and social frailty (7).

Frailty is considered a novel complication in older patients with diabetes, affecting multiple systems and increasing the risk of adverse outcomes such as disability, hospitalization, and mortality (8). Furthermore, physical frailty has been demonstrated to correlate significantly with cognitive impairment, depression, and social vulnerability (9). Frailty and diabetes are two significant health issues commonly associated with aging in the older population. These conditions frequently co-occur and are becoming increasingly prevalent among older adults. As diabetes progresses and age advances, older patients with diabetes face a heightened risk of developing frailty, and the incidence of frailty is notably higher in this group. Research indicates that diabetic patients are more susceptible to frailty compared to their non-diabetic older counterparts (10). Therefore, early and timely assessment of frailty in older diabetic patients is of great clinical significance.

Research on the interplay between frailty and diabetes has received considerable attention. For example, Chhetri et al. (11) examined the current status and influencing factors of diabetes-related frailty through a longitudinal study. Shi et al. (5) investigated the effects of diabetes and frailty on mortality. Qin et al. (12) performed a meta-analysis to assess the efficacy of various exercise intervention modalities for patients with diabetes-related frailty. However, to date, there has been no notable bibliometric study assessing the knowledge mapping related to diabetes and frailty.

Therefore, this study employs bibliometric analysis to systematically examine the existing research on diabetes and frailty, with the aim of providing a comprehensive exploration of the relationships between diabetes and various aspects of frailty. This approach will help to more thoroughly grasp current research trends, the impact of the research, and scientific collaboration, to provide quantitative evidence to guide future research endeavors.

2 Methods and materials

2.1 Data sources and search strategy

In this study, all English language articles and reviews about diabetes and frailty, published between January 1, 2005, and December 31, 2023, were retrieved from the Web of Science (WOS) database on April 23, 2024. The search strategy utilized was: TS = ("diabetes mellitus*" OR diabetes* OR "diabetes disease" OR "diabetic mellitus" OR "diabetic disease") AND (Frailty OR Frail*). A total of 1,453 publications were retrieved. After independent screening and discussion by two researchers, irrelevant publications were manually removed, resulting in a final total of 403 publications related to diabetes and frailty being included in the study analysis. All retrieved publications were exported from the online database in plain text format with full records and cited references.

2.2 Data analysis

Statistical analyses were conducted using Microsoft Excel 2021 and R Studio. Visualization analyses were performed using VOS viewer and Cite Space 6.3.R1. Microsoft Excel was primarily used to collect and analyze WOS data, create histograms, and build regression models to predict publication growth trends. Data extraction and statistics, including main information, most relevant authors, most influential journals, and most globally cited documents, were conducted by the "bibliometrix" package in R Studio (13).

VOS viewer software demonstrated remarkable potential in the field of bibliometric analysis. Its generated visual maps, characterized by their simplicity and comprehensibility, effectively transform complex information into intuitive knowledge frameworks, providing researchers with unprecedented insights (14). VOS viewer was utilized to create visual analyses of author collaboration maps and keyword clustering maps.

Cite Space facilitates identifying the developmental progress and trends within research fields by analyzing titles, abstracts, and references (15). Cite Space 6.3.R1 was used to visually analyze international collaboration maps, institutional collaboration network maps, dual-map overlays of journals, keyword burst maps, and reference timeline maps. In these visual knowledge maps, different nodes represent elements such as countries, institutions, authors, or cited references; links between nodes represent relationships such as collaboration, co-occurrence, or co-citation; the colors of the nodes and lines represent different years. Centrality measures the importance of nodes in the paths connecting any pair of nodes in the network. The parameters for Cite Space were set as follows: (1) the time span was divided from January 2005 to December 2023, with each slice representing 1 year; (2) term sources = title/abstract/author keywords/keywords plus; (3) node types (one at a time) and selection criteria (top 50 objects); (4) selecting the top 10% most cited items from each slice.

3 Results

3.1 Publications

This study utilized the citation report and citation deduplication functions within the Web of Science (WOS) database to analyze 403

articles related to diabetes and frailty published between 2005 and 2023. An Excel-generated publication trend chart, illustrated in Figure 1, reveals a consistent year-on-year increase in publications from 2005 to 2017, followed by a marked surge from 2017 to 2023, culminating in the highest publication count of 57 in 2023. To further elucidate the publication volume trend, a linear trend line equation was established: y = 3.3158x−11.947, where y signifies the annual publication volume and x represents the year. The coefficient of determination (R^2) for this model is 0.8967. Figure 2, generated by bibliometrix, provides a comprehensive overview of the analyzed articles, which collectively cite 13,509 references, with an average publication year of 5.31 years. Each article received an average of 26.94 citations, and the annual growth rate of publications was 17.77%.

3.2 Countries and regions

Through the use of Cite Space, it was found that between 2005 and 2023, research on diabetes and frailty was conducted across 50 countries. As illustrated in Figure 3, the size of each label reflects the volume of publications, indicating that the top three countries in terms of publication output are the United States, the United Kingdom, and China. The purple circles outside the labels represent centrality, where a larger centrality signifies greater influence, suggesting that countries with strong centrality in this topic area include the United Kingdom, the United States, Spain, Germany, China, and France. Table 1 presents statistics on the top 10 countries in terms of publication volume.

3.3 Institutions

A total of 288 institutions have engaged in research on diabetes and frailty. Figure 4, generated by Cite Space, illustrates that the University of London leads in publication volume in this field, followed by Hospital Universitario de Getafe and King's College London. Notably, institutions with higher centrality, indicating significant influence, include Harvard University, Hospital Universitario de Getafe, Assistance Publique-Hôpitaux de Paris, University of London, and King's College London; the lines in the figure denote collaborative relationships between institutions. Table 2 ranks institutions that have published more than 10 articles, with a total of 7 institutions having published more than 7 articles, among which there are 2 each from the United Kingdom, France, and Spain, and one from the United States.

3.4 Analysis of authors

Figure 5, generated by bibliometrix, presents the top 10 most prolific authors who have published articles in the field of diabetes and frailty between 2005 and 2023. Alan J. Sinclair is the author with the highest volume of publications in this field, having published a total of 35 articles. According to Price's Law for calculating the minimum number of publications for highly productive authors ($m = 0.749$), the minimum publication threshold for highly productive authors is calculated to be 4.4 papers. Consequently, the minimum number of publications for authors displayed by VOS viewer is set at 4, and after manual deduplication, the result is shown in Figure 6. Four distinct color clusters are formed, where nodes of the same color belong to the same cluster, and the shorter the distance between nodes, the stronger the association. Figure 7, generated by bibliometrix, is a dynamic publication chart over time for the top 10 authors, where the size of the circle represents the number of documents, and the depth of the color indicates the total number of citations. Figure 8, generated by VOS viewer, is a heat map of author activity in this field, where the deeper the color of the node label, the stronger the research impact, and Alan J. Sinclair is the most influential author in this domain.

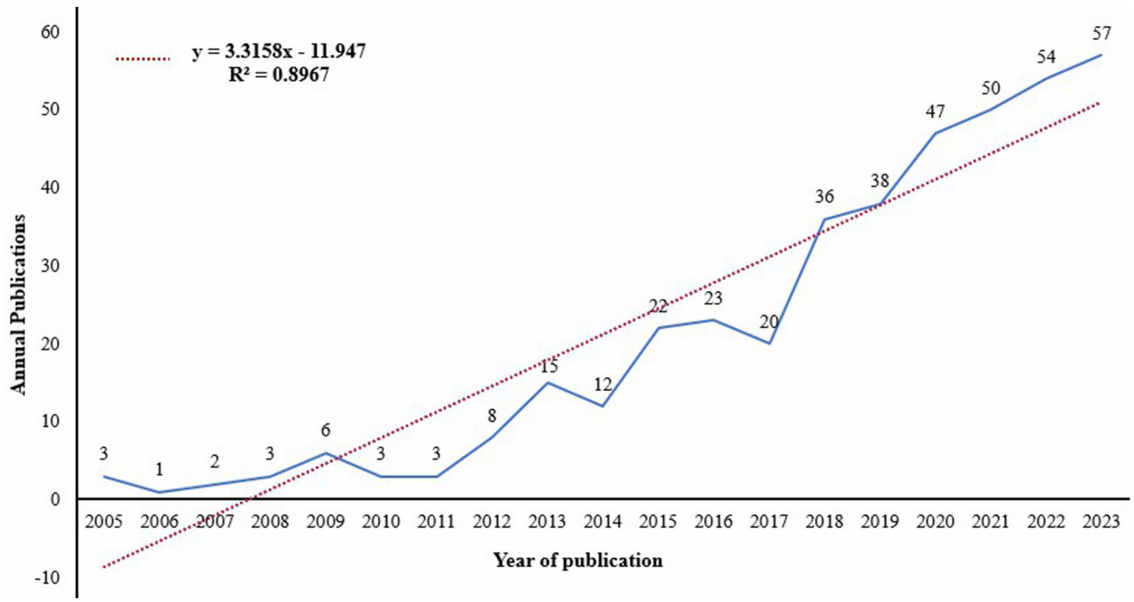

FIGURE 1
Rend of publication volumes for clinical practices on diabetes and frailty from 2005 to 2023.

3.5 Journals

Bibliometrix analysis was employed to identify influential journals in the field of diabetes and frailty by examining citing and cited journals. As shown in Table 3, among the citing journals, Journals of Gerontology Series A-Biological Sciences and Medical Sciences ranks highest, followed by BMC Geriatrics, with impact factors of 5.1 and 4.1 respectively; the journal with the highest impact factor among citing journals is Journal of the American Medical Directors Association. Among the cited journals, Diabetes Care leads the list, followed by J Gerontol A-Biol and J Am Geriatr Soc, with impact factors of 16.2, 5.1, and 6.3 respectively; the journal with the highest impact factor among cited journals is the Lancet. A dual-map overlay created through Cite Space is presented in Figure 9. The left side, labeled in blue, represents the research fields of citing journals, while the right side, labeled in purple, represents the research fields of cited journals. The lines connecting the labels on either side indicate the citation relationship between citing and cited journals in their respective research fields. Two prominent green intersecting curves in the diagram suggest that journals in the fields of Molecular Biology, Genetics, and Health Nursing Medicine are more likely to be cited by journals in the field of Medicine, Medical, Clinical.

Description	Results
MAIN INFORMATION ABOUT DATA	
Timespan	2005:2023
Sources (Journals, Books, etc)	165
Documents	403
Annual Growth Rate %	17.77
Document Average Age	5.31
Average citations per doc	26.94
References	13509
DOCUMENT CONTENTS	
Keywords Plus (ID)	923
Author's Keywords (DE)	705
AUTHORS	
Authors	2071
Authors of single-authored docs	11
AUTHORS COLLABORATION	
Single-authored docs	12
Co-Authors per Doc	6.6
International co-authorships %	27.05
DOCUMENT TYPES	
article	310
article; proceedings paper	3
review	90

FIGURE 2
Key information summary of all articles from 2005 to 2023.

3.6 Keywords

A frequency analysis of the top 100 keywords appearing in the research field of diabetes and frailty was conducted using VOS viewer. After deduplication and merging of similar keywords, a threshold of 7 occurrences was set, leading to the selection of 107 high-frequency keywords for further analysis. As illustrated in Figure 10, keywords with the same color denote that they belong to the same cluster, resulting in the formation of five distinct clusters within this domain. By analyzing the relationships among these keywords in Figure 10, three prominent research themes can be identified: complications, epidemiology, and quality of life. The red cluster focuses on complications associated with frailty, such as sarcopenia, obesity, cardiovascular disease, and insulin resistance, emphasizing their role in the mechanisms of frailty in diabetic patients. The blue cluster primarily addresses glycemic control issues in type 2 diabetic patients,

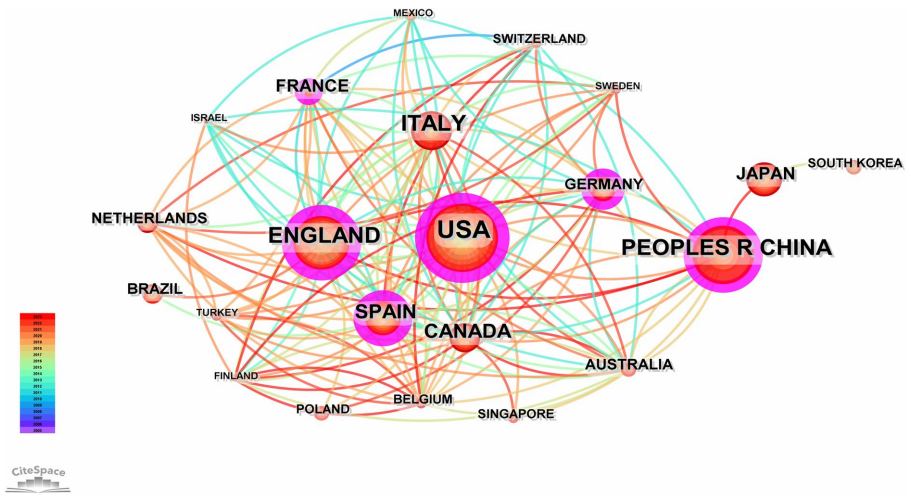

FIGURE 3
Network map illustrating international collaboration among countries publishing articles related to diabetes and frailty between 2005 and 2023.

TABLE 1 Top 10 countries publishing articles on diabetes and frailty from 2005 to 2023.

Rank	Country/Region	Counts, *n* (%)	Centrality
1	USA	99 (24.57)	0.26
2	England	75 (18.61)	0.33
3	China	61 (15.13)	0.15
4	Italy	55 (13.65)	0.03
5	Spain	45 (11.17)	0.21
6	Canada	34 (8.44)	0.04
7	Japan	30 (7.44)	0.07
8	France	28 (6.95)	0.14
9	Australia	18 (4.47)	0.02
10	Germany	16 (3.97)	0.18

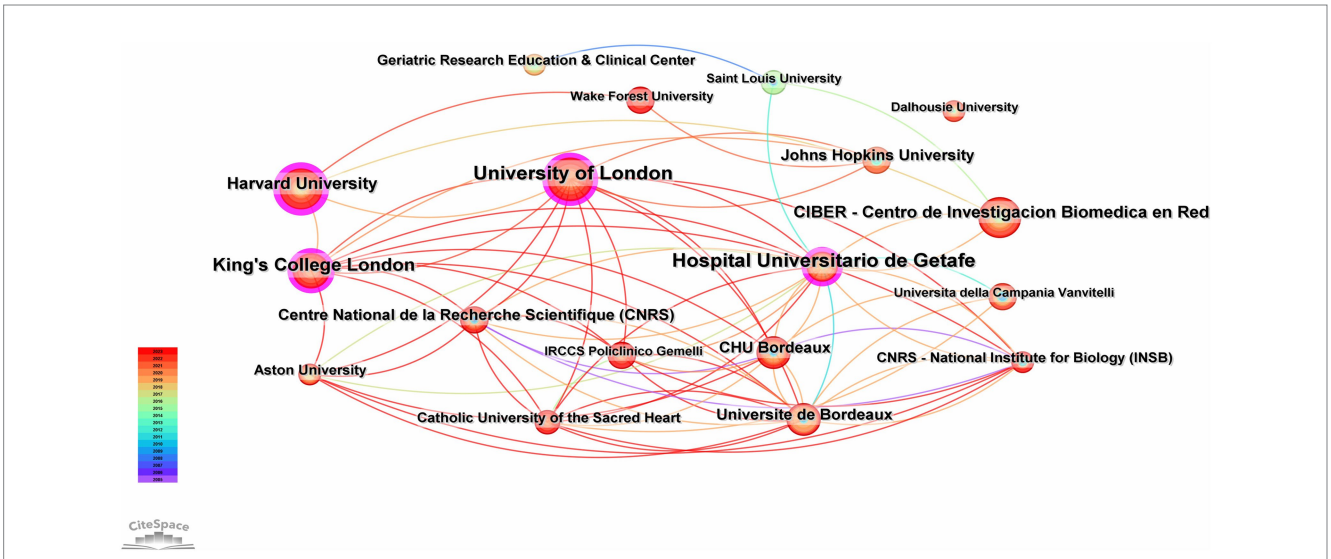

FIGURE 4
Collaboration network analysis of institutions involved in clinical practices related to diabetes and frailty from 2005 to 2023.

TABLE 2 Institutions with more than 10 publications on diabetes and frailty from 2005 to 2023.

Rank	Institutions	Count	Centrality	Country/Region
1	University of London	22	0.16	England
2	Hospital Universitario de Getafe	21	0.17	Spain
3	King's College London	19	0.13	England
4	Harvard University	15	0.22	USA
5	CIBER—Centro de Investigación Biomédica en Red	15	0.09	Spain
6	Universite de Bordeaux	12	0.02	France
7	CHU Bordeaux	12	0.01	France

including hypoglycemia and hyperglycemia, and is concentrated on related complications such as cardiovascular disease and nephropathy. The green cluster pertains to epidemiological studies, featuring key terms like mortality, prediction, and risk factors. Both the yellow and purple clusters concentrate on quality of life but from different perspectives. The yellow cluster predominantly looks at dementia, cognition, and falls, which are related to personal health status, whereas the purple cluster emphasizes management, outcomes, and care, focusing on the overall management aspects of quality of life.

Figure 11 presents the keyword heat map, where brighter colors indicate higher frequencies of keyword occurrence, and closer proximity to the center suggests higher citation and co-citation frequencies. Table 4 lists the top 10 most frequent keywords, with "Frailty" and "Diabetes" being directly relevant to the topic, while

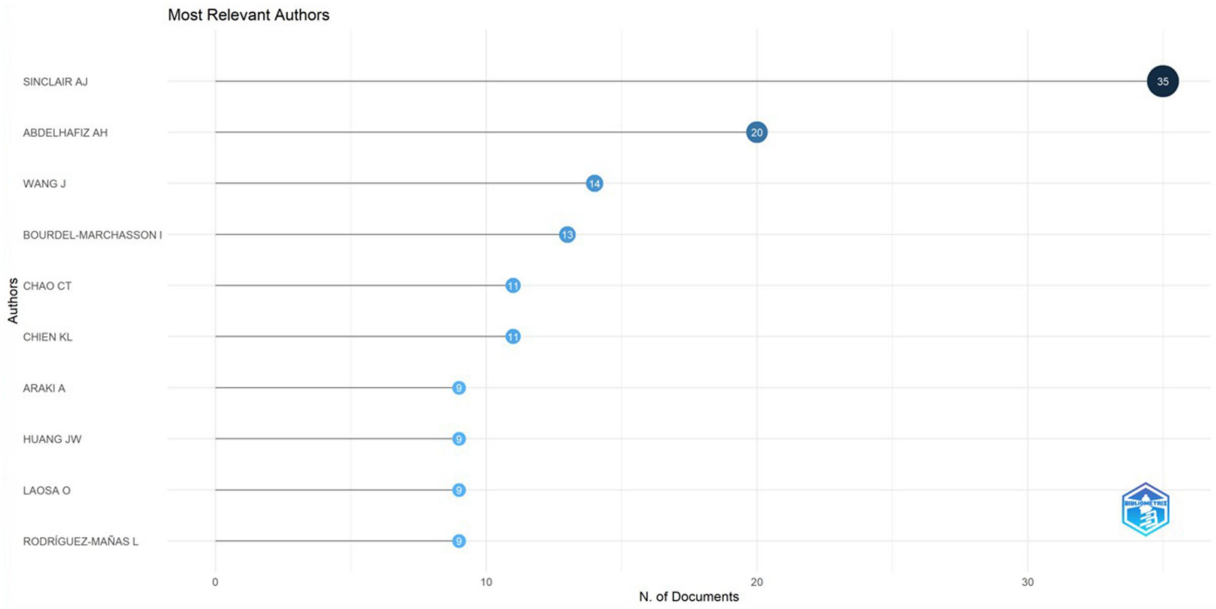

FIGURE 5
The top 10 most relevant authors in the field of diabetes and frailty.

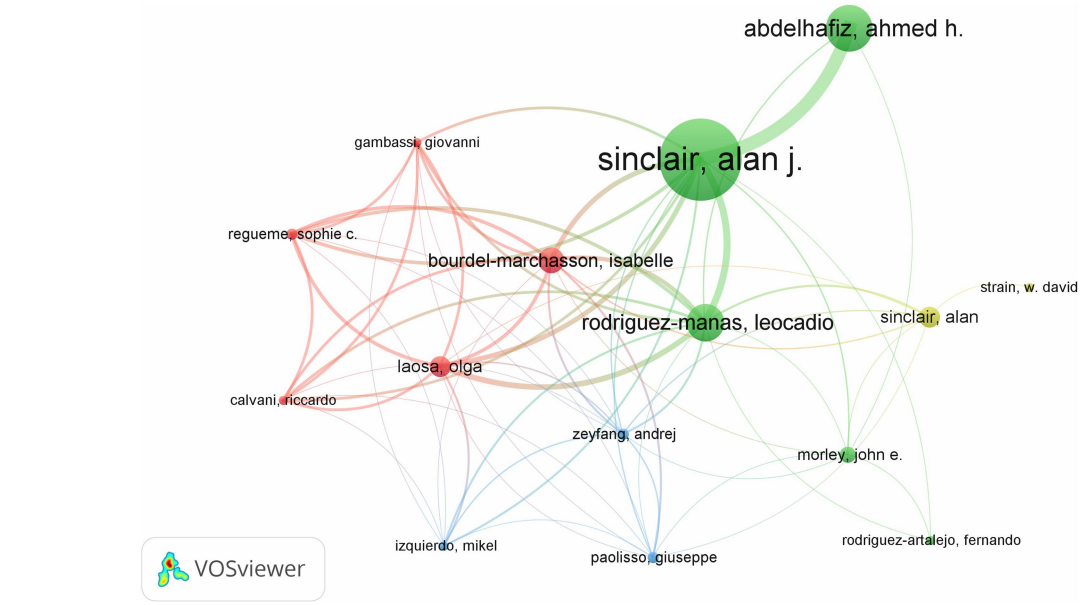

FIGURE 6
Network map depicting the collaborations among authors in the field of diabetes and frailty research.

"Older adults" and "Mortality" have high frequencies, indicating past hot topics. To pinpoint the current frontiers in research, a burst keyword map was generated by Cite Space, as shown in Figure 12. Six burst keywords are listed on a timeline, with "cognitive impairment" being the strongest burst term, and "index" representing the primary focus of current research, potentially exerting significant influence on future studies.

3.7 Co-cited references

By conducting a timeline view analysis of co-citation relationships among references using Cite Space, we can gain insights into the thematic evolution and developmental trajectory of research in diabetes and frailty. Clustering analysis of references based on keywords yields the results depicted in Figure 13. On the

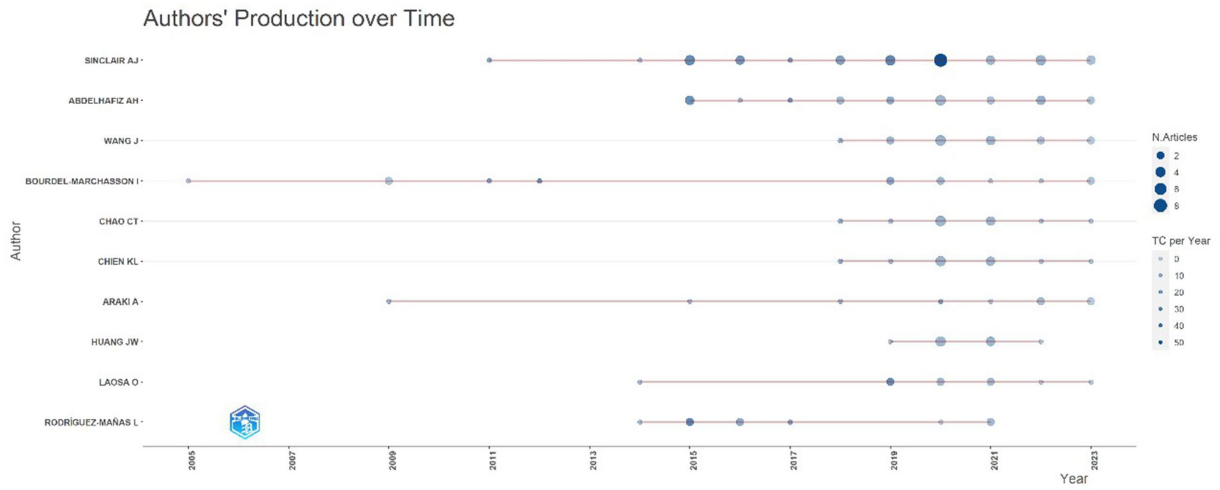

FIGURE 7
Dynamic chart showing the publication volume over time for the top 10 authors with the highest number of publications.

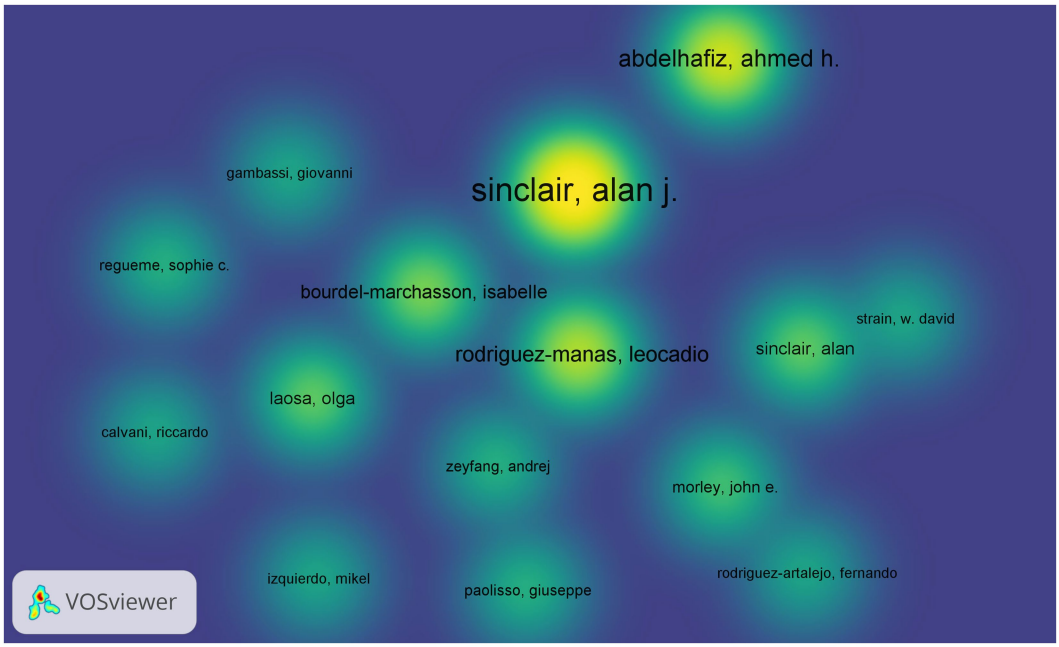

FIGURE 8
Heat map representing the activity of authors in the field of diabetes and frailty research.

left side of Figure 13, the co-citation relationships among references are displayed over time, with the size of the nodes representing the frequency of citation and the color of the nodes indicating the time of citation. On the right side, the clustering outcome is presented, where clusters with labels positioned closer to the front denote greater cluster strength. "#Sarcopenia" emerges as the most significant cluster, and "#Diabetic Kidney Disease" has continued to be a focus up until 2023. Statistical analysis was conducted using bibliometrix, Table 5 enumerates the top 10 most cited reference documents.

4 Discussion

4.1 Main information

Over the past 19 years, the number of academic articles in the field of diabetes and frailty has generally shown an upward trend. Before 2017, the growth in publication volume was relatively gradual, but post-2017, there was a significant increase. This growth could be attributed to the increasing attention of researchers to the study of diabetes and frailty. As shown in Figure 7, in 2017, three of the top 10

TABLE 3 Top 10 journals cited in research on diabetes and frailty.

Rank	Citing journals	Count	2023IF	Rank	Cited journals	Count	2023IF
1	Journals of Gerontology Series A-Biological Sciences and Medical Sciences	17	5.1	1	Diabetes Care	1,626	16.2
2	BMC Geriatrics	15	4.1	2	J Gerontol A-Biol	937	5.1
3	Journal of Nutrition Health & Aging	14	5.8	3	J Am Geriatr Soc	887	6.3
4	Journal of the American Medical Directors Association	14	7.1	4	J Am Med Dir Assoc	676	7.6
5	Journal of Diabetes and its Complications	13	3	5	New Engl J Med	558	158.5
6	Geriatrics & Gerontology International	12	3.3	6	Lancet	475	168.9
7	Aging Clinical and Experimental Research	10	4	7	Age Aging	324	6.7
8	Diabetic Medicine	10	3.5	8	J Nutr Health Aging	318	5.8
9	Journal of the American Geriatrics Society	10	6.3	9	JAMA—J Am Med Assoc	318	120.7
10	Diabetes Research and Clinical Practice	9	5.1	10	Diabetes Res Clin Pract	291	5.1

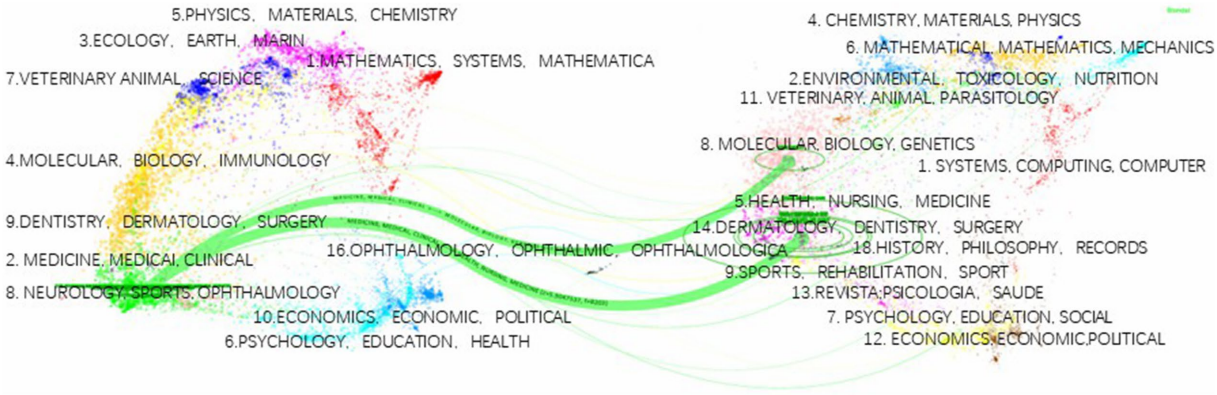

FIGURE 9
Dual-map overlay spectrum of journals in the field of clinical practice research on diabetes and frailty.

authors in terms of total publications emerged. By 2018, this number increased to six, with three authors publishing their first academic articles in this field in 2018.

The analysis of Figure 7 also indicates that international collaboration is predominantly concentrated among high-income Western countries, with the United States having the highest publication volume and the United Kingdom exhibiting the highest centrality, making it the most influential country in this field. These two countries have jointly led research in this area. Among middle- and low-income countries, only China has conducted relevant research and has closely collaborated with high-income countries. This is likely because China has the highest number of people with diabetes globally, necessitating more research efforts in this area. In Asia, only China, Japan, Singapore, and South Korea have engaged in limited collaboration (16).

In summary, research in the field of diabetes and frailty is uneven, with middle- and low-income countries lacking in contributions to this field. Asian countries should engage in more collaborative efforts and strengthen cooperation with high-income Western countries to improve research levels and international influence. Figure 9 depicts the primary research areas of citing and cited journals in this field, indicating the flow of research outcomes and showing that the primary research areas have a narrow coverage. Future research needs to span multiple disciplines, and there is considerable potential for further exploration.

This study aims to comprehensively analyze the literature in the field of diabetes and frailty, explore research hotspots, and identify future development trends by clustering keywords and references to recognize the key research areas and directions. Analyzing highly cited literature revealed that three out of the top 10 references focus on frailty

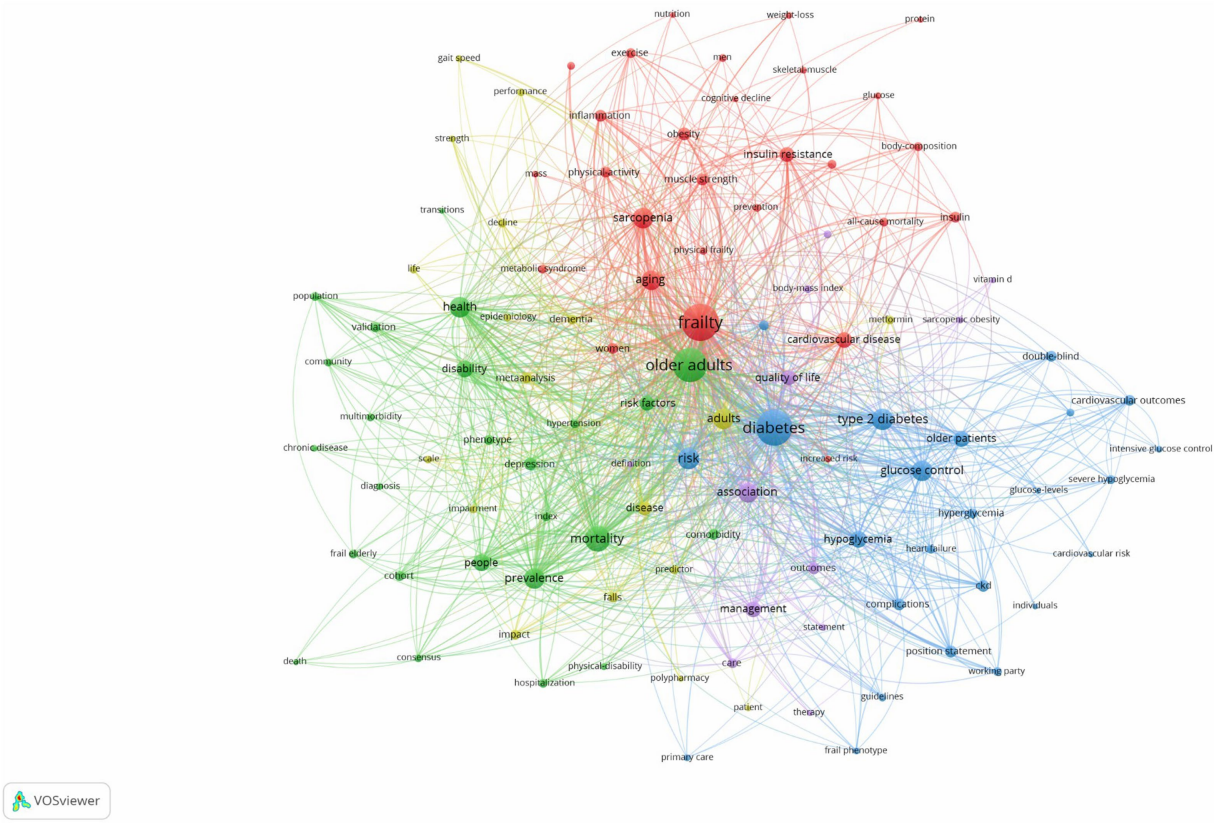

FIGURE 10
Cluster map of keywords in the field of diabetes and frailty research.

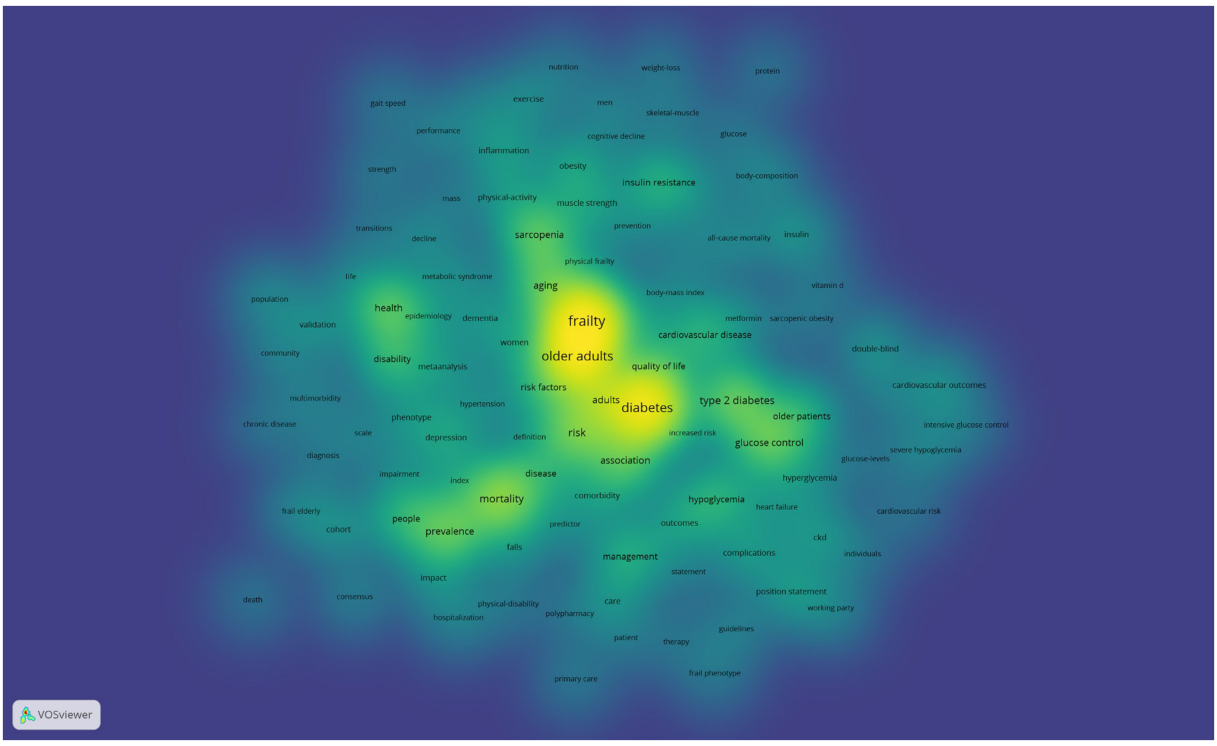

FIGURE 11
Heat map of keywords in the field of diabetes and frailty research.

assessment, indicating inconsistencies in assessing frailty among diabetic patients. Additionally, three articles study the correlation between frailty and sarcopenia in diabetic patients, highlighting a research hotspot in this field, which is confirmed by clustering analysis results.

4.2 Variations in frailty assessment among diabetic patients

Current research on diabetes and frailty primarily focuses on type 2 diabetes, with limited studies addressing frailty in older individuals with type 1 diabetes. Type 1 and type 2 diabetes are distinct diseases, and their relationship with frailty may differ. At present, the management of frailty in older individuals with type 1 diabetes is inferred from studies on type 2 diabetes patients (17). Although the American Diabetes Association (ADA) guidelines provide some guidance on the management of older individuals with type 1 diabetes, there is a need for further research to explore the unique aspects of frailty in this population and develop tailored management strategies (18). Therefore, future studies should focus on investigating the specific characteristics of frailty in older individuals with type 1 diabetes and the corresponding management approaches.

Frailty assessment should be completed for all older diabetic patients as part of diabetes management (19). Early identification of frailty, assessment of frailty levels, and timely intervention can significantly delay the progression of diabetes and its related complications (20). Some experts recommend routine comprehensive geriatric assessments (CGA), including frailty assessments, for the older diabetic population (21). To date, there is no unified, universally accepted concept or "gold standard" for the measurement of frailty internationally (22). The most commonly used assessment tools are the frailty phenotype (FP) proposed by Fried and the frailty index (FI) proposed by Rockwood (23).

FI is a direct application of the cumulative deficit frailty index, which quantifies frailty through an index composed of several equal-weighted deficits from different domains, including physical, functional, psychological, and social aspects (24). Additionally, the Montreal Cognitive Assessment (MoCA) and the Subjective Cognitive Decline Questionnaire (SCD-Q) are commonly used for the assessment of cognitive frailty (25, 26).

TABLE 4 Top 10 high-frequency keywords in the field of diabetes and frailty research.

Rank	Keywords	Counts
1	Frailty	234
2	Diabetes	220
3	Older adults	193
4	Mortality	105
5	Type 2 diabetes	81
6	Risk	80
7	Prevalence	74
8	Adults	73
9	Sarcopenia	71
10	Glucose	70
10	Health	70

4.3 Impact of complications on frailty in diabetic patients

Older diabetic patients are prone to chronic long-term complications, which cause neurological, vascular, and metabolic abnormalities, leading to muscle fatigue (27). This results in muscle weakness, slow gait, and eventually frailty. Research indicates that sarcopenia is the core pathological basis of frailty, with skeletal muscle loss playing a mediating role in its development (28). Chronic hyperglycemia in diabetic patients can inhibit the growth of skeletal muscle cells, leading to muscle atrophy. Additionally, insulin resistance can hinder glucose uptake by skeletal muscle cells, resulting in muscle contraction disorders, causing sarcopenia, and accelerating the onset of frailty (29). Therefore, early identification of sarcopenia in diabetic patients is crucial for reducing the incidence of frailty syndrome.

Frailty is closely associated with the readmission rates, mortality, and postoperative complications in older cardiovascular disease

FIGURE 12
Burst keyword chart in the field of diabetes and frailty research.

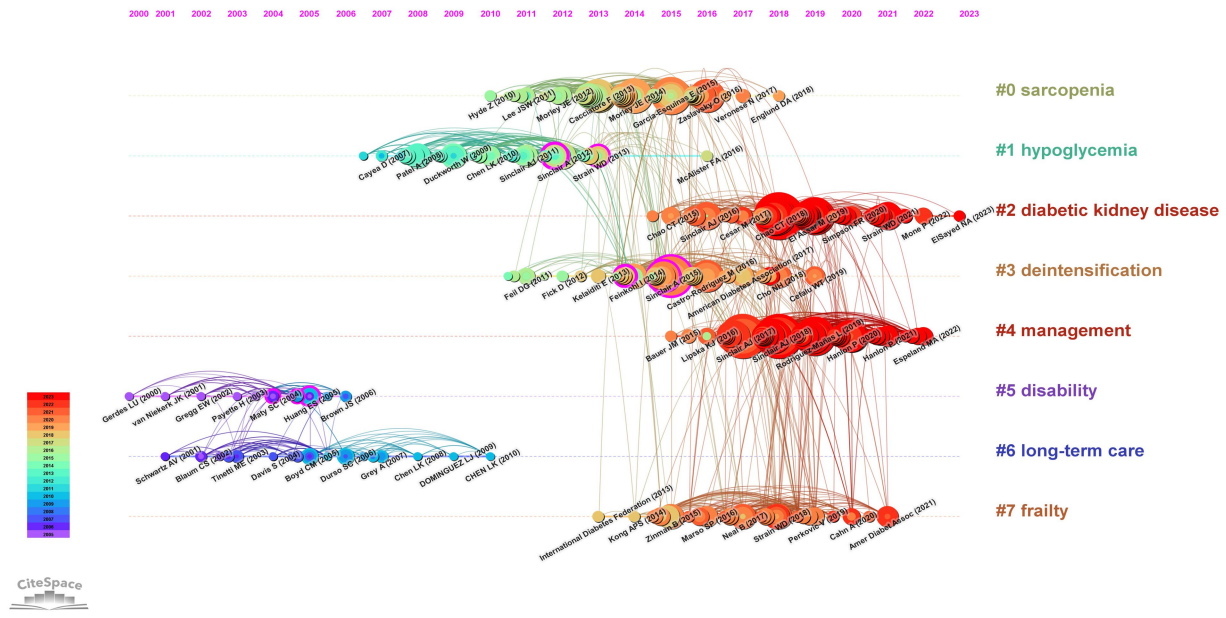

FIGURE 13
Timeline view of referenced literature in the field of diabetes and frailty research.

TABLE 5 Top 10 most cited references in the field of diabetes and frailty research.

Rank	Title	Times cited
1	Frailty in older adults: evidence for a phenotype (66)	199
2	Frailty in elderly people (67)	50
3	Frailty, sarcopenia and diabetes (68)	45
4	A global clinical measure of fitness and frailty in elderly people (69)	44
5	Diabetes and risk of frailty and its potential mechanisms: a prospective cohort study of older adults (70)	42
6	Accelerated loss of skeletal muscle strength in older adults with type 2 diabetes (71)	38
7	Frailty and sarcopenia – newly emerging and high impact complications of diabetes (72)	38
8	Clinical frailty and long-term mortality in elderly subjects with diabetes (73)	37
9	Prevalence of frailty in community-dwelling older persons: a systematic review (74)	37
10	Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes (75)	37

(CVD) patients, serving as a significant predictor of adverse clinical events and outcomes. The occurrence and development of CVD and frailty mutually reinforce each other, sharing similar pathogenesis (30, 31). Frailty predicts poor prognosis in cardiovascular disease patients, often leading to a reduced ability to respond to external stimuli and increasing the likelihood of various adverse clinical events (32). Hence, healthcare providers should emphasize the screening and early assessment of frailty in older CVD patients. Prompt and effective targeted interventions for frail patients can help reduce or delay the occurrence of severe adverse outcomes.

4.4 Epidemiological studies on frailty in diabetic patients

Current research on diabetes and frailty primarily focuses on the older population. Due to differences in geographic location, research environments, and frailty assessment tools, the reported prevalence rates vary widely, ranging from 7.5 to 56.7% (29, 33). A meta-analysis revealed that the global prevalence of frailty among older diabetic patients in the community is as high as 20.1%. In Europe, North America, and South America, the prevalence rates are 21.7, 24.9, and 22.1%, respectively, with Asia having the lowest at 14.3% (34). This indicates that the incidence of frailty among older diabetic patients is relatively high. In addition, multiple studies on older diabetic patients have found that the prevalence of frailty is higher in women than in men (33, 35). Therefore, early screening and intervention for frailty should be integrated into diabetes care for the older to prevent and mitigate its adverse effects.

Frailty is closely associated with various adverse health outcomes in diabetic patients, including hospitalization, disability, and death. Frailty can increase the risk of hospitalization and mortality in diabetic patients and significantly elevate the risk of disability (36, 37). However, the underlying mechanisms linking

frailty to adverse health outcomes in diabetic patients remain unclear. Frailty may be closely related to reduced physical activity, leading to poor prognosis (38). Additionally, increased inflammation and coagulation abnormalities during frailty may exacerbate the microvascular effects of diabetes, thereby increasing the incidence of complications, hospitalization rates, and mortality (39).

Biological studies show that both depression and frailty in the older are associated with vascular lesions, white matter changes, elevated levels of tumor necrosis factor, and interleukin-6 (40). Moreover, frailty itself implies a decline in physiological function, limited daily activities, and increased caregiving needs. When patients perceive changes due to frailty, they may experience an identity crisis and increased physical and psychological stress, thereby raising the risk of depression (41). Frailty can accelerate the progression of diabetes. Research indicates that elevated serum levels of soluble receptor for advanced glycation end-products (sRAGE) can predict mortality in frail older individuals (42).

4.5 Quality of life in frail diabetic patients

Compared to non-diabetic individuals, diabetic patients exhibit decreased cognitive abilities and face an increased risk of dementia and mild cognitive impairment (43). Although diabetic patients can effectively control blood glucose levels and prevent complications through strict self-management, cognitive decline may reduce their ability to self-manage. The concept of cognitive frailty refers to the coexistence of physical frailty and mild cognitive impairment in the absence of dementia or other pre-existing neurological conditions (44, 45). For patients with diabetes, the occurrence of cognitive frailty may further exacerbate the challenges of self-management, as they may struggle to effectively cope with disease management and treatment while simultaneously facing declines in both physical and cognitive functions.

A survey of type 2 diabetic patients over 40 years old found a significant negative correlation between frailty and self-management behaviors, particularly in diet, physical activity, and medication adherence. Frail diabetic patients are more likely to develop diabetes-related complications; studies also indicate that individuals with higher blood glucose levels are more prone to cognitive impairment, leading to difficulties with multiple and continuous medications (46, 47). Metformin, a common medication for diabetes, is supported by clinical studies for its potential benefits in extending lifespan and as an anti-aging drug (48). Pan Liu and colleagues found in a study of 422 type 2 diabetic patients over 40 years old that metformin is negatively correlated with frailty, suggesting that frailty may reduce the long-term protective effects of metformin. Early identification and intervention for frailty in diabetic patients may enhance the efficacy of metformin (49). The decline in physical activity due to frailty may also serve as a risk indicator for cognitive decline. A study found that among frail diabetic patients, those with a 4-meter walking time over 4 s exhibited significant declines in verbal fluency, indicating that gait speed could serve as a risk indicator for cognitive decline (50).

As age increases, frailty elevates the risk of adverse clinical outcomes in the older. Diabetic patients, who often have complex care needs, require special attention to frailty issues (51). Frailty is associated with an increased risk of a range of negative health outcomes in diabetic patients, including microvascular complications, impaired activities of daily living, mortality, cardiovascular events, hypoglycemia, and hospitalization. It can also predict falls and readmission in older diabetic outpatients (52, 53). Frailty in diabetic patients is linked not only to physical health decline but also to declines in psychological health and quality of life. A study indicated that frail diabetic patients had significantly lower quality of life assessments and higher severity of depressive symptoms compared to non-frail diabetic patients (54). Another study found that frail diabetic patients had higher levels of frailty, more severe depressive symptoms, and lower quality of life scores compared to non-diabetic frail individuals (55). Complications and adverse reactions to treatment in diabetic patients complicate treatment plans, making comprehensive management essential for improving their quality of life.

For older diabetic patients, frailty assessment should be a routine part of their evaluations to determine treatment plans and blood glucose control goals. The dynamic nature of frailty necessitates regular assessments, as eliminating hyperglycemia and hypoglycemia can improve frailty (56). Intensive blood glucose control targets may harm frail diabetic patients, and glucose management should focus on reducing hypoglycemia symptoms and simplifying medication regimens (57). Continuous glucose monitoring (CGM) can provide real-time, continuous blood glucose level monitoring, offering more comprehensive information on glucose fluctuations. This can help doctors formulate more personalized and precise treatment plans and enable patients to better understand their glucose patterns, enhancing their glucose management awareness and self-regulation capabilities (58, 59). Therefore, CGM may have significant application value in managing frail diabetic patients. In conclusion, addressing frailty in diabetic patients requires incorporating frailty assessments into routine management, developing individualized intervention plans, and optimizing comprehensive management strategies to delay frailty progression and improve patient quality of life.

4.6 Frontiers in frailty research among diabetic patients

As illustrated in Figure 13's reference timeline, Cluster #2 (diabetic kidney disease, DKD) represents the current research frontier, indicating future research directions in this field. The chronic course of diabetes often leads to microvascular complications such as diabetic nephropathy (DN), which has become increasingly relevant in the study of diabetes-related frailty (60). DKD is a progressive condition, primarily caused by diabetes, and is a form of chronic kidney disease. Clinically, it is often characterized by proteinuria and a progressive increase in serum creatinine levels (61). Current research indicates a bidirectional relationship between DKD and frailty in diabetic patients. DKD is a significant risk factor for frailty in diabetic patients, while frailty impacts the clinical outcomes and overall health status of patients with DKD (62).

A follow-up study of 322,109 newly diagnosed diabetic patients over a median period of 2.89 years revealed that those with chronic kidney disease (CKD) before diabetes diagnosis had the highest probability of developing frailty, being 2.597 times more likely than those without DKD. Diabetic patients who developed DKD post-diagnosis had a 2.137 times higher likelihood of frailty compared to those without DKD. Over time, the risk of frailty increases in those with pre-diabetes CKD, highlighting the potential significance of early frailty

intervention in the early stages of diabetes (63). Hormonal changes in diabetic patients, such as deficiencies in vitamin D, insulin-like growth factor-1, and testosterone, contribute to bone fragility and subsequent osteoporosis. A propensity score-matched study of 24,054 DKD patients and 12,027 DKD patients with osteoporosis revealed an increased risk of frailty in DKD patients with osteoporosis, suggesting a link between frailty and adverse outcomes in these patients (64). DKD can cause adverse symptoms such as headaches and limb pain, leading patients to use muscle relaxants for symptom relief. A propensity score-matched study of 11,637 long-term muscle relaxant users and 11,637 non-users among DKD patients found that prolonged use of muscle relaxants increased the risk of frailty, indicating that reducing muscle relaxant use may lower frailty risk in DKD patients (65). Most current research is correlational, predominantly cohort studies, lacking experimental studies to establish a causal relationship between DKD and frailty. Future research should focus on high-quality studies to explore this causality. The relationship between DKD and frailty is complex and bidirectional, forming a vicious cycle. Future research should emphasize interdisciplinary collaboration to explore the mechanisms between DKD and frailty and develop effective interventions tailored to the frailty characteristics of different DKD patients.

5 Limitations and future research directions

The limitations of this study include the fact that the literature search was conducted exclusively in the WOS database, which may have resulted in the omission of relevant studies that are indexed in other databases. However, due to the varying number of publications across different databases, it is not feasible to merge data from multiple sources. The analysis in this study did not involve the selection of a specific age range, resulting in variability in the age groups of the included study populations. Furthermore, there is a limited understanding of frailty across these diverse age groups. A limitation of the current study is the relatively limited focus on frailty in individuals with type 1 diabetes, as the majority of research has concentrated on type 2 diabetes. Furthermore, there is a lack of studies addressing the social and psychological dimensions of frailty in the context of diabetes. These aspects remain underexplored and represent valuable areas for future research, offering a more comprehensive understanding of frailty and its impact on diabetic patients. Addressing these gaps would provide a deeper insight into the multifaceted nature of frailty and enhance management strategies for diabetic patients, particularly those with type 1 diabetes.

6 Conclusion

This study found that the number of scholars focusing on the field of diabetes and frailty has increased year by year, with the primary research centers located in the United States and Europe. The University of London stands out as the institution with the most publications, and Sinclair AJ is identified as the most significant contributor to this research field. This study summarized the research hotspots in diabetes and frailty, focusing on frailty screening, the impact of complications on diabetic frailty patients, epidemiological studies of diabetic frailty patients, and their quality of life. The research frontier primarily concerns issues related to diabetic kidney disease (DKD). This bibliometric analysis of publications from the past 19 years in the field of diabetic frailty is of significant importance for future research.

Data availability statement

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

Author contributions

ZX: Methodology, Writing – original draft, Writing – review & editing. RZ: Conceptualization, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing. XZ: Conceptualization, Methodology, Visualization, Writing – original draft, Writing – review & editing. ZZ: Conceptualization, Methodology, Software, Writing – review & editing. QL: Conceptualization, Methodology, Software, Writing – review & editing. GW: Project administration, Supervision, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Acknowledgments

The authors would like to express their sincere gratitude to the reviewers and editor for their valuable suggestions, and to Xinxiang Medical University for its provision of resources.

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

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frontiers | Frontiers in Medicine

TYPE Systematic Review
PUBLISHED 09 April 2025
DOI 10.3389/fmed.2025.1483819

OPEN ACCESS

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RECEIVED 20 August 2024
ACCEPTED 18 March 2025
PUBLISHED 09 April 2025

CITATION
Deng B, Xu T, Deng Z, Jiang Y, Li L, Liang W, Zhang Y, Wang H, Xu Y and Chen G (2025) Efficacy of acupuncture-related therapy for postmenopausal osteoporosis: a systematic review and network meta-analysis based on randomized controlled trials.
Front. Med. 12:1483819.
doi: 10.3389/fmed.2025.1483819

Efficacy of acupuncture-related therapy for postmenopausal osteoporosis: a systematic review and network meta-analysis based on randomized controlled trials

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Introduction: To compare and analyze the clinical effects of acupuncture-related therapies for postmenopausal osteoporosis (PMOP) and propose the optimal scheme, we utilized a network meta-analysis to evaluate the therapeutic effects of various commonly used acupuncture methods for PMOP.

Methods: Randomized controlled trials of acupuncture-related therapies for PMOP were searched in eight databases (PubMed, Embase, Cochrane Library, Web of Science, China National Knowledge Infrastructure, China Science and Technology Journal Database, China Biomedical Literature Database, and Wanfang database) from January 1, 2002 to December 31, 2023. Our primary outcomes included overall clinical effectiveness rate, bone mineral density (BMD), and visual analog scale scores (VAS). The secondary outcome is adverse events. The entire process of literature screening and data analysis was conducted by 2 independent investigators.

Results: A total of 30 studies with 2,342 participants provided data suitable for analysis. We compared six interventions: manual acupuncture, electroacupuncture, acupoint catgut embedding, moxibustion, acupoint application, and warm acupuncture. The results of the network meta-analysis revealed that, when compared to conventional Western medication (CWM), multiple acupuncture therapies had a greater impact on the overall clinical effectiveness rate. Electroacupuncture combined with CWM demonstrated superior clinical effectiveness and lumbar spine BMD improvement. Moxibustion with CWM ranked highest for femoral neck BMD, while warm acupuncture showed optimal effects on Ward's triangle and trochanter BMD. Acupoint catgut embedding provided the greatest pain reduction. The most prevalent minor adverse effects included hematoma, discomfort, and scorching.

Conclusion: The results suggest that several acupuncture-related therapies, either alone or in conjunction with CWM, outperform CWM alone and may be regarded as an alternative or supplementary therapy to PMOP, though higher-quality trials are needed.

KEYWORDS

postmenopausal osteoporosis, acupuncture, the overall clinical effectiveness rate, systematic review, network meta-analysis

1 Introduction

Osteoporosis is an urgent public health threat characterized by a systemic decrease in bone mass, strength, and microarchitecture, which significantly increase the risk of fragility fractures (1, 2). Epidemiological reports highlight that osteoporosis has become a critical public health concern across Asia, Europe, and the United States due to its high prevalence, complex complications, and substantial economic burden (3–5). Among individuals over the age of 50, approximately 50% of women and 20% of men will suffer osteoporosis-related fractures (6, 7). Postmenopausal osteoporosis (PMOP) is the most prevalent form of osteoporosis and the bone disease most frequently observed in postmenopausal women (8, 9). With the loss of bone mass and the destruction of bone microstructure, patients with PMOP may experience symptoms such as back and leg pain, limb weakness, hunchback, and an increased susceptibility to fractures (10, 11). As global populations age rapidly, PMOP is poised to become a worldwide challenge, adversely affecting physical and mental health while imposing unsustainable societal costs (12–14). Current PMOP management strategies include lifestyle modifications, pharmacological interventions, and rehabilitation therapies (15). The most commonly employed anti-fracture strategies for PMOP involve a combination of calcium and vitamin D, hormone replacement therapy (HRT), bisphosphonates, and selective estrogen receptor modulators (SERMs), among others (13, 16). However, we cannot overlook the adverse effects and limited efficacy of the currently used medications, including vaginal bleeding, breast tenderness, deep vein thrombosis, and cardiovascular events. Therefore, there is an urgent need to explore better complementary and alternative therapies for PMOP.

Acupuncture, a traditional Chinese medicine practice with millennia of historical use, has been endorsed by the World Health Organization (WHO) for managing musculoskeletal, neurological, gynecological, and pain-related conditions (17, 18). Evidence-based medical research confirms that acupuncture-related treatments can improve patient's quality of life, regulate bone metabolism, and reduce pain through holistic adjustments (19–22). Therefore, we selected the overall clinical effectiveness rate, bone mineral density (BMD), and visual analog scale scores (VAS) as outcome indicators, with concurrent safety assessments via adverse reaction. Despite the growing adoption of diverse acupuncture-related therapies for PMOP, clinical practitioners face challenges in selecting optimal modalities due to insufficient comparative evidence. Therefore, we used network meta-analysis (NMA) to compare the efficacy of various acupuncture-related therapies across different outcome indicators, with the expectation of providing a reliable evidence-based medical basis for the promotion and evaluation of clinical acupuncture for PMOP.

Compared to previous systematic reviews and paired meta-analysis (19, 21, 22), NMA can simultaneously evaluate both direct and indirect evidence from various studies and estimate the relative effectiveness of multiple acupuncture therapies. To our knowledge, this is the first NMA to compare and rank acupuncture-related interventions for PMOP, identify the most effective clinical protocols, and inform evidence-based guidelines.

2 Methods

The article adhered to the Preferred Reporting Items for Systematic Review and Meta Analysis (PRISMA) guidelines for NMA, as detailed in Supplementary Appendix 1 (23). The review was registered in PROSPERO[1] with the registration ID of CRD42023401003. As this is a systematic literature review, ethical approval is not required. The protocol was published in *BMJ OPEN* (24).

2.1 Search strategy

We conducted a systematic review of randomized controlled trials (RCTs) investigating acupuncture-related therapies for PMOP across eight databases: PubMed, Embase, Cochrane Library, Web of Science, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (VIP), Wanfang Database, and China Biomedical Literature Database (CBM). We searched each database from January 1, 2002, to December 31, 2023, and the language was restricted to Chinese and English with a combination of Medical Subject Headings and free words. The search terms included "acupuncture" "electroacupuncture" "moxibustion" "warm needle acupuncture" "catgut implantation at acupoint" "postmenopausal osteoporosis" and their synonyms (Supplementary Appendix 2).

2.2 Inclusion criteria

Criteria for study inclusion: (1) Randomized controlled trials (RCTs) investigating various acupuncture-related methods for the treatment of PMOP, published in English or Chinese; (2) The study population consisted of patients with a clinical diagnosis of PMOP, adhering to the relevant diagnostic criteria established by the European guidelines for diagnosis and management in 2018 and the 2021 position statement of The North American Menopause Society (25); (3) Patients in the treatment group accepted acupuncture-related therapies, including acupuncture, warm needle, electro-acupuncture, fire needle, blood-letting puncture, moxibustion, acupoint catgut embedding, acupoint application, and more (26–28). The control group contained placebo, usual care, and CWM. When the treatment group was to be treated with a combination of CWM, it was ensured that these should be identical in control groups. (4) Study outcomes included the overall clinical effectiveness rate, BMD, VAS, and adverse events. We mainly incorporated the lumbar spine, femur neck, ward's triangle, and trochanter (G.T.) for BMD. The overall clinical effectiveness rate, based on the criteria of Chinese medicine clinical evidence points for the clinical standard used to judge the efficacy of acupuncture-related therapies, will be divided into four levels: clinically cured, markedly effective, effective, and invalid (21, 29). The overall clinical effectiveness rate will be calculated as: the overall clinical effectiveness rate (%) = [(number of patients clinically cured + markedly effective + effective)/number of patients] × 100% (30).

2.3 Exclusion criteria

Criteria for study exclusion: (1) Non-RCT studies, animal or basic studies; (2) Comorbidities with other diseases that may influence the assessment of efficacy, such as breast disease, thyroid dysfunction, insomnia, anxiety, and depression; (3) Interventions in which the

1 https://www.crd.york.ac.uk/prospero/#record

control group received non-conventional Western medicine or two types of acupuncture therapies simultaneously, along with unclear descriptions of the interventions; (4) Unavailability of raw data.

2.4 Study selection and data extraction

Two reviewers utilized EndNote software to eliminate duplicate documents, and then independently screened all abstracts and full papers. Any disagreements were resolved through discussion or by consulting a third reviewer. The reviewers collected detailed data including study characteristics (author, publication year, mean age, sample size), intervention and control measures (acupoints, operation, treatment duration, frequency), diagnostic criteria, and outcomes. Each evaluator cross-checked the selected studies, extracted data, and resolved any disagreements by consulting a third party.

2.5 Risk of bias assessment

Two reviewers (BD and TTX) independently assessed the risk of bias in the included studies according to the Cochrane Manual's risk of bias assessment tool for RCTs. The evaluation encompassed 7 items: random sequence generation, assignment plan concealment, blinding of participants and personnel, blinding of study outcome measures, the integrity of outcome data, selective outcome reporting, and other sources of bias. Each domain was categorized as "low," "high," and "uncertain." In cases of disagreement, a third researcher (GZC) was consulted to help determine the risk.

2.6 Statistical analysis

We performed Bayesian NMA to compare the effects of different acupuncture-related therapies. We primarily performed a pairwise meta-analysis using the software Review Manager V.5.4 and Stata 14.0. The heterogeneity of each pairwise comparison was assessed using the Q test and the I^2 statistic through RevMan V.5.4. The effect values of 95% Confidence Intervals (CIs) were measured by the software of Stata 14.0. Since the overall clinical effectiveness rate is a dichotomous type variable, the number of events and the total sample size were utilized as the effective values for these dichotomous type variables in the statistical analyses, reported using odds ratio (OR) with 95% Confidence Intervals. The BMD and VAS, which are continuous type variables, were expressed as mean difference (MD) and 95% confidence intervals.

Additionally, we employed Stata 14.0 for data analysis and graph drawing. The "sucra prob" command was used to rank the efficacy of different interventions and to create a cumulative probability graph. The surface under the cumulative ranking curve (SUCRA) indicated the relative superiority or inferiority of each intervention; a larger SUCRA value signifies better efficacy for the outcome in question. $p < 0.05$ was considered statistically significant. We generated funnel plots using stata's NMA package to evaluate publication bias and the small sample size of the included literature. We conducted a narrative review and summarised the evidence if the available data were not suitable for synthesis.

The I^2 statistic and p values were applied to assess the heterogeneity across all individual studies. To obtain more reliable estimates of the effect, I^2 greater than or equal to 50% and $p < 0.1$ were used as thresholds to indicate significant heterogeneity. If the heterogeneity is small, we chose the fixed-effects model. Based on the information we collected, subgroup analyses of bone density were performed at different sites, including the bone density of the lumbar spine, femoral neck, ward's triangle, and trochanter.

3 Results

3.1 Literature search and screening

A total of 648 potentially relevant articles were identified, of which 358 were duplicate records. Additionally, 152 articles that were literature reviews, systematic reviews, or animal experiments were further excluded. After reviewing the titles, abstracts, and full texts, we found that 108 articles were ineligible for inclusion because they were not RCTs, or because the studies or interventions did not align with our criteria. Ultimately, we included 30 eligible studies (31–60). The PRISMA flow diagram illustrating the study inclusion process is presented in Figure 1.

3.2 Study characteristics

These studies all were from China and were published between 2004 and 2022. A total of 2,342 participants were involved in these studies. Among 30 RCTs, four studies were three arms and twenty-six studies were two-arm trials. The acupuncture-related therapeutic interventions in the treatment groups included electroacupuncture (EA) (31–33), moxibustion (MO) (34–38), warm acupuncture (WA) (31, 39–44), acupoint application (AA) (45, 46), acupoint catgut embedding (ACE) (47–54), and manual acupuncture (MA) (55–60). The control groups all utilized oral Western medications for the treatment of PMOP. The majority opted for a combination of Calcium Carbonate and Vitamin D or used either alone, and only one study chose estradiol as the control (60). The basic characteristics of the included studies are shown in Table 1 and acupuncture-related therapies are described in more detail in Table 2.

3.3 Study quality assessment

Thirteen studies randomized participants using a random number table (31, 34, 38–40, 44, 46–50, 58, 60), while one study employed Doll's clinical case randomization table grouping method (52), two studies were grouped by the order of patient visits in a non-randomized manner (36, 57). Three studies utilized sealed opaque envelopes for allocation concealment (39, 54, 59), whereas the remaining twenty-seven studies made no mention of their randomization procedures. Because of the specificity of acupuncture-related therapies, blinding of participants and personnel requires a specialized design, such as the use of sham acupuncture devices in the control group. However, this was not specified in any of the studies we included. Regarding detection bias, only one study has been described (59). No other biases were detected in the included studies. The data integrity of the

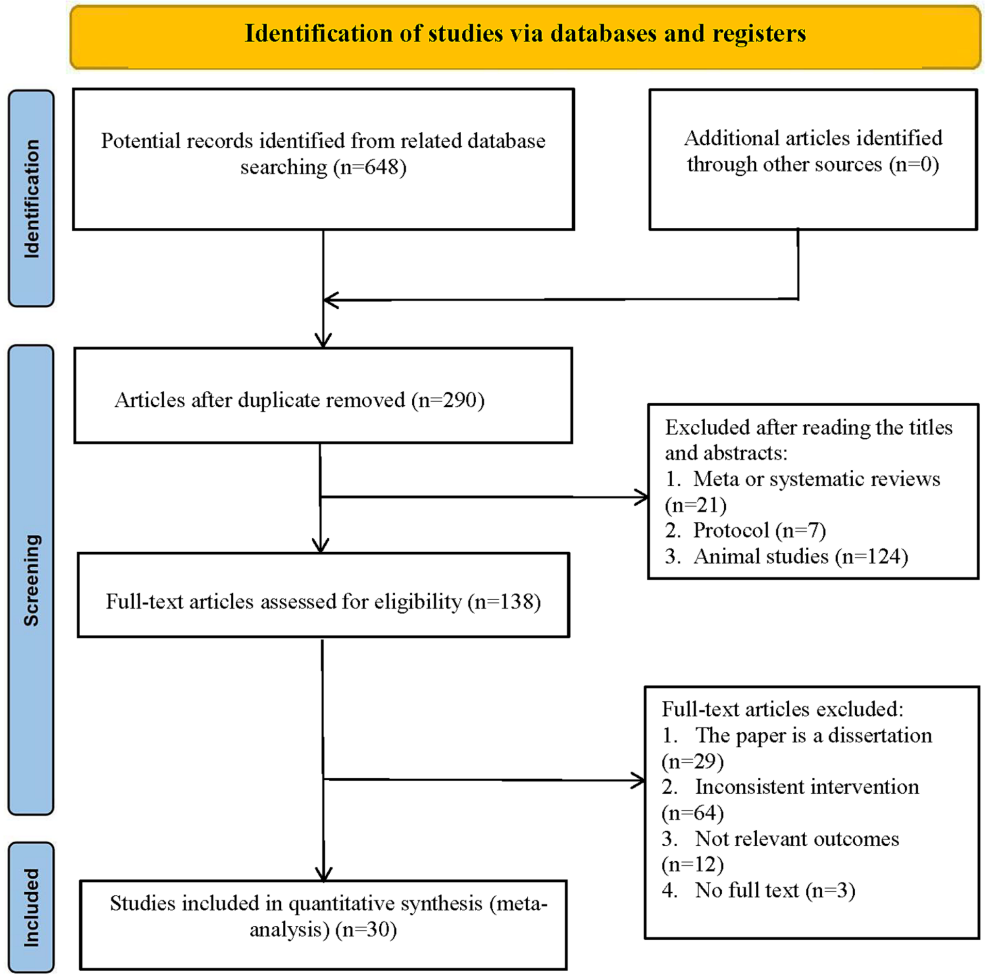

FIGURE 1
Preferred reporting items for systematic reviews and network meta-analyses (PRISMA) flowchart of the literature inclusion process.

included literature was good, and other risks of bias were unknown. The results of the risk of bias evaluation are presented in Figures 2A,B.

3.4 Network meta-analysis results

3.4.1 The overall clinical effectiveness rate

Twenty-two studies were included in the statistical analysis of the efficacy of treatments for PMOP, with the network relationship between interventions shown in Figure 3A (32, 33, 35, 36, 39, 41–44, 47, 49–60). Line thickness corresponds to the number of studies included in the comparison of each treatment, while the area of the circles indicates the overall sample size associated with each intervention. Depending on the thickness of the line linking, the number of RCTs between ACE+CWM and CWM was the highest. Additionally, the sample size for CWM was the largest, followed by that of ACE+CWM. Due to the formation of two closed loops, the overall clinical effectiveness rate was initially assessed using an inconsistent model (Figure 3B), where the p in the ACE-ACE+CWM-CWM and EA–EA + CWM-CWM closed loops were 4.37 and 2.39, suggesting that the inconsistency was not statistically significant.

Figure 3C is about the pairwise comparison results of ten types of interventions with controls. The findings indicated that WA + CWM (OR = 3.89, 95%CI:1.60–9.44), MA (OR = 3.27, 95%CI:1.90–5.63), ACE (OR = 5.05, 95%CI:1.91–13.36), ACE+CWM (OR = 7.96, 95%CI:3.88–16.31), WA (OR = 3.85, 95%CI:1.49–9.97), EA + CWM (OR = 10.29, 95%CI:3.47–30.52), MO + CWM (OR = 4.28, 95%CI:1.60–11.46), and MA + CWM (OR = 3.89, 95%CI:1.49–10.16) had superior efficacy rates for improving postmenopausal osteoporosis compared to the CWM ($p < 0.05$). However, there was no significant difference among the various acupuncture-related treatments. The results of pairwise comparisons and ranking from the reticular meta-analysis were presented in Figure 3D. According to SUCRA values, EA + CWM (89.6%) > ACE+CWM (83.9%) > ACE (63.0%) > MO + CWM (55.2%) > WA + CWM (50.2%) = MA + CWM (50.2%) > WA (50.1%) > MA (40.0%) > EA (16.4%) > CWM (1.5%) the differences were statistically significant ($p < 0.05$). We found that EA + CWM group ranked first as the optimal treatment for PMOP. A comparison-adjusted funnel plot was used to analyze the publication bias of the overall clinical effectiveness rate. The differently colored points in this funnel plot represented different direct comparisons and the number of the same color points indicated the frequency of those comparisons

TABLE 1 Characteristics of included studies.

Author (year)	Sample size			Mean age (years) (T/C)			Interventions			Acupoints	Course of treatment	Outcomes
	T1	T2	C	T1	T2	C	T1	T2	C			
Chen et al. (2004) (39)	30	-	30	58.12 ± 7.25	-	57.63 ± 7.68	WA + CC + VD	-	CC + VD	DU14, ST36, BL23, BL26	6 M	①②
Wang et al. (2004) (55)	50	-	50	47.87	-	49.62	MA	-	CC	BL23, BL18, ST36, KI1, SP10	3 M	①②
Lin et al. (2005) (47)	18	20	18	60.06	62.55	60.83	ACE	ACE+CC + VD	CC + VD	BL23	3 M	①③
Lin et al. (2006) (48)	18	20	18	60.06 ± 6.12	62.55 ± 5.91	60.83 ± 5.65	ACE	ACE+CC + VD	CC + VD	BL23	6 M	②③
Gao et al. (2008) (56)	30	-	28	63.50 ± 3.85	-	63.50 ± 3.85	MA	-	CC + VD	RN13, RN12, RN6, RN4, ST25	3 M	①
Zhao et al. (2008) (44)	20	-	20	64.00 ± 5.99	-	66.90 ± 5.89	WA	-	CC + VD	BL11, BL18, BL23, ST36, GB34	3 M	①②
Wang (2009) (60)	56	-	56	55.3	-	55.3	MA	-	E2	BL23, GV4, CV4	3 M	①
Du (2011) (57)	32	-	32	64 ± 8	-	66 ± 9	MA	-	CC + VD	LR4, BL18, BL23, BL20, ST36, GB34, GB39, SP6, KI3, LR3	3 M	①②
Liu et al. (2011) (49)	45	-	45	62.5 ± 9.7	-	59.8 ± 8.6	ACE+CC + VD	-	CC + VD	BL23, BL18, BL20, EX-B2, BL40	6 M	①②③④
Liu et al. (2011) (49)	35	-	35	63.7 ± 3.8	-	62.8 ± 5.9	ACE+CC + VD	-	CC + VD	BL23, BL18, EX-B2, BL40	6 M	①②③④
Zhou et al. (2012) (32)	50	-	50	58 ± 5	-	56 ± 7	EA + VD	-	VD	BL20, BL21, BL23, BL18, DU3, DU4, RN12, ST25, RN4, ST36, SP6, KI3, GB39	6 M	①②③④
Liang et al. (2013) (51)	60	-	60	65.7 ± 6.9	-	66.9 ± 5.8	ACE+CC + VD	-	CC + VD	BL23, BL18, EX-B2, BL40	6 M	①②③④
Lin et al. (2013) (34)	32	-	31	-	-	-	MO + CC + VD	-	CC + VD	From DU2 to DU14	3 M	③
OuYang and Xu (2013) (35)	29	-	28	62.45 ± 7.68	-	62.45 ± 7.68	MO + CC + VD	-	CC + VD	BL20, BL21, BL23, DU4, DU3, DU9	3 M	①
Wang et al. (2013) (33)	50	50	50	-	-	-	EA + VD	EA	VD	BL20, BL21，BL18, BL23, RN12, RN4, ST36, SP6	6 M	①②③
Cai et al. (2014) (31)	30	30	30	51 ± 6	52 ± 7	50 ± 6	WA	EA	CC + VD	BL11, BL23, GB39	1 M	③
Lu (2014) (52)	25	-	22	60.84 ± 6.956	-	62.14 ± 6.342	ACE+CC + VD	-	CC + VD	BL23	6 M	①②③
Cai et al. (2015) (40)	43	-	42	51 ± 7	-	50 ± 6	WA + CC + VD	-	CC + VD	BL11, BL23, GB39	1Y	②
Yu (2015) (36)	20	-	20	62.27 ± 8.73	-	62.01 ± 0.73	MO + CC + VD	-	CC + VD	DU4, BL23	1Y	①②
Luo (2015) (41)	18	-	18	54.8 ± 6.2	-	54.8 ± 6.2	WA	-	CC + VD	BL18, BL23, GB34, ST36, BL11, SP6, GB39, RN4	6 M	①②
He et al. (2015) (45)	85	-	91	-	-	-	AA+VD	-	CC + VD	DU4, BL23, BL22, BL52, RN6, RN4, DU3, BL24, BL26	6 M	②③
Hu (2016) (58)	32	-	35	61.4 ± 8.3	-	62.1 ± 8.7	MA + CC + VD	-	CC + VD	BL20, BL21, BL23, BL18, ST36	3 M	①②
Chai and Liang (2017) (42)	33	-	32	50. 26 ± 5. 91	-	49. 85 ± 5. 69	WA + CC + VD	-	CC + VD	BL23, DU4, RN4, RN6	3 M	①②
Li (2017) (43)	60	-	60	65.35 ± 5.73	-	66.17 ± 5.65	WA	-	CC + VD	BL18, BL23, GB34, ST36, BL11, RN4, SP6	6 M	①③

(Continued)

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TABLE 1 (Continued)

Author (year)	Sample size			Mean age (years) (T/C)			Interventions			Acupoints	Course of treatment	Outcomes
	T1	T2	C	T1	T2	C	T1	T2	C			
Gu et al. (2018) (54)	30	-	30	62 ± 5	-	62 ± 5	ACE+VD	-	VD	stellate ganglion	24 W	①②
Wu et al. (2018) (37)	28	-	28	59.25 ± 2.91	-	58.04 ± 3.20	MO + CC + VD	-	CC + VD	RN8	16 W	②③
Lin et al. (2020) (38)	30	-	30	59.50 ± 5.92	-	60.75 ± 5.09	MO + CC + VD	-	CC + VD	From DU2 to DU14	3 M	③
Yang et al. (2021) (53)	58	-	52	57.3 ± 3.5	-	56.2 ± 3.7	ACE	-	CC + VD	CV4, RN6, BL23, SP6, GB30, ST36	24 W	①④
Chen et al. (2022) (59)	31	-	32	64 ± 5	-	64 ± 5	MA + CC + VD	-	CC + VD	BL23, BL20, RN4, ST36, GB39, SP6	12w	①②④
Li et al. (2022) (72)	50	-	51	57.92 ± 3.46	-	56.63 ± 3.19	AA+CC + VD	-	CC + VD	BL20, BL23, RN8, KI1, RN4	6 M	②

T: Intervention of treatment; C: Intervention of control; Interventions: EA, electroacupuncture; MO, moxibustion; WA, warm acupuncture; AA, acupoint application; ACE, acupoint catgut embedding; MA, manual acupuncture; CC, Calcium Carbonate; VD, Vitamin D; E2, estradiol; Course of treatment: W, weeks; M, months; Y, years; Outcomes: ① The overall clinical effectiveness rate, ② The lumbar spine bone mineral density, ③ Visual analog scale score, ④ Adverse events.

in the original study. In the Figure 3E, most of the points were evenly distributed on both sides of the middle vertical line. The majority of the research included had moderate sample sizes, and the funnel plot suggested that these studies were biased to a low degree.

3.4.2 The BMD

21 studies were included in the statistical analysis of the BMD in the treatment of postmenopausal osteoporosis, we focused primarily on the outcomes of the lumbar spine, femoral neck, trochanter, and Ward's triangle (32, 33, 36, 37, 39–42, 44–46, 48–52, 54, 55, 57–59). The lumbar spine BMD exhibited two closed loops: ACE-ACE+CWM-CWM and EA–EA + CWM-CWM (Figure 4A), while the *p*-values for the two closed-loop inconsistencies were 3.13 and 1.13, indicating that these inconsistencies were not statistically significant (Figure 5A). In the lumbar spine BMD of pairwise comparison results (Figure 6A), WA + CWM (MD = 1.09, 95%CI:1.01–1.17) and EA + CWM (MD = 1.21, 95%CI:1.12–1.30) increased bone density better than conventional Western medicine ($p < 0.05$), and other acupuncture-related therapy did not have statistical differences in increasing bone density. What's more, EA + CWM was more effective than most other acupuncture-related therapies, such as ACE+CWM, MO + CWM, and MA + CWM, among others. According to SUCRA values in Figure 7A, the order of the acupuncture-related treatments to improve lumbar spine BMD: EA + CWM (98.9%) > WA + CWM (69.4%) > MA (68.7%) > WA (64.3%) > MO + CWM (53.2%) > MA + CWM (49.5%) > ACE+CWM (49.2%) > ACE (31.4%) > AA+CWM (25.5%) > EA (20.9%) > CWM (19.0%) all the differences were statistically significant ($p < 0.05$). EA + CWM was the most favorable intervention for enhancing the lumbar spine BMD.

The network of femoral neck bone density had a closed loop: ACE-ACE+CWM-CWM (Figure 4B). Femoral neck BMD was examined using an inconsistency model, which showed $p = 1.23$, indicating that inconsistency was not significant (Figure 5B). According to pairwise comparison results in Figure 6B, WA (MD = 1.16, 95%CI:1.06–1.25) and MO + CWM (MD = 2.71, 95%CI:2.47–2.97) were more effective than CWM. The probability ranking of SUCRA was as follows (Figure 7B): MO + CWM (100.0%) > WA (75.8%) > MA (58.7%) > ACE+CWM (47.3%) > ACE (46.3%) > WA + CWM (37.4%) > MA + CWM (24.5%) > CWM (10.1%). The ranking results demonstrated that the top intervention to improve femoral neck BMD was MO + CWM.

Both ward's triangle and trochanter formed a closed loop (Figures 4C,D): ACE-ACE+CWM-CWM, since they were all from the same literature, no inconsistency test was required. According to pairwise comparison results in Figure 6C, WA + CWM (MD = 1.07, 95%CI:1.02–1.12) and WA (MD = 1.19, 95%CI:1.10–1.29) increased ward's triangle BMD better than CWM. The probability ranking of SUCRA was as follows (Figure 7C): WA (95.1%) > MA (66.1%) > WA + CWM (50.7%) > ACE+CWM (45.7%) >ACE (33.3%) > CWM (9.2%). About trochanter BMD in Figure 6D, WA + CWM (MD = 1.08, 95%CI: 1.04–1.13), ACE+CWM (MD = 1.09, 95%CI:1.01–1.17) and WA (MD = 1.11, 95%CI: 1.04–1.19) improving trochanter BMD of postmenopausal osteoporosis was better than the CWM. The probability ranking of SUCRA was as follows (Figure 7D): WA (82.3%) > ACE+CWM (64.0%) > WA + CWM (63.8%) > MA (54.4%) > ACE (48.1%) > MA + CWM (35.1%) > CWM (2.3%). WA was best for improving BMD in both.

TABLE 2 Definitions of the acupuncture-related therapies included in this study.

Acupuncture-related therapy	Definitions
Manual acupuncture (MA)	Manual acupuncture involves the insertion of fine needles into acupuncture points for treatment. The needles are usually manipulated by a physician with the aim of eliciting the Deqi sensation.
Electroacupuncture (EA)	After Deqi by inserting the acupoint with a needle, a trace current wave of the body's bioelectricity is sensed on the needle.
Moxibustion (MO)	It is the use of moxa leaves made of moxa sticks, moxa pillars, produced by the heat of moxa to stimulate the human body acupuncture points or specific areas.
Acupoint catgut embedding (ACE)	Catguts are embedded into specific acupoints by means of needles to produce long-lasting stimulation of the acupoints to achieve the therapeutic effect.
Acupoint application (AA)	A combination of acupoint and medicine. The medicine is applied directly to the acupoints and stimulated by transdermal absorption through the skin at the acupoints.
Warm acupuncture (WA)	A combination of acupuncture and moxibustion. During the process of needle retention, moxa floss is rolled and twisted and wrapped around the handle of the needle and ignited, and the heat is transmitted into the acupuncture point through the body of the needle.

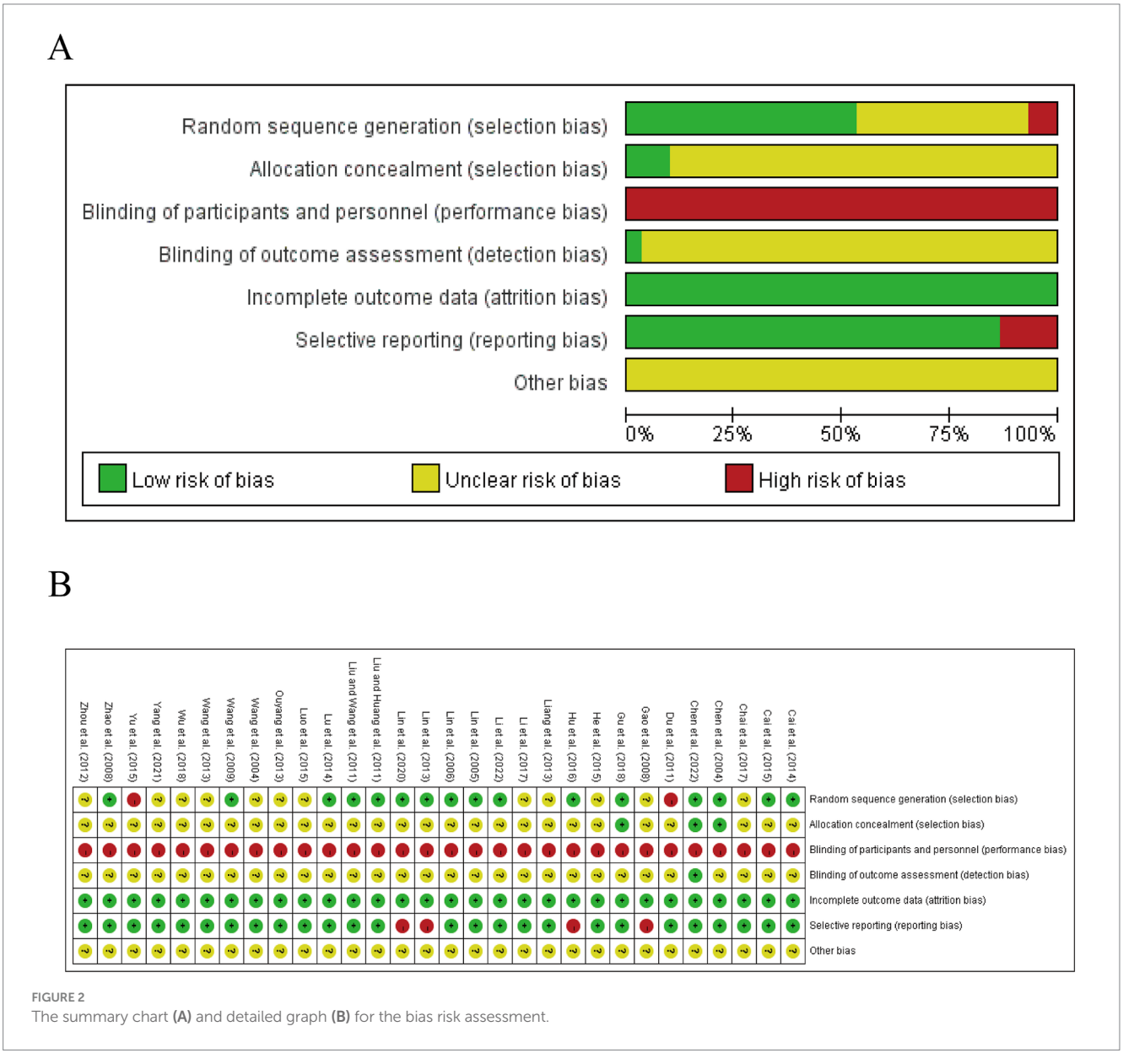

FIGURE 2
The summary chart **(A)** and detailed graph **(B)** for the bias risk assessment.

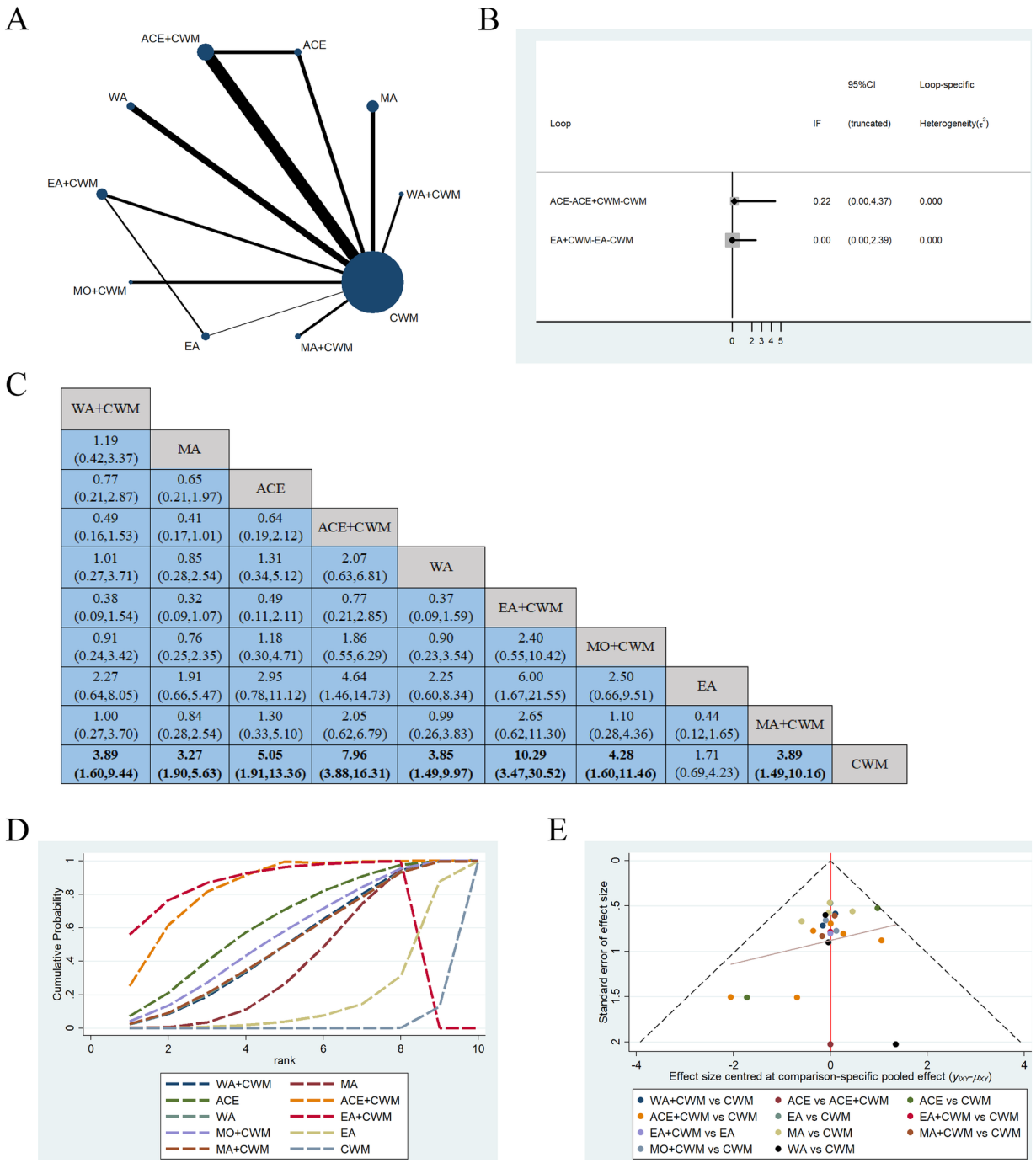

FIGURE 3
Network meta-analysis of multiple acupuncture-related treatments for clinical effectiveness rate, the line thickness is related to the number of comparisons, and the node size is proportional to the sample size **(A)**. Inconsistency test of the overall clinical effectiveness rate, $p > 0.05$ indicates good consistency **(B)**. The league figure of the incidence rate of improving the clinical effectiveness rate **(C)**. SUCRA value of the overall clinical effectiveness rate of PMOP, a bigger SUCRA value represents better efficacy of the intervention **(D)**. Funnel plot of the overall clinical effectiveness rate for the network meta-analysis, the symmetrical distribution suggests a low risk of publication bias **(E)**. PMOP, postmenopausal osteoporosis.

3.4.3 The VAS

Fourteen studies were included in the statistical analysis of the VAS of postmenopausal osteoporosis treatment (31–34, 37, 38, 43, 45, 47–52). The network relationship between interventions is illustrated in Figure 8A, which shows that the sample size for the ACE+CWM was the largest and the evidence network formed three closed loops. The *p*-value for all three closed loops was greater than 0.05, indicating that this inconsistency was not statistically significant (Figure 8B).

Figure 8C is about the pairwise comparison results of nine types of interventions with controls. In terms of pain relief, ACE (MD = 12.98, 95%CI:2.33–72.23), ACE+CWM (MD = 4.44, 95%CI:1.81–10.87), EA + CWM (MD = 7.20, 95%CI:1.94–26.77), WA (MD = 4.74, 95%CI:1.27–17.66), AA+CWM (MD = 7.32,

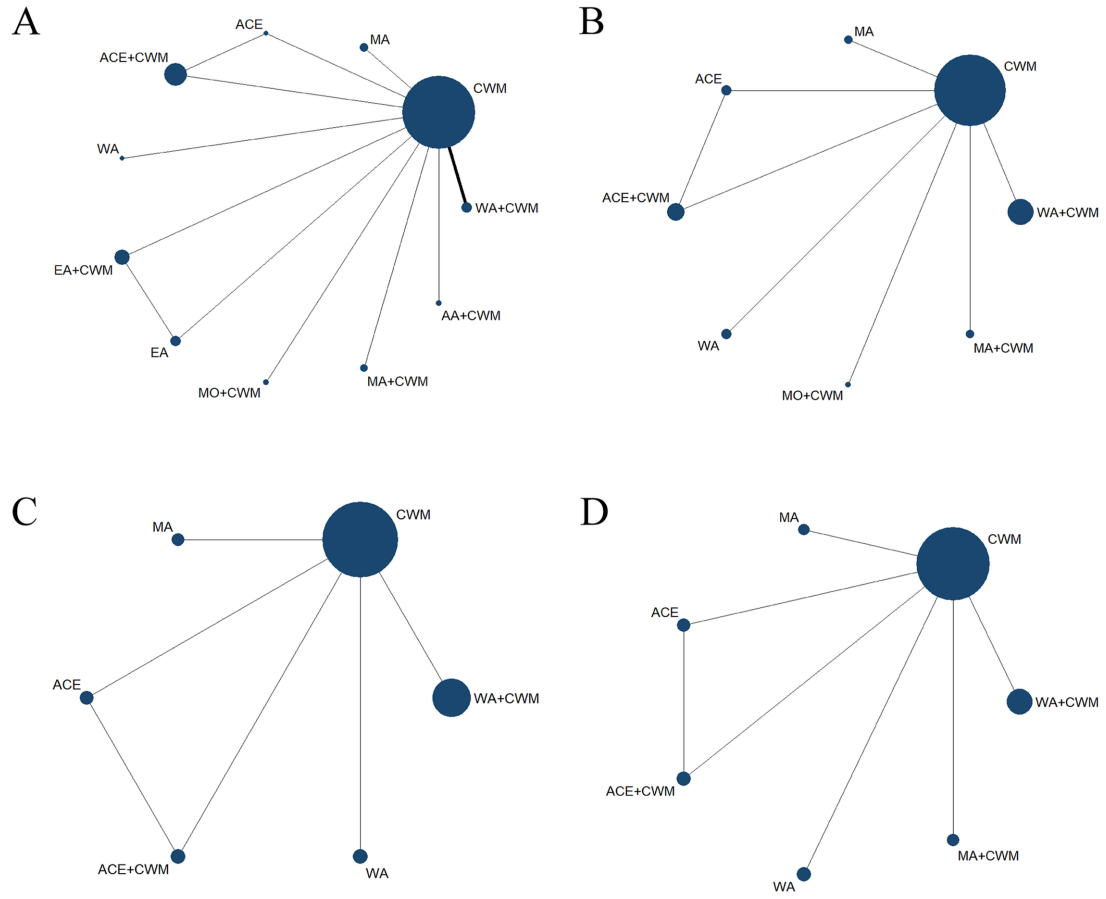

FIGURE 4
Network diagrams of comparisons of bone density at different sites of treatments in patients with PMOP, the line thickness is related to the number of comparisons, and the node size is proportional to the sample size. Network meta-analysis of multiple acupuncture-related treatments for lumbar spine BMD **(A)**. Network meta-analysis of multiple acupuncture-related treatments for femoral neck BMD **(B)**. Network meta-analysis of multiple acupuncture-related treatments for ward's triangle BMD **(C)**. Network meta-analysis of multiple acupuncture-related treatments for trochanter BMD **(D)**. BMD, bone mineral density.

FIGURE 5
Inconsistency test. Lumbar spine BMD **(A)**; femoral neck bone density **(B)**.

95%CI:1.04–51.38) were more efficacious than CWM. Also ACE (MD = 10.42, 95%CI:1.23–88.42) and EA + CWM (MD = 5.78, 95%CI:1.22–27.40) were more efficacious compared to EA. The SUCRA values in Figure 8D, provided a possible rank for improving VAS: ACE (87.9%) > EA + CWM (76.6%) > AA+CWM (74.4%) > WA (64.9%) > ACE+CWM (62.2%) > EA (26.0%) > MO (21.9%) > CWM (18.9%) > MO + CWM (17.2%) the differences were statistically significant ($p < 0.05$), ACE ranked first as the optimal choice. In Figure 8E, the points on the VAS funnel plot are scattered, suggesting a potential publication bias in the research.

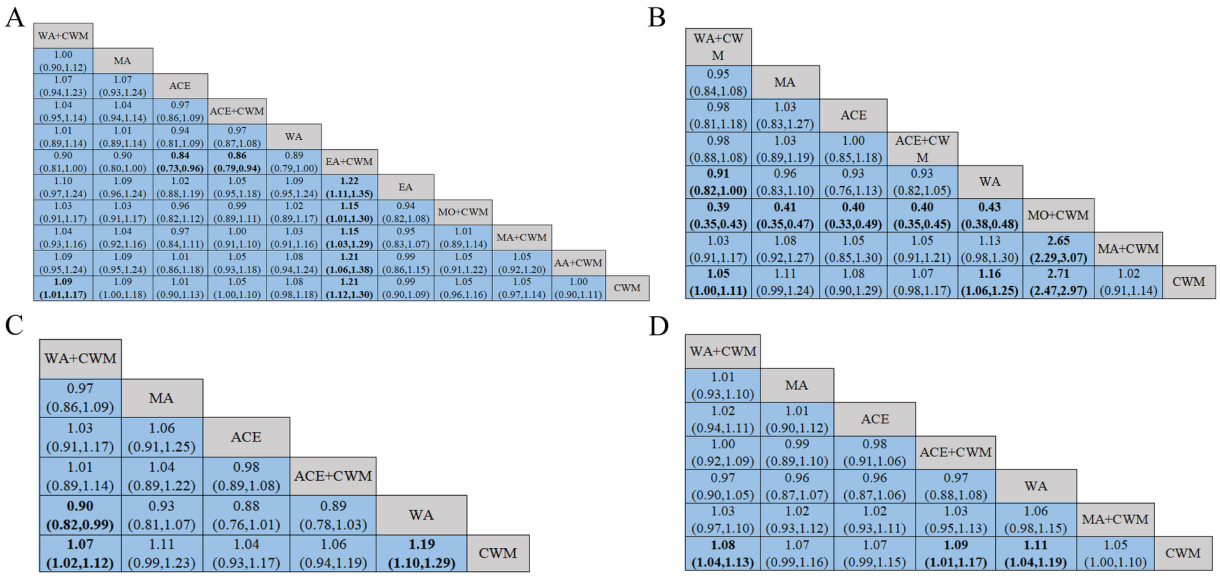

FIGURE 6
League figure. The bold font indicates a statistical difference. League figure of response rate of lumbar spine BMD **(A)**. League figure of response rate of femoral neck BMD **(B)**. League figure of response rate of ward's triangle BMD **(C)**. League figure of response rate of trochanter BMD **(D)**. BMD, bone mineral density.

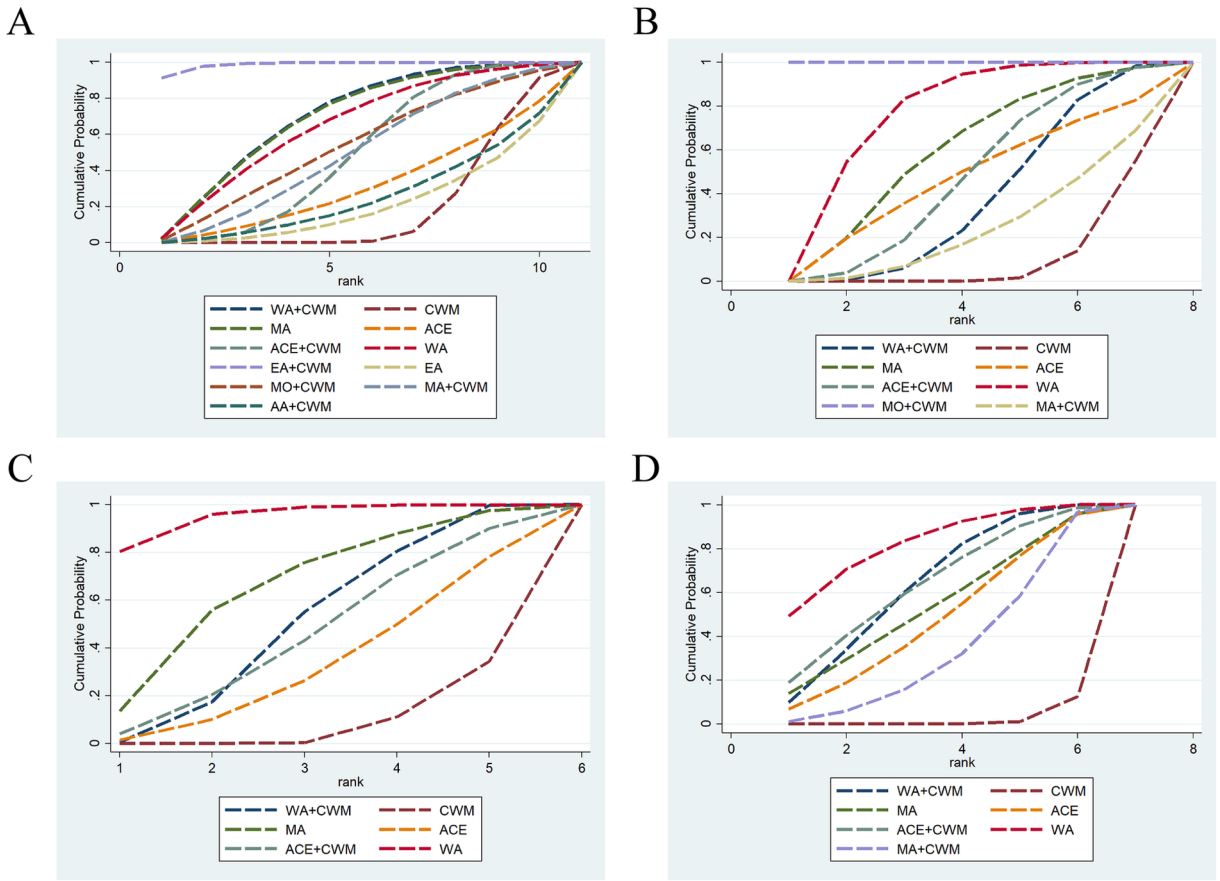

FIGURE 7
SUCRA value. A bigger SUCRA value represents better efficacy of the intervention. SUCRA value of lumbar spine BMD **(A)**. SUCRA value of femoral neck BMD **(B)**. SUCRA value of ward's triangle BMD **(C)**. SUCRA value of trochanter BMD **(D)**. BMD, bone mineral density.

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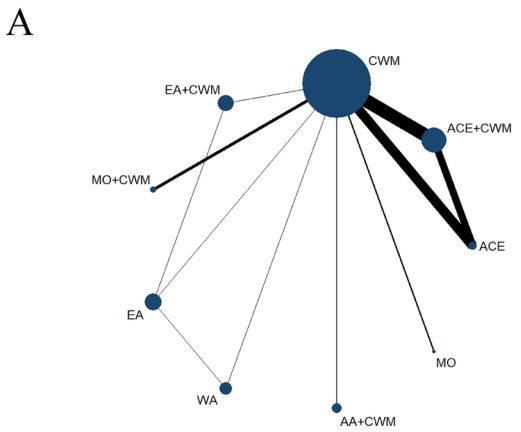
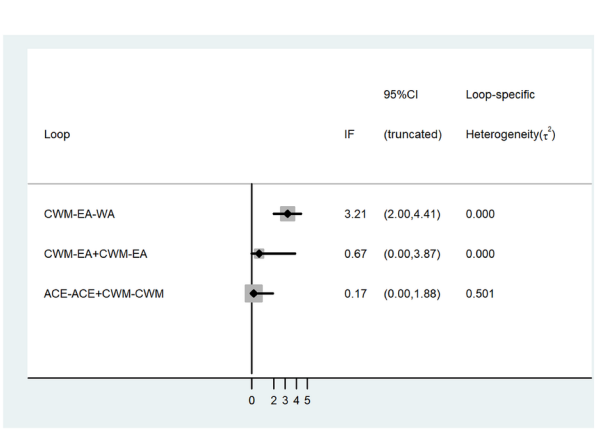
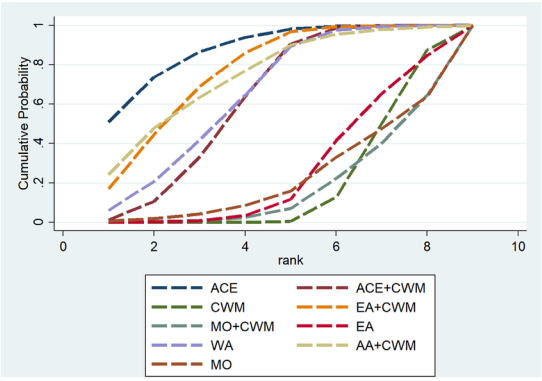




C

ACE								
2.93 (0.56,15.21)	ACE+CWM							
1.80 (0.21,15.64)	0.62 (0.13,3.02)	EA+CWM						
15.15 (1.62,141.89)	5.18 (0.95,28.14)	**8.41 (1.20,59.00)**	MO+CWM					
10.42 (1.23,88.42)	3.56 (0.75,16.93)	**5.78 (1.22,27.40)**	0.69 (0.10,4.71)	EA				
2.74 (0.32,23.80)	0.94 (0.19,4.60)	1.52 (0.25,9.06)	0.18 (0.03,1.27)	0.26 (0.06,1.25)	WA			
1.77 (0.13,23.82)	0.61 (0.07,5.18)	0.98 (0.09,10.32)	0.12 (0.01,1.32)	0.17 (0.02,1.75)	0.65 (0.06,6.80)	AA+CWM		
13.78 (0.97,195.90)	4.71 (0.51,43.12)	7.65 (0.68,85.41)	0.91 (0.08,10.91)	1.32 (0.12,14.48)	5.03 (0.45,56.28)	7.77 (0.47,129.10)	MO	
12.98 (2.33,72.23)	**4.44 (1.81,10.87)**	**7.20 (1.94,26.77)**	0.86 (0.20,3.62)	1.25 (0.35,4.46)	**4.74 (1.27,17.66)**	**7.32 (1.04,51.38)**	0.94 (0.12,7.13)	CWM



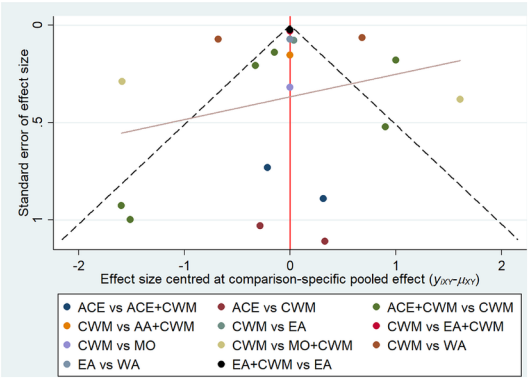


FIGURE 8
Network meta-analysis of multiple acupuncture-related treatments for VAS, the line thickness is related to the number of comparisons, and the node size is proportional to the sample size **(A)**. Inconsistency test of VAS, $p > 0.05$ indicates good consistency **(B)**. The league figure of the incidence rate of VAS **(C)**. SUCRA value of VAS, a bigger SUCRA value represents better efficacy of the intervention **(D)**. Funnel plot of VAS for the network meta-analysis, the symmetrical distribution suggests a low risk of publication bias **(E)**. VAS, visual analog scale score.

3.4.4 Adverse events

Six studies reported the occurrence of adverse events (32, 49–51, 53, 59). One trial involving MA noted that one patient developed a local hematoma at RN4, which dissipated within one week after the application of local hot compresses. Four trials concerning ACE indicated that the treatment group appeared local hard nodules, pain, palpitation, and chest tightness. A study on EA reported adverse effects of stomach pain and insomnia in the acupuncture group. However, these symptoms were mild, and the side effects subsided spontaneously. Some conditions only appeared in the first treatment.

4 Discussion

Osteoporosis is the most prevalent skeletal disorder affecting humans and is a widespread bone disease characterized by diminished bone strength. PMOP, caused by ovarian dysfunction and estrogen deficiency in postmenopausal women, severely compromises patients' quality of life while imposing substantial socioeconomic costs (61, 62). Current first-line pharmacological interventions, though partially effective, are limited by non-negligible adverse effects (63, 64), prompting exploration of complementary and alternative therapies (17, 65, 66). Several basic and clinical studies have confirmed that acupuncture-related therapies have the effect of correcting endocrine metabolic disorders, relieving pain, regulating mental health, and improving quality of life, and may have biological mechanisms such as central sensitization, neurotransmitters, intestinal flora, immune regulation, oxidative stress, and neuroinflammation (67, 68). In this context, as one of the most widely accepted complementary alternative therapies for PMOP, since different acupuncture-related therapies each have their unique advantages, it can be challenging for clinicians to evaluate the therapeutic value of various acupuncture treatments for different conditions (19–22, 69). Therefore, further prospective studies are needed to conduct a comprehensive evaluation of the efficacy of various acupuncture-related therapies for PMOP.

Our analysis incorporated 30 randomized trials (2,342 participants) evaluating six acupuncture modalities. For clinical effectiveness, both direct comparisons and SUCRA rankings identified EA + CWM (89.6%) as the most effective intervention. To evaluate the efficacy of BMD treatments, we performed several subgroup analyses. The first was lumbar spine BMD, the results of which were consistent with the overall efficacy rate, both suggesting that EA + CWM (98.9%) was the most effective option. For femoral BMD, the most effective for increasing BMD in the femoral neck was MO + CWM (100.0%), while ward's triangle and trochanter were WA (95.1%). In the results of VAS in NMA, according to SUCRA values, ACE (87.9%) may be the best choice for relieving pain associated with PMOP. The optimal treatment modality indicated by each outcome indicator was not identical. The results of adverse events depicted that the side effects of acupuncture-related therapies were mild and largely self-resolving. Since the optimal treatment modality suggested by each outcome index differs. In clinical practice, physicians need to integrate their diagnostic and therapeutic experiences to identify and select the most appropriate treatment. Traditional Chinese medicine hypothesizes that kidney essence and liver-kidney deficiency are the basic pathogenesis for PMOP (70). The treatment principle should focus on tonifying the liver and kidney to strengthen bones and tendons. The selection of acupoints and the method of administration are critical factors in ensuring that acupuncture has a positive effect on the patient. Our research indicated that Shenshu (BL23), Zusanli (ST36), Ganshu (BL18), Guanyuan (RN4), Pishu (BL20), and Xuanzhong (GB39) were the most frequently utilized in different acupuncture-related therapies. However, in the MO, from DU2 to DU14 on the Governor was the most popular. These high-frequency acupuncture points are related to the meridians of the liver, spleen, and kidney meridians.

Acupuncture-related therapy has long been linked to the regulation of homeostasis (Yin/Yang) within the body. Many previous studies elucidated the mechanisms underlying acupuncture-related therapies for the treatment of PMOP. It is believed that these therapies help balance the body and restore its physiological functions by targeting specific acupuncture points. Additionally, they can increase the uterine index, elevate serum estrogen levels, and modulate the HPA axis function in the ovariectomized (OVX) rat model (71, 72). EA is a method of acupuncture that integrates traditional acupuncture with electrical impulses to enhance the stimulation of specific acupoints, which can increase BMD in PMOP rats by elevating levels of insulin-like growth factor (IGF-I and IGF-BP1) and modulating the Wnt-β-catenin signaling pathway (73, 74). MO has the function of harmonizing qi and blood, supporting the positive and dispelling the evil, and activating the meridians. Clinical studies have demonstrated its effectiveness in reducing lower back pain and improving bone density (75). WA is a combination of acupuncture and moxibustion, in which needles are inserted into acupuncture points, while a lit moxa stick is placed on the handle of each needle to provide simultaneous warm stimulation (22). ACE, a specialized form of acupuncture therapy, can create a continuous needling effect by inserting catgut at specific acupuncture points (76). ACE can alleviate lipid peroxidation, restore glucose homeostasis, and partial reversion of the OVX-altered amino acid metabolism to improve menopausal syndrome (77). These approaches are frequently employed in both research and therapeutic practice and are among the best treatments for PMOP in our research. Therefore, in this study, we used network meta-analysis to compare the effectiveness of commonly used acupuncture treatments and to rank their efficacy. Our findings may offer a valuable clinical reference for future investigations into the use of acupuncture in treating PMOP.

This study has several limitations: (1) The quality of the original studies is a concern, as all included studies were domestic single-center investigations, lacking multicenter research. (2) The site and nature of pain were not categorized in detail in the original studies included, and a more specific description of pain with clinical practice needs to be considered in subsequent studies. (3) There are inherent limitations associated with acupuncture therapy itself. Due to the challenges in the acupuncture procedure and the variability in patients' sensations, achieving blinding for both patients and practitioners is particularly difficult. In acupuncture practices such as MO, ACE, and WA, the selection of acupuncture points, depth of insertion, frequency of stimulation, and retention time of needles are not clearly defined, leading to potential implementation bias. (4) Some acupuncture therapies, such as EA and WA, were included in fewer studies, which may increase the chances and reduce the reliability of the results. Furthermore, most of the original studies did not report adverse effects, preventing a comprehensive evaluation of safety. (5) While all control groups received CWM, variations in specific drugs, dosages, and treatment durations were noted. We aggregated these pharmacological approaches rather than stratifying them by individual regimens.

This study indicates that different acupuncture-related therapies may be advantageous for different outcome indicators of PMOP, potentially due to the unique characteristics of each therapy. In the future, we should consider establishing multicenter clinical trials for these therapies, standardizing methodologies, and creating a multicenter efficacy registry system utilizing blockchain technology. By integrating the results of clinical trials, we can enhance research on the underlying mechanisms, allowing different acupuncture-related therapies to leverage their strengths. The aim is to elevate acupuncture-related therapies from adjunct therapies to a central component of the precision treatment system for PMOP, thereby fostering innovation in

the integration of traditional Chinese medicine and Western medicine within the bone health management paradigm.

5 Conclusion

The effectiveness of acupuncture-related therapies for PMOP has been systematically evaluated in this NMA. This study demonstrated that acupuncture-related therapies are superior in treating PMOP. Furthermore, EA + CWM emerged as the most effective intervention in terms of the overall clinical effectiveness rate. EA + CWM, MO + CWM, and WA all showed advantages in improving BMD. ACE ranked highest as the optimal choice for the improvement of VAS. However, potential heterogeneity among studies and acupuncture-related interventions due to the number of included studies, and sample size, resulted in some of the comparisons failing to achieve the required level of statistical significance. It is hoped that this study will provide some references for future clinical studies on different acupuncture-related therapies for the treatment of PMOP. Therefore, more multicenter, large-sample, randomized controlled clinical trials with appropriate design and methodology are necessary in the future to further validate the efficacy of different acupuncture therapies. It is hoped to further improve the mechanism study based on the clinical results and to standardize and precise the treatment of different clinical symptoms of PMOP by acupuncture-related therapies in combination with artificial intelligence technology to enhance the treatment response rate. Upgrading acupuncture-related therapies from PMOP complementary alternative therapies to the core module of the precision treatment system gives full play to the advantages of different therapies.

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 here: doi: 10.6084/m9.figshare.28705172.

Author contributions

BD: Data curation, Writing – original draft. TX: Data curation, Writing – original draft. ZD: Software, Writing – original draft. YJ: Software, Writing – original draft. LL: Writing – review & editing. WL: Writing – review & editing. YZ: Writing – review & editing. HW: Writing – review & editing. YX: Funding acquisition, Writing – original draft, Writing – review & editing. GC: Funding acquisition, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research and/or publication of this article. We sincerely appreciate all the authors who included the original study. This work was supported by the Natural Science Foundation of Guangdong Province (No. 2024A1515011874 and 2023A1515011123), the Shenzhen Science and Technology Innovation Committee (No. JCYJ20210324124613037), the Shenzhen Bao'an Traditional Chinese Medicine Development Foundation (No. 2022KJCX-ZJZL-10), and Bao'an District Shenzhen Traditional Chinese Medicine Association (No. 2023ZYYLCZX-20).

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/fmed.2025.1483819/full#supplementary-material

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frontiers | Frontiers in Medicine

TYPE Mini Review
PUBLISHED 07 August 2025
DOI 10.3389/fmed.2025.1549733

OPEN ACCESS

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RECEIVED 21 December 2024
ACCEPTED 21 July 2025
PUBLISHED 07 August 2025

CITATION
Cheng J-P, Chen X and Chen J-X (2025) Rsearch progress on the relationship between aging and microbiota in sarcopenia. *Front. Med.* 12:1549733. doi: 10.3389/fmed.2025.1549733

Rsearch progress on the relationship between aging and microbiota in sarcopenia

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Sarcopenia is an age-related skeletal muscle disease associated with adverse outcomes such as falls, decreased function, frailty, and death, and is a significant global public health problem that impairs the functioning of individuals. Aging is intensifying, the number of people with sarcopenia is increasing, and there are currently no specific treatment drugs for sarcopenia. The clinical pathogenesis of sarcopenia is extremely complex, and the underlying mechanism of immunosenescence and dysbiosis associated with aging on sarcopenia is not well studied, and they are also potential therapeutic targets for sarcopenia. This review mainly discusses the relationship between sarcopenia from the perspective of intestinal microbiota dysbiosis and T cell changes in immunosenescence, and looks for promising targets for diagnosis or intervention of sarcopenia in the future, hoping to achieve early detection, early diagnosis and early treatment of sarcopenia and prolong the life span of healthy aging.

KEYWORDS

sarcopenia, gut microbiota, immunosenescence, T cell senescence, intestinal dysbacteria

1 Introduction

Sarcopenia, initially coined by researcher Irwin Rosenberg in 1989, is characterized as the age-related decline in lean body mass that impacts physical function and nutritional status (1). The European Working Group on Sarcopenia in Older People (EWGSOP) has promulgated a widely adopted definition of sarcopenia, which is globally acknowledged: It denotes a geriatric syndrome characterized by age-related diminution in muscle mass, muscle strength, and/or physical function. This definition is recommended for sustained utilization in the 2023 Chinese expert consensus on the prevention and management of sarcopenia in the elderly (2, 3).

Sarcopenia is associated with adverse outcomes such as falls, functional decline, frailty, and mortality. This includes an elevated risk of falls and hospitalizations, diminished capacity for activities of daily living, increased functional impairment, heightened incidence of multisystem diseases (cardiovascular (4), respiratory (5), neurological (6), etc.), reduced quality of life, loss of independence or necessity for long-term care placement, and even death (7). Consequently, this has significantly augmented the burden on individuals and society (8–10).

The pathogenesis of sarcopenia is highly complex. The investigation into immune senescence induced by aging, dysbiosis, and sarcopenia remains incomplete, and there is a lack of precise understanding regarding the potential mechanism of sarcopenia. This article primarily summarizes and analyzes the correlation between intestinal flora imbalance and T-cell alterations in immune senescence and sarcopenia. In the future, further scientific

research is imperative to gain a profound understanding of the potential mechanisms linking immune senescence, intestinal flora imbalance, and sarcopenia, as well as to identify early diagnostic targets and therapeutic drugs for sarcopenia.

2 Contemporary epidemiological trends in sarcopenia

In 2016, the World Health Organization officially included sarcopenia as a separate and independent disease with distinct characteristics in the tenth edition of The International Statistical Classification of Diseases and Related Health Problems (ICD-10) code (2, 11). This recognition marks an important step in distinguishing sarcopenia as a treatable disease and increasing attention to it (11, 12). In recent years, there has been a substantial increase in the global population of individuals aged 60 years and older. According to the "Aging and Health" report released by the World Health Organization on October 1, 2022, it is projected that the number of people over 60 will rise from 1 billion in 2020 to 1.4 billion by 2030, and further to reach 2.1 billion by 2050. As aging becomes more prominent, the prevalence of sarcopenia is expected to increase concurrently. Currently, approximately 50 million individuals worldwide are estimated to be affected by sarcopenia, with this number anticipated to escalate to 500 million by the year 2050 (13).

Sarcopenia, a geriatric syndrome, is increasingly recognized as a prevalent yet frequently underdiagnosed health concern. Its prevalence among the elderly is widely acknowledged to be variable, ranging from 5 to 50%, influenced by factors such as gender, age, comorbidities, and diagnostic criteria (14). The data revealed that the prevalence of sarcopenia among foreign community residents was 11% in males and 9% in females. In nursing home residents, the prevalence of sarcopenia was 51% for both sexes. However, hospitalized patients exhibited a prevalence of 23% in males and 24% in females (14, 15). Notably, sarcopenia appears to be more prevalent among individuals from non-Asian regions compared to Asian counterparts. The most recent epidemiological survey on sarcopenia in China indicates that the prevalence of sarcopenia among elderly community dwellers is 12.9% in males and 11.2% in females. Among hospitalized elderly individuals, the prevalence stands at 29.7% for males and 23.0% for females (16).

The wide range of prevalence is due not only to differences in Settings and populations, but also to the diversity of diagnostic criteria used. For example, a review published in "Metabolism-clinical And Experimental" in 2023 stated that sarcopenia affects 10–16% of the global elderly (17). The prevalence of sarcopenia ranges from 18% in patients with diabetes to 66% in patients with unresectable esophageal cancer (17). In Brazil, according to the 2015–2016 data, the critical point to define low muscle strength is <36 kg for men/<23 kg for women, and the prevalence of sarcopenia is 13.8% and the prevalence of possible sarcopenia is 40.1% (18). In Italy, a cross-sectional analysis of 655 participants in a multicenter observational study of older adults in 12 acute hospital wards concluded that the overall prevalence of sarcopenia was 34.7% and increased dramatically with age (19). In Taiwan, a 2021 study counted 173 participants aged ≥65 years from day care centers in northern Taiwan and found that the prevalence of sarcopenia was 50.9%, with probable sarcopenia 47.4% and normal 1.7%. In Europe and the United States, the prevalence of sarcopenia with different diagnostic criteria ranges from 4.6 to 43% in the community and from 23 to 68% in clinical Settings (20).

3 Immunosenescence and sarcopenia

The pathogenesis of sarcopenia is exceedingly complex, particularly with regard to age-related mechanisms contributing to its onset, including inflammation, immune dysfunction, cell senescence, anabolic resistance, abnormal skeletal muscle repair, intestinal microbiota imbalance, reduced physical activity levels and increased oxidative stress (21, 22). Our understanding of age-related immune senescence and dysbiosis and their association with sarcopenia remains incomplete. Moreover, the underlying mechanism of sarcopenia lacks precise comprehension. Currently, there are no effective pharmaceutical treatments for sarcopenia. Some researchers have proposed that immune aging and intestinal flora may regulate the development of sarcopenia and thus represent potential therapeutic targets worthy of further investigation (23, 24).

3.1 Immunosenescence

As a key pathogenic factor of sarcopenia, immunosenescence has a complex mechanism. Immunosenescence is the dysfunction and decline of the immune system that occurs during aging (25), involving innate and adaptive immunity. The alterations in the adaptive immune system (including B cells, $CD4^+$T cells, and $CD8^+$T cells) are particularly significant, with T cell changes being the most prominent (23, 26). Over the past few decades, extensive research has been conducted on immunosenescence in human and animal models. This process is marked by thymic degeneration, accumulation of senescent T cells, impaired function of innate immune cells (such as natural killer cells, macrophages, and neutrophils), as well as compromised maintenance and functional response of lymphocytes. Age-related alterations in skeletal muscle immune function have also been observed (27), with thymic degeneration playing a predominant role in immunosenescence. It is extensively documented that the thymus serves as a primary lymphoid organ responsible for T cell differentiation, development, and maturation (26).

The alterations in T cells are most prominent during immune aging, and these changes may not only diminish normal immune function but also trigger an inflammatory tendency (28), which is considered the primary cause for the heightened frequency and severity of diseases and infections in the elderly (29). Furthermore, it is also a significant factor influencing the onset and progression of sarcopenia.

In both CD4 and CD8 cells, naive T cells' proportion and absolute number progressively decline with age. This phenomenon is attributed to thymic degeneration and inadequate homeostatic proliferation (30). Given these characteristics, it is imperative to consider interventions to enhance T cell production and restore thymic function to prevent future immune senescence.

Regulatory T cells (Tregs), a specialized subset of CD4 + T cells that emigrate from the thymus and are generated through peripheral conversion of conventional CD4 + T cells, play a crucial role in maintaining central and peripheral immune tolerance and are distributed throughout various tissues and mucosal surfaces, including

the intestine (31). In addition to regulating inflammation, Tregs can also modulate muscle regeneration (31, 32). Dysregulated Tregs cell homeostasis has long been observed in aged mice and the elderly (33).

3.2 Immunosenescence and sarcopenia

At present, the evidence that immunity is related to sarcopenia is increasing year by year. Studies have confirmed that immunosenescence plays a role in age-related muscle atrophy, muscle fiber denervation, and reduced regeneration after injury (34). Previous reports have suggested a potential link or interaction between sarcopenia and immunosenescence through skeletal muscle (35), with immunosenescence exacerbating the effects of muscle wasting during aging, thus serving as a key factor in the development of sarcopenia.

Prior investigations have established that immunosenescence is characterized by an imbalance of immune cells and their subtypes, as well as the production of aging-related secretory phenotypic factors (26), which can attenuate muscle protein synthesis and enhance muscle protein breakdown (35, 36), ultimately leading to sarcopenia. Furthermore, immunosenescence may also contribute to the age-related decline in regeneration following muscle atrophy (34) and could potentially hinder the repair of skeletal muscle injury to some extent (37). The intricate relationship between changes in T cells during immune aging and sarcopenia warrants further investigation. Several potential mechanisms are outlined below.

Firstly, T cells not only release perforin and granzyme B cytotoxic particles but $CD28^-$ T cells also have the capacity to produce inflammatory cytokines such as TNF-α and IFN-γ (38). The elevated inflammatory state can lead to the occurrence of sarcopenia. It has been reported that the levels of biomarkers of the immune system, such as C-reactive protein (CRP), Tumor necrosis factor-α (TNF-α), reactive oxygen species (ROS), and interferon-α, increase slightly with age (39). Studies have found that TNF-α activates signal transduction by binding to its cell surface receptors, TNFR1 and TNFR2. By binding to TNFR1, Tnf-α increases the recruitment and activation of inflammatory cells, promotes the release of inflammatory factors, and ultimately exacerbates the chronic inflammatory state (40). Excessive production of these cytokines can accelerate the deterioration of skeletal muscle fiber diameter and protein content. They can also bind to corresponding receptors, initiating nuclear apoptosis in skeletal muscle through a series of reactions (36), thereby impacting muscle regeneration. Furthermore, they can promote metabolic breakdown in skeletal muscle leading to proteolysis and apoptosis of muscle cells (41). It has been shown that TNF-α disrupts the PI3 kinase /PKB signaling pathway, leading to L6 myotubes atrophy and cell death. In addition, it also directly acts on skeletal muscle cells by activating nuclear factor kappa light chain enhancer (NF-κB) and MAPK signaling pathways in activated B cells, promoting muscle protein breakdown and inhibiting muscle synthesis (40). For example, elevated expression of TNF-α in muscles is associated with muscular weakness; loss of muscle strength and mass is linked to worsening sarcopenia which results in degradation of skeletal muscle protein content and subsequent fatigue along with limitations on physical activity (42). TNF-α is implicated not only in the pathogenesis of sarcopenia but also in the downregulation of CD28 expression on T cells, leading to the accumulation of CD28—T lymphocytes, a hallmark of immune aging that contributes to a vicious cycle of sarcopenia (36). A genetic mouse model has shown that targeting NF-κB is critical to preventing skeletal muscle loss by genetically expressing a constitutively active endogenous inhibitor of NF-κB (IkappaBalpha, IκB) mutant to achieve muscle-specific inhibition of NF-κb. Denervation-induced atrophy was significantly reduced (40, 43). Therefore, the improvement or regulation of skeletal muscle function through TNF-α signaling pathway should be further studied in the future.

Immunosenescence results in a significant reduction in the number and function of satellite cells, as well as in the regenerative capacity of aging muscles (44, 45), and shifts satellite cells to a fibrogenic phenotype (46), thereby impairing muscle regeneration and leading to muscle atrophy. In response to the diminished capacity of T cells to regulate the function of satellite cells (skeletal muscle stem cells) during aging, relevant studies using T cell-deficient mice and activated splenic T cell mice have been conducted by some researchers. They have found that the adaptive immune response of T cells, releasing cytokines into damaged muscles, promotes the continuous proliferation of satellite cells. Additionally, aging may modify the function of muscle precursor cells induced by T cells and lead to sarcopenia (42, 47, 48). Studies have indicated that primary sarcopenia's pathogenesis is linked to the disruption of satellite cell characteristics. A decrease in both number and function of satellite cells has also been observed in sarcopenia patients (49). Therefore, as crucial contributors to muscle growth, senescent T-cells will reduce their proliferative ability, subsequently impacting muscle regeneration and leading to sarcopenia. Henceforth, it is imperative for further research on interventions targeting T-cell influence on satellite cell function aimed at enhancing muscular proliferation and differentiation among older individuals as a means to prevent or reverse age-related muscle loss.

Secondly, the direct cytotoxic effect of T cells can compromise the structural integrity of muscle fibers (50). The accumulation of memory T cells, particularly CD8+, is also considered detrimental in older individuals (51, 52). It has been proposed that the modification decline of T cell phenotype from $CD8^+$ to $CD4^+$ during immune aging may be associated with the loss of muscle mass (38).

Thirdly, a certain proportion of Treg cells not only facilitate muscle repair by regulating double regulatory protein (a growth factor targeting muscle stem cells) and extending the proliferation cycle of satellite cells (53) but also suppress muscle inflammation, making them crucial for muscle repair and regeneration (54, 55). However, in comparison to young individuals, T cells (especially Treg cells) in older adults fail to release appropriate factors (such as produced growth factors and cytokines (33, 56, 57) necessary for satellite cell proliferation and differentiation) into the microenvironment. This leads to inadequate muscle recovery and age-related deficiencies in muscle size and function (33). Another study found an increased frequency of Tregs in the spleen in aged mice, but they were unable to migrate to and accumulate in the injured skeletal muscle. This may lie in the fact that Tregs in aged mice show reduced expression of genes for the chemokine receptors CXCR6 and CCR7 and the S1P1 receptor that controls lymphocyte efflux from lymphoid organs (45). Research has revealed that without stimulation from Tregs during immune senescence, muscle satellite cells tend to proliferate rather than differentiate, resulting in the accumulation of satellite cells and loss of muscle mass (58). Pharmacological intervention targeting Tregs could

facilitate muscle satellite cell expansion and promote muscular repair, thereby enhancing overall muscle regeneration.

In summary, these studies suggest that an aging immune system, as well as the inability of aging T cells to accumulate in injured muscle, is a key cause of the impaired regenerative capacity of aging muscle.

4 Relationship between sarcopenia and gut microbiota dysbiosis

4.1 Gut microbiota

The gastrointestinal tract functions as the body's primary immune organ. Research indicates that it can accommodate up to 70% of the body's lymphocyte population and plays a crucial role in maintaining immune balance (59). The microbiota and the immune system have established a mutually beneficial relationship (60). Key metabolites, such as Short-Chain Fatty Acids (SCFAs) including acetate, butyrate, and propionic acid, permeate the intestinal epithelial barrier and interact with host cells to regulate immune responses and disease susceptibility (60). Additionally, age-related gut flora dysbiosis may increase susceptibility to various diseases, such as sarcopenia, inflammatory bowel disease, diabetes, and cardiovascular disease, by compromising intestinal barrier integrity and inducing immune dysfunction (61).

4.2 Aging/dysbiosis of gut microbiota

Research indicates that the gut microbiota undergoes age-related alterations (Dysbiosis of intestinal flora) in older individuals. This is characterized by a general decline in resilience of the gut microbiota after the age of 65, leading to significant changes in its overall composition due to factors such as medication and diseases (62, 63). These changes entail reduced species richness, decreased biodiversity, increased presence of opportunistic Gram-negative bacteria, and diminished representation of species with purported health-promoting functions. For instance, there is a decrease in the abundance of core symbionts like Bacteroides, Bifidobacterium, and short-chain fatty acid (SCFA) producers (e.g., *Faecalibacterium prausnitzii*, Eubacterium, Rozella and Ruminococcus) (64–66), while Proteobacteria and other opportunistic microorganisms (such as Fusobacterium, Paracbacteroides, and Ruminococcaceae), which are normally low in healthy young individuals, are expanded among the elderly (66, 67).

4.3 Dysbiosis in the gut microbiota contributes to immune system aging

The maintenance of intestinal homeostasis is intricately regulated by the activity of intestinal T cells. These T cells intricately secrete both anti-inflammatory and pro-inflammatory cytokines to ensure a balance in the self-renewal and differentiation of intestinal stem cells, thereby maintaining a high turnover rate of the intestinal epithelium (68). However, as individuals age, the control of intestinal homeostasis by T cells diminishes, leading to inflammatory pathology: proinflammatory cytokines can induce differentiation of intestinal stem cells and may result in damage to the intestinal barrier (69). Clark et al. demonstrated using the Drosophila model that with aging, dysfunction in the intestinal barrier and imbalance in gut flora can induce systemic immune activation through the JAK–STAT pathway, ultimately contributing to mortality (70). Additionally, an intricate germinal center response is coordinated among various cell types including steady-state T follicular helper (TFH) cells, T follicular regulatory (TFR) cells, TH17 cells, and Treg cells aimed at establishing a symbiotic relationship between host and microbe through secretion of microbiota-specific IgG and local high-affinity IgA by plasma cells. Due to the abnormal composition of T cells in the germinal center during aging, this reciprocal relationship is disrupted, resulting in perturbation of the intestinal microbial community (68, 71–73). This disruption manifests as intestinal dysbiosis caused by dysregulated T-cell response and may underlie aging-related inflammation. In summary, age or disease-induced imbalance of intestinal microbiota disrupts its composition and disturbs the equilibrium between microbiota and immune system. Consequently, immune tolerance to commensal bacteria is compromised, epithelial barrier function is impaired, intestinal permeability is enhanced, and there is an imbalance in activation between anti-inflammatory T regulatory lymphocytes and pro-inflammatory Th17 lymphocytes (60, 74, 75). As a result, systemic inflammation becomes chronically activated and continues to impact gut microbiota. Thus, a detrimental cycle forms between intestinal flora and the immune system (76). Furthermore, microbe-T cell interactions have emerged as a promising therapeutic target for age-related diseases (68).

The decrease in microbial diversity as individuals age results in a decline in the availability of short-chain fatty acids (SCFAs), such as acetate, butyrate, and propionate. This reduction facilitates uncontrolled bacterial proliferation, leading to inflammation and the onset of chronic diseases in older individuals (77). SCFAs are renowned for their pivotal role as signaling molecules in maintaining host metabolic and immune homeostasis (playing a crucial part in T cell homing (78)) and preserving intestinal barrier integrity (79, 80). Specifically concerning the intestinal barrier, butyrate acts as a distinctive energy source for colonic cells, regulating intestinal energy metabolism while suppressing colonic inflammation (81) and enhancing the intestinal barrier through the AMPK pathway (82). The protective impact of butyrate on the intestinal barrier is critical for preventing the translocation of microbe-associated molecular patterns (MAMPs) into the bloodstream and alleviating chronic inflammation in peripheral organs, including muscle (83). Regarding immune regulation, reduced microbial diversity heightens infection risk at distal mucosal sites like the lungs and affects host immune function (84). Co-housing young germ-free mice with old mice was found to elevate cytokine levels and impair macrophage function in young germ-free mice (85), indicating a causal relationship between age-related microbial dysbiosis and immune senescence for the first time. Another study confirmed that transferring gut microbiota from aged conventional mice to young germ-free mice promoted T-cell activation and small intestinal inflammation (86). In conclusion, the aging process leads to decreased SCFAs-producing microorganisms in the gut, such as *Faecalibacterium*, and a reduced availability of SCAFs. This has a detrimental impact on the integrity of the intestinal barrier, inflammation control, and immune function.

4.4 Imbalance in the gut microbiota and sarcopenia

Despite the anatomical separation between skeletal muscle and the gut, signals originating from the gut due to its interaction with the gut microbiome play a crucial role in connecting gut microbiota activity with skeletal muscle. The convergence of altered gut microbiota composition, physiological balance disruption, and muscle catabolic state induction suggest that the microbiota may directly or indirectly impact muscle mass status and regulation (87). Hence, the concept of a "gut-muscle axis" (i.e., the influence of gut microbiota and its interactions with the host gut on skeletal muscle metabolism and function) is particularly relevant in older sarcopenic adults (87). Increasing evidence has emphasized the pivotal role of the myenteric axis in sarcopenia.

Numerous studies have demonstrated an association between dysbiosis of gut microbiota and sarcopenia. For example, age-related increases in Firmicutes abundance and decreases in Bacteroidetes abundance observed in animal studies may be linked to reduced muscle mass and function. This unfavorable intestinal ecological environment could contribute to the development of sarcopenia. Conversely, a favorable intestinal ecological environment is conducive to preventing and treating sarcopenia (74). Animal studies have indicated that short-chain fatty acids (SCFAs), particularly butyrate, produced by gut microbes are beneficial for skeletal muscle mass (80, 88). It has been reported that acetate and propionate may be inversely correlated with muscle mass development (89). Unlike other SCFAs, butyrate exhibits histone deacetylase inhibitory activity, modulating DNA unwinding to regulate intestinal macrophages and promote peripheral Tregs cells, enhancing muscle differentiation and reducing muscle atrophy. However, with aging, there is a decrease in gut microbes producing SCFAs, which may be associated with sarcopenia (90). Professor Henderson's research has unveiled a significant correlation between fecal butyrate and human skeletal muscle mass in sarcopenia. This study has identified butyrate as a biomarker associated with muscle mass in older adults. Furthermore, Professor Henderson has substantiated that elderly individuals with low muscle mass exhibit diminished gut microbiome and fecal butyrate levels, suggesting a potential link between gut microbiome composition and muscle mass rather than muscle function. Certain gut microbes, including Marvinbryantia, Akkermansia, Subdoligranulum, Flavonifractor, and F.prausnitzii (also known as *Faecalibacterium prausnitzii*), have been found to be significantly linked to low skeletal muscle mass in the elderly, providing valuable insights into microbial-mediated pathways contributing to sarcopenia (81). A separate study demonstrated a significant increase in fecal butyrate levels among elderly individuals with preserved skeletal muscle mass (81), reinforcing the association between gut microbiota and skeletal muscle mass. It has been postulated that a transition of the gut microbiota from a protective to a proinflammatory role may disrupt immune response and host metabolism, ultimately resulting in a state of low-grade inflammation that upregulates molecular pathways associated with sarcopenia, ultimately leading to skeletal muscle injury and frailty (91). Nevertheless, insufficient evidence supports the direct impact of the gut microbiome on increasing muscle mass. Further research is warranted to explore the relationship between intestinal microbes and skeletal muscle mass and investigate which metabolites produced by intestinal microbes are linked to skeletal muscle mass.

4.5 Improved immune aging through the regulation of intestinal flora imbalance

It has been proposed that maintaining a useful or beneficial gut microbiota structure during the aging process potentially delays or restricts immune senescence (92). As such, regulating immune senescence in elderly individuals by modulating the gut microbiota represents a promising therapeutic approach. For instance, oral supplementation of bifidobacterium can enhance the proportion of lymphocytes (85). Cho et al., in animal experiments, observed that syringaresinol (SYR) could notably increase the Firmicutes/Bacteroides ratio by promoting beneficial bacteria (Lactobacillus and Bifidobacterium) while reducing opportunistic pathogenic bacteria. This alteration in microbial diversity would lead to an increase in total CD3T cells and naive T cells, thereby delaying immune aging (93).

5 Conclusion

In conclusion, given the intricate interplay among gut microbiota imbalance, sarcopenia, immune senescence, and T cells, the modulation of gut microbiota holds potential not only for enhancing immune function but also for improving muscle mass and strength. Therefore, can modulating gut microbiota improve muscle mass/strength by bolstering immune function in patients with sarcopenia? Further research is warranted to address this question.

Furthermore, the current understanding of the potential interplay among these three factors and the precise role of T cells in regulating intestinal microbiota in sarcopenia patients still needs to be completed. It remains to be elucidated which specific targets and pathways within these interconnected mechanisms could be leveraged to prevent and ameliorate sarcopenia. Additionally, it is essential to identify pharmaceutical agents that can modulate these targets and pathways to prevent and treat sarcopenia. Furthermore, it is crucial to determine whether these interventions can be effectively translated into clinical practice for predicting, diagnosing, and preventing sarcopenia and developing innovative microbiome-based or immunosenescence interventions for promoting healthy aging. Identifying targets that may lead to therapeutic agents enhancing muscle regeneration and mitigating the impact of muscle wasting during aging and disease is also imperative. Is it feasible to conduct individualized interventions targeting intestinal flora in sarcopenia patients? These are all areas requiring further exploration in future research.

Sarcopenia is a significant global public health concern that damages individual physical function. Currently, the Food and Drug Administration (FDA) has not sanctioned specific medications for sarcopenia treatment, thus necessitating urgent resolution of these issues. Addressing sarcopenia can facilitate the promotion of healthy aging. Presently, there remains a lack of awareness among the elderly regarding sarcopenia. Therefore, communities, hospitals, and society must enhance dissemination and education on knowledge related to sarcopenia so that older individuals can proactively prevent its onset and progression through physical exercise, improved nutrition, and probiotic supplementation. Aging poses a serious challenge in our

country, and instilling an ethos of "self-sustained health" in older people can effectively alleviate familial and societal burdens.

Author contributions

J-PC: Conceptualization, Funding acquisition, Methodology, Writing – original draft, Writing – review & editing. XC: Conceptualization, Funding acquisition, Methodology, Writing – original draft, Writing – review & editing. J-XC: Conceptualization, Funding acquisition, Methodology, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research and/or publication of this article. This work was supported by the Funding for Scientific Research Projects from Wuhan Municipal Health Commission (No. WX23B33).

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

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frontiers | Frontiers in Aging

TYPE Original Research
PUBLISHED 14 August 2025
DOI 10.3389/fragi.2025.1589730

OPEN ACCESS

EDITED BY
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RECEIVED 20 March 2025
ACCEPTED 07 July 2025
PUBLISHED 14 August 2025

CITATION
Stephenson JC, Tran TD and Graber TG (2025) Effects of high-intensity interval training on physical and cognitive function in middle-aged male mice.
Front. Aging 6:1589730.
doi: 10.3389/fragi.2025.1589730

Effects of high-intensity interval training on physical and cognitive function in middle-aged male mice

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Introduction: Declining functional capacity, both physical and cognitive, is a consequence of aging. However, exercise is a promising intervention to mitigate normal age- related decline. Although numerous studies have elucidated the benefits ofexercise per se, the effect of high-intensity interval training (HIIT) on a middle-aged population is less well-studied.

Objective: Our primary purpose was to assess the effect of 3 months of HIIT on physical and cognitive performance in middle-aged (17-month-old at the end) male C57BL/6J mice compared to sedentary controls (SED). We hypothesized that exercised mice would be resistant to age-related decline in cognitive and physical ability.

Methods: To measure physical function, we used the well-validated comprehensive functional assessment battery (CFAB) scoring system, comprised of determinants including voluntary wheel running, inverted cling, grip test, treadmill maximum speed, and rotarod performance. We measured cognition using open field test, novel object recognition, Y-maze, and puzzle box. Additional assessments included body composition (via MRI) and in vivo contractile physiology (plantar flexor torque).

Results: Training resulted in significant improvements in aerobic capacity for the HIIT group, increasing treadmill time by 28%, while the SED group demonstrated a 41.4% decline in treadmill time. However, we found no significant differences in overall cognitive function. Contrary to our previous research in other age groups, the current study found a negligible effect of HIIT on body composition.

Discussion: We note that at 17 months of age, mice did not exhibit any evidence of cognitive deterioration in either group over the training period, thus potentially explaining the lack of an exercise effect. We found that HIIT had less influence on both physical and cognitive function than expected, which may be because function in this age group remains relatively stable. Future work will investigate the adult cognitive response to HIIT in older adults, at ages where there is well-documented cognitive decline.

KEYWORDS

cognitive function, exercise, high-intensity interval training, physical function, treadmill training, body composition, muscle contraction, aging

Introduction

In the United States alone, the percentage of adults aged 65 years or older increased by 38.6% between 2010 and 2020 (Bureau, 2020). Compared to that in 2015, the global percentage of adults aged 60 years or older is projected to reach 16.5% or more by 2030, marking an increase of more than 4% (UN, 2017). Such developments and age distribution shifts toward an older population will increase the prevalence of age-related functional (physical and cognitive) declines, along with an increased need for medical interventions, skilled nursing facilities, and in-home care.

As we grow older, mild changes in cognition are expected and considered a normal feature of the aging process (Hugo and Ganguli, 2014), also known as *normal cognitive decline*. Evidence suggests there are a variety of genetic, environmental, health, and lifestyle factors that play a role in the brain's aging and cognitive capabilities as we age (Cadwallader et al., 2022). Certain health and lifestyle factors potentiate various forms of cognitive impairments and are modifiable risk factors (i.e., sedentariness, hypertension, obesity, etc.) that can be mitigated via exercise (Hugo and Ganguli, 2014). A 2019 meta-analysis observed significant associations between exercise-induced improvements in physical and cognitive function (Falck et al., 2019).

Regular exercise engagement throughout the lifespan may prove protective against age-related cognitive decline (ARCD), with studies showing that higher rates of exercise from early to mid-adulthood likely reduce the risk of cognitive decline later in life (Middleton et al., 2010; Yaffe et al., 2009). However, research also suggests that starting regular exercise later in life is still beneficial (Colcombe and Kramer, 2003). Studies in older adult populations have found that participating in exercise programs and increasing cardiorespiratory fitness are correlated with reductions in age-related neural changes (Erickson et al., 2011; 2010) and improvements in cognitive performance (Colcombe and Kramer, 2003; Falck et al., 2019; Freudenberger et al., 2016; Suzuki et al., 2012). Reported benefits of cardiorespiratory (aerobic/endurance) exercise on the brain include improvements in executive function and divided attention (Baker et al., 2010) and specific executive function skills such as inhibitory control and working memory (Cadwallader et al., 2022).

In this study, we examined the effects of high-intensity interval training (HIIT) on physical and cognitive performance in middle-aged male mice (aged 17 months at study completion). Previously, we demonstrated that HIIT can preserve physical function in adult (10-month-old) and older adult (26-month-old) mice (Pajski et al., 2024). HIIT is a type of exercise performed in pre-determined intervals of higher intensity interspersed with low-intensity (active rest) intervals. We hypothesized that there would be less cognitive and functional decline—as measured by the comprehensive functional assessment battery (CFAB) and a cognitive assessment battery (CAB) testing protocols—in the HIIT-exercised group (HIIT) than in the sedentary control group (SED). We measured exercise capacity and physical function with the previously-validated CFAB (Graber et al., 2021; Pajski et al., 2024; Pajski et al., 2025) and assessed cognitive function with a battery of commonly used cognitive/behavioral tests for mice (open-field test, Y-maze, novel object recognition, and puzzle box) (Ben Abdallah et al., 2011; Ohtomo et al., 2021; Sabaghi et al., 2019; Shepard et al., 2017; Szatmari et al., 2021; Wu et al., 2020). In addition, we determined the impact of HIIT on body composition (EchoMRI), muscle wet weight, and maximal isometric plantar flexor torque. We observed significant changes between the two groups' aerobic capacity and treadmill speed but did not observe significant improvements in cognitive performance.

Methods

Subjects

We obtained C57BL/6J male mice (n = 16) from The Jackson Laboratory at 10 m (months) of age. Within a week of arrival and before pre-testing processes began, one subject died of natural causes, leaving 15 mice for the remainder of the study. Mice started exercise training at 14 m (middle-aged mouse) Hagan, 2017) and completed training at the middle-aged timepoint of 17 m, which is equivalent to a human in their mid-50s (see supplemental section of Pajski et al., 2024). Mice were treated humanely in accordance with guidelines approved by the ECU Institutional Animal Care and Use Committee (IACUC). Mice were group-housed under 12-h light/dark cycles at 22 °C, with *ad libitum* access to food and water. Due to aggressive behavior/fighting and resulting injuries, some mice were unavoidably singly housed during the study, as recommended by our staff veterinarians and required by the IACUC.

Study design

Figure 1 shows the study design. After an acclimation period, we completed pre-intervention performance assessments (physical and cognitive) and then randomized the mice into two groups: SED (n = 7) and HIIT (n = 8). Next, we conducted a 12-week HIIT intervention where the HIIT intervals were based on a treadmill maximum speed test. During this time, we subjected the SED mice to sham treatment. As the HIIT intervention concluded, post-testing and maintenance training commenced. Maintenance exercise training was performed during the post-testing phase to preserve any exercise-induced adaptations in the HIIT mice until testing was complete. Finally, following post-testing, we performed tissue collection for later analysis.

Intervention

After baseline testing and data analysis, we randomized the mice into their respective groups and began intervention. The intervention period consisted of one treadmill acclimation week, followed by 12 weeks of HIIT on the treadmill. The mice completed 6 weeks of training before they were re-evaluated on a treadmill, after which, the last 6 weeks of training commenced with an adjusted baseline for their intervals based on the retest. HIIT training was three times per week, one session every other day (i.e., Monday, Wednesday, and Friday), to allow for rest and recovery between exercise sessions. During the intervention, mice were group-housed in cages with environmental enrichments, such as a block or tunnel

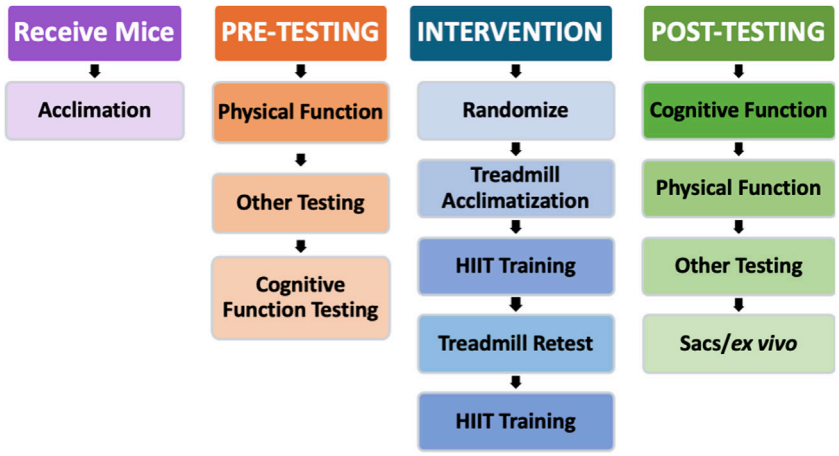

FIGURE 1
Study design. After the initial acclimation period and baseline testing, the mice began the intervention stage of the experiment. The HIIT group acclimated to treadmill training for 1 week, trained for 6 weeks, retested for maximum speed on the treadmill, and then trained for another 6 weeks. Following the HIIT intervention, all mice were retested for physical and cognitive function. Physical and cognitive function testing were reversed between pre- and post-testing to account for any biases potentially created by testing in the same order.

for stimulation and play, but no means of structured exercise (i.e., running wheels) was provided, aside from general physical activity (PA). Some mice needed individually housing due to over-aggression and fighting; these housing changes were made in consultation with the veterinarians from our Department of Comparative Medicine, who oversee the animal facility.

High-intensity interval training

Acclimation and training

Before the first week of HIIT, we acclimated the mice to the treadmill and interval speed changes for 1 week (three sessions). They ran one interval on the first day, two intervals on the second day, and three intervals on the third, with warm-ups and cool-downs on each day. By the first week of training, the mice were running for three HIIT intervals at 75% of their cohort's average maximum speed, transitioning to higher percentages and more intervals throughout the intervention. We added additional intervals as tolerated, up to a maximum of five, as the intensity/speed was also increased to the tolerance of the mice. If a mouse was unable to complete the scheduled training at the expected intensity, it moved to the next slowest group until improvements were observed. After the sixth week (midpoint) of the intervention, the mice were retested for a new maximum speed. Then, we adjusted relative interval speeds accordingly.

Exercise sessions

We used the average maximum speed ($Speed_{max}$) of the mice—as measured by the baseline treadmill test—to determine percent maximum speed ($\%Speed_{max}$) for the HIIT intervals. Based on their fastest recorded speeds, we grouped the mice into exercise cohorts with similar maximum speeds. We exercised the mice 3 days/week, with one rest day between training sessions (i.e., Monday, Wednesday, and Friday) and two rest days on weekends. Each HIIT session began with a 2-min warm-up at the base speed (4 m/min), followed by 1-min intervals at sprint speed (with 30-s ramp-ups and 30-s ramp-downs, for a total of 2 min per interval), and interspersed with 1-min relative rest (walking speed). After the final HIIT interval, each session concluded with a 2-min cool-down at the base speed.

Sham treatment

To equalize the experiential environment of HIIT and SED mice, the SED group received a sham treatment. For this sham treatment, SED mice were placed on the treadmill each day that HIIT training was conducted. SED mice did not exercise, but they explored the unmoving treadmill for the same total time as each HIIT session, with the shock grid activated.

Performance assessments

The same investigators performed the physical function and cognitive assessments throughout the study, with baseline and end-point assessments in the same order and at the same time of day. We used maintenance exercise training to maintain adaptations throughout the post-testing period.

Physical function assessments

Functional performance

We assessed mouse physical function and exercise capacity via CFAB pre- and post-intervention. We previously validated the CFAB for male mice at three different ages (adult 6 m and older adult at 24 and 28 m) and longitudinally in male and female mice across the lifespan (Graber et al., 2021; Pajski et al., 2024). In summary, we tested the mice using a series of commonly used well-validated determinants, including grip meter (forelimb strength), inverted cling (full-body strength/endurance), voluntary wheel running (VWR; volitional exercise and individual activity levels), rotarod (overall motor function, gait speed, balance/coordination, and power generation), and

treadmill (maximum running speed and endurance/aerobic exercise capacity). The methodology for the determinants comprising CFAB has been previously described (Graber et al., 2021; Pajski et al., 2024).

CFAB data analysis

Traditionally, CFAB data analysis uses a reference group of 6-month-old mice (mean and standard deviation; SD), and test results for each mouse are standardized (difference in SD from previously published 6-month means) and summed together to quantify a composite CFAB score, a single numeric value representative of overall physical function capacity (Graber et al., 2023; 2021; Pajski et al., 2024). In the current study, baseline standardization was based on the pre-intervention mean and SD of the entire sample ($n = 15$), assessed prior to randomization. Individual mouse scores were then compared to this baseline. We compared the differences between pre- and post-testing ($\Delta CFAB = CFAB_{post} - CFAB_{pre}$), similar to our frailty intervention assessment value (FIAV), as previously explained (Graber et al., 2015).

Other physical measures

Body and muscle mass

We determined body composition (fat percentage, fat%) from pre- to post-intervention using an EchoMRI-700d. The EchoMRI-700™ (Echo Medical Systems) is a quantitative nuclear magnetic resonance system that provides precise whole-body composition measurements *in vivo*.

In vivo contractile physiology

We determined plantar flexor torque using the Aurora Whole Mouse 3-in-1 Physiology Suite (Aurora Scientific), as previously described (Brightwell et al., 2021; Graber et al., 2021). In brief, each mouse was anesthetized on a 37 °C heated platform to maintain body temperature using ~3% isoflurane delivered at 1.5 L/min of O_2 via a VetEquip Vaporizer and nosecone, effectively eliminating conscious control of skeletal muscles. We positioned the knee at 90°, with the tibia aligned parallel to the platform. The femur was stabilized by clamping the lateral and medial epicondyles to prevent leg movement while still allowing for free movement below the knee. We set the foot into a footplate connected to a force transducer and then adjusted the height to firmly set the heel into the bottom of the plate. Using subcutaneously placed needle electrodes, we determined the optimal location and current needed to produce a maximum torque twitch. This current and needle placement were maintained during a torque/frequency curve (a single pulse and then 10, 40, 80, 100, 120, 150, 180, and 200 Hz) to determine the maximum tetanic isometric torque of the plantar flexor muscles (triceps surae).

Cognitive function assessments

Cognitive performance

We assessed cognitive function with our cognitive assessment battery (CAB) pre- and post-intervention. We determined cognitive performance through the application of memory, behavioral, and executive function tasks. The tests included in CAB were as follows: open-field test for anxiety, locomotor, and exploratory behavior (Creighton et al., 2019; Szatmari et al., 2021); Y-maze for exploratory behavior and spatial working memory (Sabaghi et al., 2019); novel object recognition (NOR) for exploratory behavior and long-term memory (Creighton et al., 2019; Szatmari et al., 2021); and puzzle box for memory and executive function (Ben Abdallah et al., 2011; Shepard et al., 2017). We recorded all cognitive/behavioral assessments using a GoPro Hero 6 Black for later analysis and data quantification. We analyzed CAB outcome measures individually. The CAB determinants are briefly explained as follows.

Open field

The Open field (OF) test is a commonly used behavioral test for assessing general locomotor activity, anxiety-like behavior, and exploratory tendencies in mice (Creighton et al., 2019; Szatmari et al., 2021). The testing arena was a 58 × 58 × 40 cm box, made of a non-abrasive plastic, with an open top for direct lighting and video recording. Before testing, we assessed light distribution using the Light Meter LM-3000 to ensure uniformity of brightness (750 ± 10 lux) across the testing arena. We applied direct lighting using a single LED lamp positioned over the center of the arena. The outcome measures for OF were the number of entries into the center and the time (s) spent in the perimeter.

Y-maze

The Y-maze assessed spatial working memory, as described in the literature (Sabaghi et al., 2019). We used a custom-built symmetrical Y-shaped maze with a non-reflective, neutral-colored surface (beige); the details are provided in Supplementary Information. In brief, we positioned each mouse in one arm of the maze (designated Arm A), facing the center, and allotted them 8 min of uninterrupted exploration time. We defined entry into an arm as the animal having all four paws inside the arm. We assessed locomotor activity via total arm entries, and any latency to leave the starting arm was an indication of emotionality-related behavior. The percentage of spontaneous alternation performance (%SAP) was our outcome measure for this test. We defined a spontaneous alternation (SA) in this experiment as sequential entries into all three arms in overlapping triplet sets (i.e., ABC, BCA, CAB, or vice versa), as shown in Supplementary Figure S3. We calculated the %SAP as the ratio of total alternations to possible alternations (%SAP = SA/[total arm entries – 2] x 100).

Novel object recognition

We administered NOR to assess long-term memory and exploratory behavior in mice (Creighton et al., 2019; Szatmari et al., 2021). Discrimination of novel versus familiar stimuli requires intact perceptual systems. Therefore, if a mouse spends more time exploring a novel object (NO) compared to a familiar object (FO), it is indicative of an intact memory (Creighton et al., 2019). We calculated a discrimination ratio (DR) to quantify novelty preference. We did so by subtracting the time (s) spent exploring the FO from the time spent exploring the NO and then dividing the difference by the total object exploration time (s; DR = (NO – FO)/ total exploration). DR was the outcome measure for the NOR test.

TABLE 1 Main findings: statistics: *p*-value (*p*-val) for between groups from independent t-test and for within groups from paired t-test. *p*-val is given in bold if significant. KEY: HIIT, high-intensity interval training group; SED, sedentary control group; mN*m/gbm, milliNewtons-meters normalized to grams of body mass; pre, prior to the intervention period; post, following intervention period.

Between groups						
Test	Variable	Units	Group	Mean ± SE	Effect size	*p*-val
Treadmill	Time to failure	Seconds	HIIT	630.75 ± 43.06	2.883	**<0.001**
			SED	308.14 ± 37.48		
		%change	HIIT	36.42 ± 14.80	1.974	**0.002**
			SED	−34.68 ± 10.46		

Within groups							
Test	Variable	Units	Group		Mean ± SE	Effect size	*p*-val
Treadmill	Treadmill time/aerobic capacity	Seconds	SED	Pre	525.86 ± 70.23	1.475	**0.008**
				Post	308.14 ± 37.48		
			HIIT	Pre	492.63 ± 49.72	−0.923	**0.035**
				Post	630.75 ± 43.06		
Body composition	Body mass	Grams	SED	Pre	35.46 ± 1.72	−1.385	**0.019**
				Post	40.08 ± 3.33		
			HIIT	Pre	35.51 ± 1.62	−1.118	**0.016**
				Post	39.17 ± 2.59		
	Fat%	%	SED	Pre	19.72 ± 4.06	−1.311	**0.013**
				Post	26.11 ± 3.17		
			HIIT	Pre	22.00 ± 3.61	−2.169	**<0.001**
				Post	27.28 ± 3.48		
Plantar flexor torque	Normalized torque	mN*M per gbm	HIIT	Pre	0.86 ± 0.064	0.076	0.873
				Post	0.86 ± 0.067		
			SED	Pre	0.83 ± 0.067	0.612	0.243
				Post	0.74 ± 0.056		
Open field	Time spent in perimeter	Seconds	SED	Pre	435.29 ± 5.30	−0.863	0.063
				Post	450.71 ± 7.37		
			HIIT	Pre	433.38 ± 5.29	−1.119	**0.016**
				Post	458.63 ± 5.08		
Y-maze	Spontaneous alternations (SAs)	Count	SED	Pre	14.43 ± 1.02	−1.330	**0.013**
				Post	19.14 ± 1.16		
			HIIT	Pre	11.88 ± 1.37	−1.63	**0.002**
				Post	18.00 ± 1.10		
	Spontaneous alternation %	SA/(total-2)	SED	Pre	63.11 ± 3.22	−0.110	0.781
				Post	64.05 ± 4.24		
			HIIT	Pre	60.15 ± 3.34	0.330	0.381
				Post	56.75 ± 2.08		
	Total arm entries	Count	SED	Pre	25.00 ± 1.45	−1.501	**0.007**
				Post	32.29 ± 2.00		

(Continued on following page)

TABLE 1 (*Continued*) Main findings: statistics: *p*-value (*p*-val) for between groups from independent t-test and for within groups from paired t-test. *p*-val is given in bold if significant. KEY: HIIT, high-intensity interval training group; SED, sedentary control group; mN*m/gbm, milliNewtons-meters normalized to grams of body mass; pre, prior to the intervention period; post, following intervention period.

Within groups							
Test	Variable	Units	Group		Mean ± SE	Effect size	*p*-val
			HIIT	Pre	22.00 ± 2.53	−1.881	**0.001**
				Post	33.88 ± 1.89		

Puzzle box

The puzzle box is a commonly used test that is designed to assess executive function skills in mice via working memory and problem-solving requirements. We based our adaptation on previously used versions (Ben Abdallah et al., 2011; Shepard et al., 2017). For this adaptation of the puzzle box assessment, a PVC pipe connects the big OF arena to a much smaller "puzzle box" (17.3 × 21 × 17.6 cm). The OF arena was the open, brightly illuminated starting area, while the smaller, darker puzzle box was the objective area. To access the objective area, subjects must climb into the tunnel and make their way across.

We began the puzzle box tasks by positioning each mouse in the center of the wall, directly across from the puzzle box access. We released the mice and started a timer. The outcome measure was the latency to complete each objective. We used a treat/prize (i.e., an unsalted walnut, almond, or plain Cheerio) as an additional incentive. With each test, we modified the access point to increase the difficulty of reaching the puzzle box. First, we evaluated the mice without any obstacle to accessing the puzzle box (day 1). Next, we added an obstruction, blocking the exit of the PVC pipe, which the mice had to simply knock down to gain access to the puzzle box (day 2). The last task had two trials (T1 and T2), and for each trial, the entrance point faced a different direction (day 3). For analysis of this test, we used a 0–1 scoring system based on the completion of certain objectives (i.e., entering the tunnel and removing the barricade). Subjects were allotted a 0 for each objective that they failed to complete or a 1 for each objective successfully completed. The outcome measure for this test was the total score achieved on all objectives.

Statistical analysis

We used Student's independent samples, paired t-tests, and 2 × 2 ANOVA, as appropriate, to compare dependent variables with the results reported in the appropriate tables, alongside the mean, SD, SEM, effect size (Cohen's D or η^2), skew, kurtosis, and the results of the Kolmogorov–Smirnov and Shapiro–Wilk tests for normality (details are reported in online-only Supplementary Datasheets S1–6 and Table 1). We used independent-samples t-tests to compare the mean differences in CFAB and CAB performance scores between the HIIT and SED groups. We compared changes within the groups using paired sample t-tests. We also assessed CFAB functional determinants using a 2 × 2 mixed-design ANOVA (see results for more details). Differences were deemed significant at $p < 0.05$. Data were expressed as the mean ± SE (standard error), unless otherwise indicated, with the effect sizes reported as appropriate.

Results

Further details can be found in online-only Supplementary Datasheets S1–6 and Table 1.

Physical function (CFAB): improved aerobic capacity from HIIT

We determined physical function and exercise capacity pre- and post-intervention using CFAB. Note that all CFAB determinants were normally distributed, as we have previously determined and published (Graber et al., 2021), with the exception of inverted cling, which we transformed to log10 to meet the criteria of normality for our statistical tests.

There were no significant changes (2 × 2 mixed ANOVA [two groups: SED and HIIT; and two time points: pre- and post-intervention]) in grip meter (strength), inverted cling (overall strength/endurance), voluntary wheel running (volitional exercise), or rotarod (overall motor function) with training either between or within subjects compared to sedentary mice. More details can be found in Supplementary Datasheet S1 and Figure 2.

To assess changes in aerobic capacity and running speed, we administered the treadmill maximum speed test pre- and post-intervention for both groups. In the HIIT group, treadmill time significantly increased by 28.0% from pre- to post-training, while the SED group showed a decline in performance by 41.4% (2 × 2 ANOVA within-subjects interaction effect of time*groups: $F = 21.381$, $p < 0.001$, and partial $\eta^2 = 0.622$; between-subjects effect of time*groups: $F = 5.572$, $p = 0.035$, and partial $\eta^2 = 0.300$). On average, the HIIT group increased treadmill time by 138.1 s, while the SED group declined by 217.7 s (see Supplementary Datasheet S1 and Figure 3) from pre- to post-intervention (between-group *post hoc* testing using an independent-samples t-test $t = 5.572$ and $p < 0.001$; within-subjects *post hoc* paired-samples t-tests showed that both groups experienced significant changes with large effect sizes: SED $t = 3.901$, $p < 0.008$, and Cohen's $d = -1.475$; HIIT $t = 2.612$, $p = 0.035$, and Cohen's $d = 0.923$). In addition, between the groups, the mean maximum speed was equal during pre-testing ($p = 0.555$) but was significantly altered from pre- to post-training ($p = 0.00008$) (see Figure 4). Within the groups, the mean maximum speed increased in the HIIT group ($p = 0.038$) and decreased in the SED group ($p = 0.019$). Overall physical function, as measured by the CFAB, did not

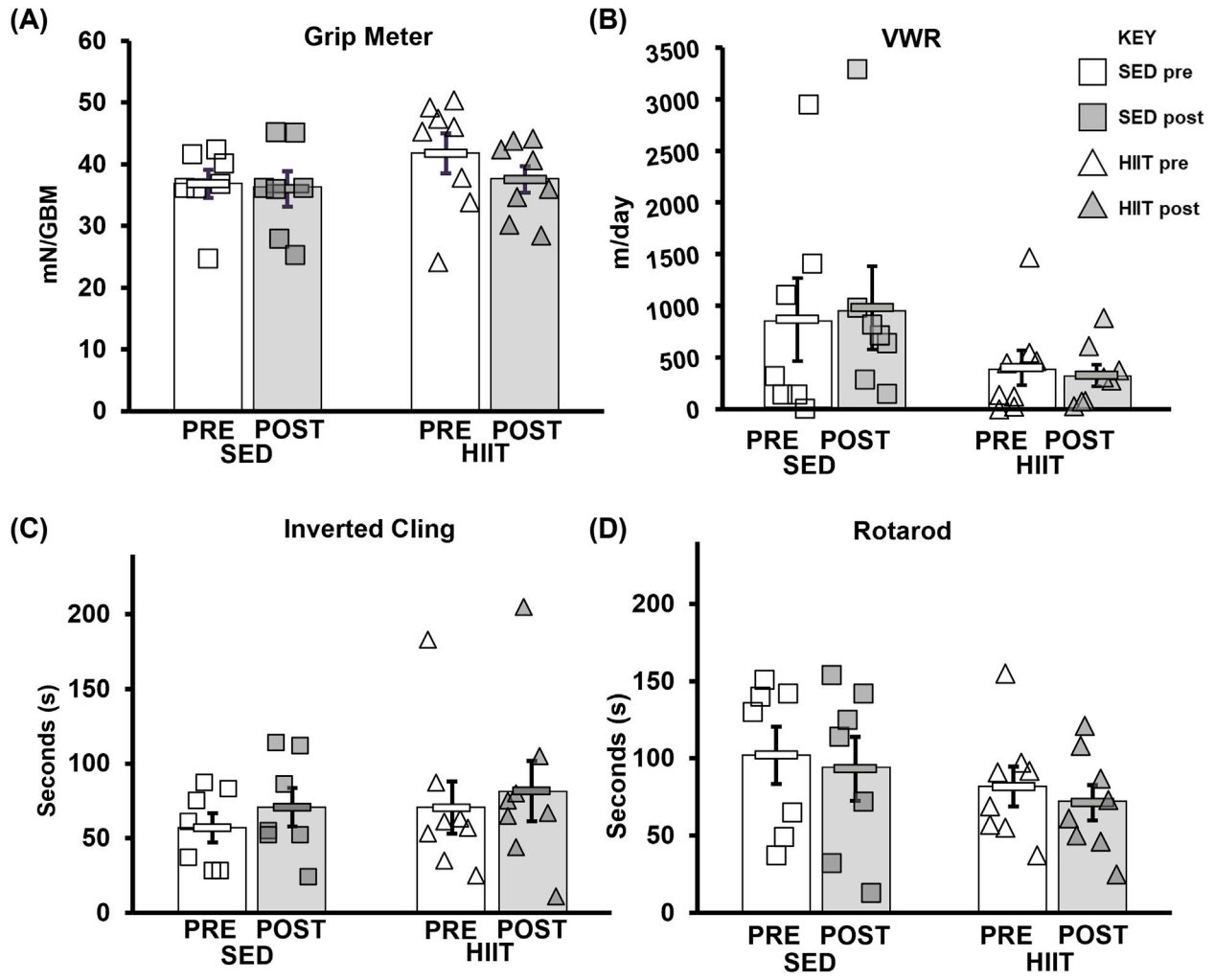

FIGURE 2
CFAB determinants. **(A)** Grip meter. **(B)** VWR. **(C)** Inverted cling. **(D)** Rotarod. From pre- to post-intervention, none of these tests demonstrated significant training effects. KEY: mN/GBM, milliNewton per gram of body mass. SED, sedentary control group; HIIT, high-intensity interval training group; PRE, baseline before the intervention period; POST, value after the intervention period.

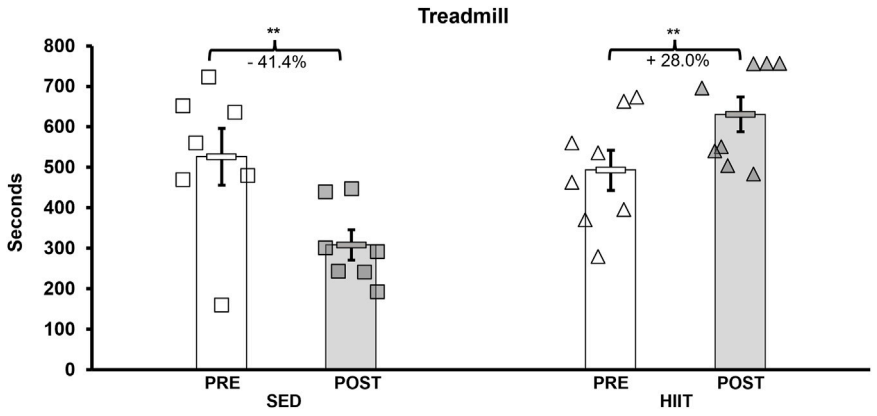

FIGURE 3
Treadmill maximum speed test. Pre-intervention testing revealed no significant difference in aerobic capacity, and after training, HIIT aerobic capacity increased (+138.1 s) and SED decreased (–217.7 s). KEY: SED, sedentary control group; HIIT, high-intensity interval training group; PRE, baseline before the intervention period; POST, value after the intervention period; ** = $p < 0.01$.

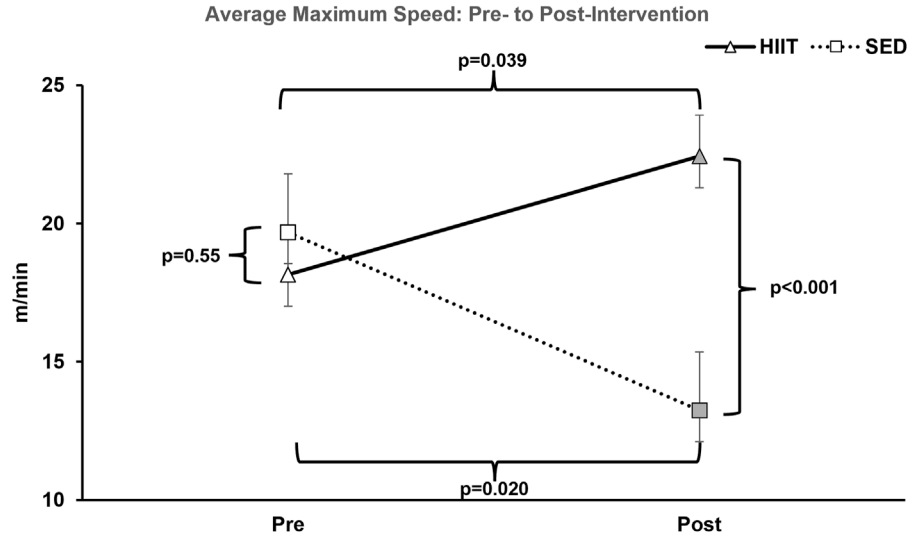

FIGURE 4
Average maximum treadmill speed. At pre-intervention testing, there was no significance observed between groups. However, after the training period within-group, HIIT significantly increased and SED decreased; between-group HIIT > SED. KEY: SED, sedentary control group; HIIT, high-intensity interval training group; PRE, baseline before the intervention period, POST, value after the intervention period.

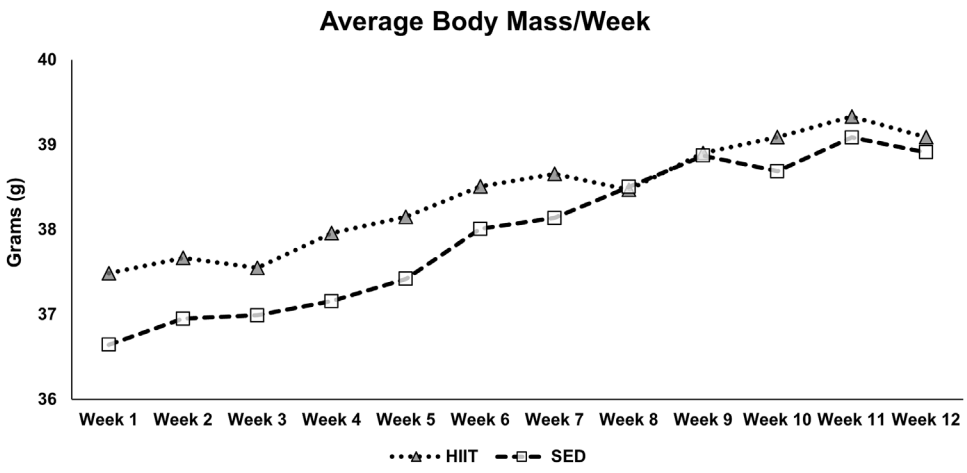

FIGURE 5
Average body mass by week. The mice were exercised or exposed to sham treatment for 3 days/week. Every week, before their third session, the mice were weighed, and the average body mass was calculated. KEY: SED, sedentary control group; HIIT, high-intensity interval training group.

alter from pre- to post-training (within-subjects effect of time*groups: F = 0.070, p = 0.795, and partial η^2 = 0.005; between-subjects effect of time*groups: F = 0.037, p = 0.851, and partial η^2 = 0.003). Further details can be found in Supplementary Figure S1 and Supplementary Datasheet S1.

Other measurements

Body composition

We measured the body mass (grams; g) weekly throughout the intervention (see Figure 5), prior to each EchoMRI, and at euthanasia. There was no difference in any of the measurements prior to training. The within-group differences in body mass, fat mass, and fat% measured by EchoMRI were significantly greater from pre- to post-training (2 × 2 repeated measures ANOVA: F = 20.062, 46.845, and 35.899, respectively; all $p < 0.001$). Lean mass (within groups) tended to decrease in SED and yet remained the same in HIIT from pre- to post-training (2 × 2 repeated measures ANOVA: F = 3.551 and $p = 0.082$). Between groups, the lean mass difference had a strong effect size (−0.746) though it was not statistically significant (independent samples t-test, $p = 0.173$), potentially due to large individual variability. Further details can be found in Supplementary Datasheet S2 and Figure 5.

Muscle mass

At euthanasia, we collected the gastrocnemius (GAS), plantaris (Plant), tibialis anterior (TA), extensor digitorum longus (EDL), soleus (SOL), and heart. We blotted the tissues dry and weighed them (grams; g) before flash-freezing for later analysis. Between-groups analysis (independent-samples t-test) showed no significant differences for each muscle or the total muscle mass (composite of GAS, Plant, TA, EDL, and SOL). Further details can be found in Supplementary Datasheet S3.

In vivo contractile physiology

We determined the maximum isometric plantar flexor torque before and after the intervention period. There were no significant differences between the groups at pre-intervention testing. We found no significant changes within groups (paired samples t-test) in either the maximum torque (mN*m) or normalized torque (mN*m/grams of body mass; paired samples t-test: SED $t = 1.369$, $p = 0.243$, and Cohen's $d = 0.612$; HIIT $t = 0.170$, $p = 0.873$, and Cohen's $d = 0.076$) following training. Further details can be found in Supplementary Figure S4.

Cognitive function

We measured different parameters of cognitive function using four different tests administered pre- and post-intervention and then analyzed the results using independent-samples t-tests between groups and paired samples t-tests within groups. Further details can be found in Supplementary Datasheet S5, Table 1.

Open field

For the OF test, we counted entries into the center and the time spent in the perimeter. Within the HIIT group, pre- to post-intervention changes demonstrated a significant increase in time spent in the perimeter ($p = 0.016$, effect size 1.2), which is indicative of greater anxiety-like behavior. The SED group tended ($p = 0.063$, effect size 0.86) toward a similar result. However, there were few defecation and urination events during both pre- (four total for all mice) and post-testing (none), indicating limited evidence of anxiety in this regard. The details can be found in Supplementary Figure S2.

Y-maze

The Y-maze assesses subjects' spatial reference memory by measuring the number of spontaneous alternations (SAs) made in the allotted test time and converting the SAs into a percentage of the total number of arm alternations (%SAP). The number of SAs increased significantly in both groups (within groups: HIIT, $p = 0.002$, effect size 1.63; SED, $p = 0.013$, effect size 1.33 from pre- to post-intervention). However, the total arm entries also increased significantly in both groups (within groups: HIIT, $p = 0.001$, effect size 1.99; SED, $p = 0.007$, effect size 1.50), thus resulting in no significant improvements in %SAP. Although the total arm entries increased in both groups, the increase was greater in the HIIT group (54% versus 31.2% in SED). The details can be found in Supplementary Figure S3.

Novel object recognition

There were no significant changes in NOR between groups ($p = 0.757$) from pre- to post-training. No changes were observed within the groups (SED $p = 0.20$; HIIT $p = 0.502$). The details can be found in Supplementary Figure S4.

Puzzle box

We did not find significant overall changes in the puzzle box tests between groups after training with our total point system ($p = 0.689$, effect size 0.212), and there was no difference in pre-testing ($p = 0.452$, effect size 0.40). The total point system also showed no changes within-group from pre- to post-intervention (SED $p = 0.356$, effect size 0.38; HIIT $p = 0.32$, effect size 0.13). However, for the blocked exit task, the between-group analysis showed that the SED group was significantly faster at *entering the tunnel* ($p = 0.036$, effect size 1.33) pre-intervention, but this was not replicated in post-testing ($p = 0.306$, effect size 0.55). Although between-group analysis showed significance for other test variables collected, none fit normality. For example, in the differing entrance task, analyses showed that the SED group was significantly better at locating the second (T2) entrance during the pre-intervention assessment ($p = 0.005$), but this advantage was not observed post-intervention ($p = 0.904$). The details can be found in Supplementary Figure S5.

Exercise intensity/work

HIIT intensity and work increased through middle age

Throughout the intervention, the HIIT group's exercise intensity and work performed increased relative to how each mouse was responding to their current exercise load. Over the course of the HIIT intervention, exercise intensity (%$Speed_{max}$) increased by an average of 14.36%. Between the midway point (week 6) treadmill retest and the last day of training (week 12), exercise intensity increased by an average of 15.27%. We calculated the total amount of work (m*gbm, meters*grams of body mass) for each HIIT session performed. The average significant difference ($p < 0.05$) in power produced (work performed per minute) between each subject's first and last HIIT session was equal to 40.32 (m*g)/min. This indicates evidence of exercise adaptation.

Discussion

We designed the current study to determine the pre- to post-training effects of a 12-week HIIT treadmill protocol (Pajski et al., 2024) on the functional and cognitive performance in middle-aged C57BL/6J male mice compared to that in a sedentary control group. Overall, CFAB did not change with exercise in this population, though we observed significant improvements in the HIIT aerobic capacity and treadmill speeds, with a corresponding decline in SED. We observed significant increases from pre- to post-training in both HIIT and SED for body mass, fat mass, and fat % (within groups) and a strong effect size for lean mass difference between groups (HIIT retains lean mass, though not significantly). Finally, we did not detect any significant cognitive changes between the two groups. However, in the Y-maze test, there was an overall increase in exploratory behavior (more SA and more arm entries), yet there was no change in the ratio, indicating no increase in memory function. The increased level of exploratory behavior may

be indicative of reduced anxiety during the repeated measurement, perhaps due to memory of the prior test or increased handling leading up to the second assessment.

HIIT

In recent years, HIIT has been popularized as a safe and time-conscious alternative mode of exercise. HIIT exercise research has reported positive effects on several chronic diseases (Askim et al., 2014; Molmen-Hansen et al., 2012; Rose et al., 2020; Støa et al., 2017) often associated with cognitive decline/diseases in older adults (Annual Congress, 2020). Furthermore, even short-term (6 weeks) HIIT has produced physiological and physical fitness improvements similar to, and better than, endurance and/or resistance training in middle-aged men (Callahan et al., 2021).

We adapted our 12-week treadmill HIIT protocol from previous studies (Pajski et al., 2024; Seldeen et al., 2018). While Seldeen et al. (2018) used mice aged 22 m, the findings from Pajski et al. (2024) were based on adult mice aged 6 m–10 m and older mice aged 22 m–26 m. Thus, there remains a gap in the literature for the 14 m–17 m (middle age) age range.

Graber et al. (2021) validated the use of CFAB in male mice at 6 m, 24 m, and 28 + m of age, observing an overall age-related physical function decline. In the current study, we detected no significant changes in CFAB or the CFAB determinants of grip meter, inverted cling, VWR, and rotarod. This contrasts with prior findings of significant improvements in, or preservation of, physical function (Pajski et al., 2024; Seldeen et al., 2019; Seldeen et al., 2018). However, Seldeen et al. (2019); Seldeen et al. (2018) did not observe improvements in rotarod for the HIIT group in their 2018 study, nor did they observe significant changes in rotarod or inverted cling for either group (SED or HIIT) in their 2019 study. Notably, these studies investigated different age groups than the current study. In a recent work, a relative plateau in functional capacity between 12 m and 18 m in male C57BL/6 found by Pajski et al. (2024) indicated a stability of function, instead of decline, in early-to-later middle-age, which might partly explain our results. Although overall CFAB scores did not improve with training, there was a marked improvement in aerobic capacity (treadmill time) and treadmill speeds in the HIIT group, while the sedentary control mice exhibited a decline. This finding is consistent with prior studies (Callahan et al., 2021; Pajski et al., 2024; Seldeen et al., 2019; Seldeen et al., 2018) in both animals and humans.

Contrary to our hypothesis, neither group showed a decline in cognitive function, nor did exercise result in any improvement. With no decline in either group, there was no preservation of function either. In the literature, there appears to be a correlation between age and cognitive performance in C57BL/6 male mice (Daneshjoo et al., 2022; Pettan-Brewer et al., 2013). Pettan-Brewer et al. did not demonstrate changes measured by the radial water tread maze in male mice (measured at 4, 12, 20, and 28 months of age) between 12 m and 20 m. Daneshjoo et al. (2022) showed a naturally occurring age-related cognitive decline using the same measurement in male mice, with statistically significant differences observed between the younger (4 m) and older (28 m) age groups; and again, although the 12 m–20 m age group was not significantly different, there was a trend. However, age-related cognitive impairments in memory and learning behavior have been identified in C57BL/6 mice at 10 m and 14 m in age, respectively (Fouquet et al., 2011; Mechan et al., 2009). Furthermore, regarding C57BL/6 mice, a review study by Radulescu et al. (2021) revealed that notable deficits in cognitive function can be observed as early as 12 m–13 m and become progressively worse with age, with clear deficits apparent at 17 m of age (Buscher et al., 2017; Lamberty and Gower, 1990). Thus, age-related cognitive function patterns during normal aging in BL/6 mice, particularly in unexamined age-groups and through longitudinal analysis, warrant further investigation.

In human research, there are mixed reviews on whether exercise, or specific types of exercise, has any significant effect on cognition. A review by Gates et al. (2013) on the effects of exercise on cognitive function in older adults (65–95 years old) with mild cognitive impairment (MCI) revealed limited evidence supporting exercise-induced functional improvement (Gates et al., 2013). However, in 2022, results from a comparison study on the effects of HIIT and moderate-intensity continuous training (MICT) on cognitive function indicated that exercise alone could promote cognitive function independent of the exercise type (de Lima et al., 2022). A meta-analysis by Cammisuli et al. (2017) reported aerobic exercise as beneficial for patients with mild cognitive impairment (MCI), but they observed only moderate effects of aerobic training on global cognition, inhibitory control, logical memory, and divided attention (Cammisuli et al., 2017). Subsequently, Cammisuli et al. (2018) reported limited evidence for improvements in AD patients' cognition from aerobic exercise (Cammisuli et al., 2018). However, other reviews and meta-analyses present evidence of the efficacy of exercise training to improve cognition, with resistance training often observed as a superior intervention in some cognitive domains and relative exercise intensity playing a central role, though very limited information on HIIT is available (Bliss et al., 2021; Gallardo-Gómez et al., 2022; Huang et al., 2022; Zhang et al., 2023).

The literature suggests that exercise intensity may be a critical factor in maintaining/improving memory, with higher intensities reportedly improving memory in sedentary older adults (Kovacevic et al., 2020). Contrary to our findings, where significant aerobic capacity improvements in the HIIT group showed no cognitive improvements, Kovacevic et al. (2020) found a significant correlation between increased cardiorespiratory fitness and memory improvements in humans aged above 60 years. However, by the end of the study, our mice were only equivalent in age to humans in their mid-50s.

Thus, the absence of cognitive changes—as a result of exercise intervention—observed in the current study could be attributed to multiple confounders ranging from the type of exercise, the volume/intensity/length of the protocol, the ages of the mice, or even housing conditions since social isolation in middle-aged mice can exacerbate anxiety-driven behaviors (Magalhães, et al., 2024). Additionally, there could be a ceiling and/or plateau effect in cognitive changes from 12 m to 17 m in age, where early cognitive impairment in C57BL/6 mice may begin before the start of our age range, but clear deficits are not evident until 17 m or later (Buscher et al., 2017; Daneshjoo et al., 2022; Fouquet et al., 2011; Mechan et al., 2009; Pettan-Brewer et al., 2013; Radulescu et al., 2021). The specific tests we used (open-field test, puzzle box, Y-maze, and NOR) have been successful in determining cognitive changes in various mouse

models, including middle-aged mice. However, most studies in the literature showing efficacy to detect cognitive change in middle-aged mice are either cross-sectional (comparing younger adults to middle-aged adults, for example) (Magalhães, et al., 2024; Morgan, et al., 2018) or compare interventions/models with the expectation of extreme cognitive effects (e.g., NOR: Alzheimer's model, Lourenco, et al., 2019; y-maze: ischemia/reperfusion model, Ohtomo, et al., 2021; open field/NOR: lipopolysaccharide model, Dockman, et al., 2022; and puzzle box: high-fat diet, Williams, et al., 2020). Only a limited number of short-term longitudinal studies exist in this age group in wild-type mice, although some demonstrate the ability of the tests to detect changes when they exist (Tsai, et al., 2018). Thus, our mice may have already been mildly affected by the cognitive effects of aging, with further decreases that are not evident at our study endpoint—especially during the relatively short, 3-month intervention period. This emphasizes the need for further research on exercise interventions that start in middle age and extend into older adulthood, when clear cognitive deficits typically emerge, or on the effects of lifelong exercise.

Exercise and body composition

We observed significant increases in body mass, fat mass, and fat % within groups from pre- to post-training and a strong effect size for lean mass difference between groups, but it was not significant. Using older-adult (24 m) mice, Seldeen et al. (2018) reported significant declines in fat % for their SED mice, while their HIIT group exhibited no such decline, maintaining greater fat % than the control group. Previously, we reported marked fat% declines in both 26-m exercise groups (voluntary wheel running and HIIT) compared to increases in controls, while that in the 10-m groups all increased, although we significantly mitigated increased fat gain with exercise (Pajski et al., 2024). Natural body composition patterns observed in humans and rodents may explain the findings of Seldeen et al. (2018), Pajski et al. (2024), and the current study. A recent review found that, on average, peak fat mass in mice that are provided food *ad libitum* occurs between 12 m and 24 m, while researchers observed fat mass decline between 17 m and 24 m (Nagy and Pappas, 2019). As such, it was reasonable for our mice to continue gaining fat regardless of training or sedentary behavior.

Caveats

One limitation of the current study is that due to within-house fighting, certain mice in both groups required individual housing, while the remaining were group-housed. According to a meta-analysis reviewing common methodological issues in animal research investigating the effects of exercise on cognition, singly housed rodents may suffer from social isolation (Hatchard et al., 2014). The study found that social isolation was associated with a greater effect of exercise on cognitive performance. The greater effect of exercise observed in socially isolated animals could be attributed to reduced environmental impoverishment as singly housed mice do not compete with cage mates for environmental nourishment (activity space, food, bedding, etc.), or it could be attributed to innate species-specific mannerisms where the male mice compete for control in each housing environment. As explained by Mechan et al. (2009), female mice may be more suitable for aging studies given that they can be group-housed for lengthy periods and placed in diverse groups, unlike male mice. Due to randomization and the fighting that occurred before and after randomization, 42.85% of the SED mice were singly housed, while just 25% of the HIIT mice were singly housed. This limitation could potentiate the lack of cognitive differences observed between the groups as it may have mitigated the overall cognitive performance of HIIT compared to that of SED. However, as previously noted, social isolation in middle-aged mice has been found to increase anxiety behaviors during open-field tests and reduce spatial memory performance in the Morris water maze (Magalhães, et al., 2024). Group-housed mice also tend to demonstrate less anxious or depressed behaviors (Liu, et al., 2013). Nevertheless, in the wild, adult male mice do not associate socially but rather exist in family units consisting of a single adult male, a number of female mice, and their offspring, and thus, aggressive behavior between group-housed adult male mice remains a constant challenge to bridge and reconcile animal welfare and study-design considerations (Kappel, et al., 2017). An optimal solution, which should be the focus of future work, would be to house individual adult male mice with age-matched ovariectomized female mice, providing companionship without innate evolutionary territorial aggression that could confound outcomes. We believe that the effects of social isolation can also be context-dependent since our prior work has not consistently demonstrated negative outcomes under similar conditions. Thus, we conclude that further research is needed regarding the interaction of social dynamics, housing, exercise, and cognition in adult, middle-aged, and older adult male mice.

Additionally, the current study only used male mice of a single strain and age-range, limiting generalization of the findings to other ages, strains, or female mice. Furthermore, our small sample size per group may have had insufficient power to detect potential subtle changes in cognition in this age group due to the sensitivity of the tests and considering high individual variability in functional testing. In our future work, we will study different age groups and female cohorts in larger numbers.

Conclusion

We did not observe statistically significant changes between groups, pre- to post-intervention, in grip meter, inverted cling, VWR, rotarod, or overall function (ΔCFAB). However, the HIIT group showed significant increases in aerobic capacity and treadmill time, while those in the SED group exhibited significantly declines. Thus, we observed HIIT to be effective at improving aerobic capacity and running speed in middle-aged mice. We observed no significant between-group differences for any of the cognitive measures assessed. However, SED mice had no changes in cognition either; thus, we cannot conclude that HIIT is ineffective at preserving cognition in middle age. The lack of cognitive changes observed could be due to the age of the mice as they may not have started experiencing extensive age-related cognitive decline yet, which would mitigate any potential effects of the HIIT intervention to preserve function. Lack of sensitivity in the tests, the small group size, and large individual variability may also have masked subtle changes. Therefore, further research is needed to determine the

interactive effects of exercise and cognition. Specifically, future research should focus on a broader range of ages in mice and assess whether biological factors such as sex and strain contribute to these differences. Our laboratory is currently addressing this research with older subjects and female mice. Additionally, with a greater sample size, future research should investigate the relationship between social isolation and exercise influence on cognition using the various CAB tests in both male and female subjects of different age groups.

Data availability statement

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

Ethics statement

The animal study was approved by East Carolina University IACUC. The study was conducted in accordance with the local legislation and institutional requirements.

Author contributions

JS: Formal Analysis, Investigation, Methodology, Writing – original draft, Writing – review and editing. TT: Conceptualization, Methodology, Writing – review and editing. TG: Conceptualization, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review and editing.

Funding

The author(s) declare that financial support was received for the research and/or publication of this article. This work was supported by ECU internal funding (TGG) and ECU College of Allied Health Sciences Pilot Grant (TGG).

Acknowledgments

The authors wish to acknowledge Brandon Baucomb for technical assistance. They also acknowledge the East Carolina Obesity and Diabetes Institute for their role in providing resources and equipment for this study (e.g., EchoMRI).

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/fragi.2025.1589730/full#supplementary-material

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frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 18 August 2025
DOI 10.3389/fmed.2025.1522531

OPEN ACCESS

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RECEIVED 04 November 2024
ACCEPTED 24 July 2025
PUBLISHED 18 August 2025

CITATION
Lv H, Li J, Chen L, Lu K, Zhao X, Guo M and Lu H (2025) Associations between folate metabolism biomarkers and cognitive impairment in older Chinese adults: a cross-sectional study.
Front. Med. 12:1522531.
doi: 10.3389/fmed.2025.1522531

Associations between folate metabolism biomarkers and cognitive impairment in older Chinese adults: a cross-sectional study

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Background: The role of folate metabolism–related biomarker profiles in age-related cognitive impairment (ARCI) remains unclear. This cross-sectional study aimed to examine the association between folate metabolism-related biomarkers and cognitive performance in older Chinese adults.
Methods: We conducted a cross-sectional analysis of 100 participants aged between 56 and 87 years. Cognitive status was classified as ARCI if participants met the cutoff criteria on both the MMSE (<27) and MoCA (<26). Those meeting the cutoff criteria on both MMSE (≥27) and MoCA (≥26) were classified as cognitively normal (CN). Serum levels of folate metabolism-related biomarkers were compared between groups and analyzed for their associations with cognitive scores. Logistic regression was used to examine associations between individual biomarkers and cognitive impairment status. Multiple linear regression analyses were conducted to assess relationships with MMSE and MoCA scores, adjusting for age and education.
Results: Cognitive impairment was prevalent among older adults at a rate of 56.3% ($P < 0.05$). The ARCI group showed significantly lower levels of vitamin B2 (VB2), folate (VB9) and lower MMSE and MoCA scores compared to the CN, while S-adenosylhomocysteine (SAH) and homocysteine (Hcy) levels were higher. MMSE and MoCA scores were positively correlated with serum VB2, VB9, and plasma S-adenosylmethionine (SAM) levels and negatively correlated with Hcy levels. Logistic regression showed that education and serum Hcy were significantly associated with cognitive impairment (AUC = 0.73). In addition to age, VB2, SAM and Hcy in the folate metabolic profile were significantly associated with MMSE and MoCA scores, accounting for 45.9 and 42.7% of the variance in these scores, respectively.
Conclusions: VB2, SAM and Hcy may be associated with cognitive impairment in older Chinese adults and warrant further investigation as potential biomarkers.

KEYWORDS

vitamin B2, S-adenosylmethionine, homocysteine, folate metabolism, age-related cognitive impairment, cross-sectional study

1 Introduction

China is facing an increasingly severe challenge of population aging. According to national projections, the number of Chinese citizens aged 60 and above is expected to reach 254 million in 2019 and exceed 402 million by 2040, accounting for ~28% of the total population (1). This dramatic shift poses pressing public health challenges, particularly in managing chronic conditions and geriatric syndromes. Geriatric syndromes refer to a condition that significantly impacts the quality of life in older adults due to the gradual decline in bodily functions associated with aging and the presence of multiple chronic diseases (2).

Among the various manifestations of geriatric syndromes, age-related cognitive impairment (ARCI) stands out due to its high prevalence and the growing demands it places on long-term care and healthcare systems. The concept of ARCI was first proposed by the International Psychogeriatric Association in 1994 to describe cognitive deterioration stemming from age-related dysregulation in neural networks (3). ARCI encompasses impairments in domains such as perception, attention, memory, language, or executive function, significantly interfering with daily and social functioning, yet do not meet the diagnostic threshold for dementia. ARCI represents a spectrum of cognitive dysfunction that differs from dementia in severity but is nonetheless clinically significant. In recent years, the term ARCI has been increasingly adopted in geriatric and cognitive aging research. It is used to describe early cognitive decline that does not meet criteria for dementia, as reported in both clinical and animal model studies (4–6). Epidemiological studies estimate that ~10%−20% of older adults experience mild cognitive impairment or eventually develop dementia (7). Cognitive impairment significantly compromises self-care capacity and quality of life in older adults. It is also associated with increased hospitalization rates, elevated mortality risk, and heightened social care expenditures, thereby imposing a substantial economic burden on society (8–10). Thus, early and accurate identification of cognitive impairment is essential to enable timely intervention, slow disease progression, and mitigate both familial and societal burdens.

Recent advances in folate metabolic research have highlighted its mechanistic relevance to cognitive function, offering novel perspectives for early diagnosis and pathophysiological understanding of cognitive impairment. The folate metabolic pathway involves the conversion of homocysteine (Hcy) to S-adenosylmethionine (SAM) in the presence of vitamin B12 (VB12), supplying methyl groups essential for the central nervous system. During methyl transfer, SAM is converted to S-adenosylhomocysteine (SAH), which is subsequently broken down into Hcy. vitamins B2 (VB2) and B6 (VB6) act as coenzymes in these reactions, supporting the smooth transfer of one-carbon units and ensuring proper methylation in neurotransmitter synthesis (11, 12). This process plays a crucial role in regulating cognitive functions. Disruptions in this cycle may lead to elevated Hcy, reduced SAM levels, and impaired methylation capacity, all of which have been implicated in cognitive impairment (13).

Despite growing mechanistic evidence, gaps remain in the clinical application of folate-related biomarkers in cognitive assessment. Previous studies have consistently identified associations between low levels of serum folate or B vitamins and poorer cognitive outcomes, with clinical evidence indicating that supplementation with B vitamins may enhance cognitive performance and mitigate brain atrophy (14, 15). In a large cohort of older Chinese adults, Chen et al. (16) found that higher plasma folate levels were associated with a 59% reduction in the risk of cognitive impairment. However, the relationship between folate metabolism and cognitive impairment remains unclear, partly due to the lack of studies investigating multiple folate-related biomarkers simultaneously. Most previous research has focused on single nutrients in isolation, without considering their interactive roles within the metabolic pathway, particularly in older Chinese adults (12, 13, 16).

Therefore, this cross-sectional study aimed to estimate the prevalence of cognitive impairment among older Chinese adults, compare folate metabolism–related biomarker levels across cognitive status groups, and examine the cross-sectional associations between these biomarkers and cognitive performance.

2 Methods

2.1 Human participants

One hundred patients, aged 56–87 years, were hospitalized in the Geriatrics Department of the Affiliated Hospital of Xuzhou Medical University (XZMU) and divided into two groups based on their Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) scores. Among them, 71 individuals aged 65 years or older were selected for analysis. Inclusion criteria: (1) good mental status, able to cooperate with medical instructions and complete assessments; (2) informed consent signed by the patient or their legal representative. Exclusion criteria: (1) neurological diseases affecting cognitive function, including Alzheimer's disease (AD), Parkinson's disease (PD), vascular dementia, stroke, epilepsy, or central nervous system infections; (2) history of psychiatric disorders, such as schizophrenia or depression; (3) previous cerebrovascular diseases, including transient ischemic attack, stroke, or intracranial hemorrhage; (4) serious infections, tumors, anemia, or history of medications affecting cognition, including benzodiazepines, antidepressants, and anxiolytics; (5) alcoholic encephalopathy. This study was reviewed and approved by the Ethics Review Committee of the Affiliated Hospital of Xuzhou Medical University (XYFY2022-KL053-01).

2.2 Blood collection and biochemical measurements

Scales were used to collect demographic information, including gender, age, and years of education. Physical measurements such as weight and height were obtained using a standard balance beam scale, and body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Blood samples were collected between 7:00 and 8:00 a.m. after an overnight fast. Routine biochemical parameters (e.g: AST, ALT, GGT, ALP, total protein,

albumin, bilirubin, glucose, and lipids) were measured using standard automated analyzers (BS-2000M, Mindray, China) as part of the baseline clinical assessment. Tau-181 and Aβ1-42 were quantified using ELISA kits from Shuangying Biotechnology Co., Ltd. (Shanghai, China). All biomarker assays were conducted in a blinded manner, and batch effects were minimized by analyzing all samples in a single run.

2.3 Folate metabolic profiles test

In this study, blood samples were collected after participants fasted from food and water beginning at 10:00 p.m. on the day of admission. Venous blood was drawn from the median vein between 7:00 and 8:00 a.m. the following morning. Two tubes of blood were collected from each subject: 3 ml in a procoagulant tube and 3 ml in an EDTA-K2 anticoagulant tube. The samples were gently mixed and allowed to stand for 30 min before centrifugation at 5,000 rpm for 15 min. Serum and plasma were separated and transferred into 1.5 ml EP tubes, which were then stored at −80°C for batch analysis. Folate metabolism–related biomarkers were subsequently analyzed using an ACQUITY ultra-performance liquid chromatography (UPLC) system coupled with a Xevo TQ-S triple quadrupole mass spectrometer (Waters Corporation, USA).

2.4 Cognitive function assessment and classification

In a quiet, distraction-free environment, two specialized neurologists assessed cognitive function using the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA). The MMSE evaluates orientation, memory, attention and calculation, recall, and language abilities (naming, repetition, command following, reading, writing, and figure drawing), while the MoCA covers short-term memory, visuospatial skills, executive functioning, attention, working memory, language, and temporal orientation. Both tests are scored out of 30 points. For MoCA, one additional point was added for participants with 12 or fewer years of education to adjust for educational background.

Participants were classified into two groups based on their performance: those meeting the cutoff criteria on both MMSE (<27) and MoCA (<26) were classified as having ARCI, while those meeting the cutoff criteria on both MMSE (≥27) and MoCA (≥26) were classified as cognitively normal (CN). The MMSE cutoff of <27 was selected based on Mitchell's meta-analysis, which showed improved sensitivity for detecting MCI compared to the conventional threshold (17). Although validation studies using this MMSE threshold in mainland China are limited, this threshold has been adopted in East Asian populations with similar socio-cultural and educational contexts (18). The MoCA cutoff of <26 was derived from its original validation study, which demonstrated 90% sensitivity and 87% specificity for detecting mild cognitive impairment (19), and has further been validated in Chinese older adults with excellent diagnostic performance (20). Combining both criteria may help improve the robustness and diagnostic performance of cognitive screening.

2.5 Statistical analysis

Statistical analyses were performed using JASP 0.19.1. No imputation was performed for missing data. Analyses were based on complete cases only. Measurement data that followed a normal distribution were described as mean ± standard deviation ($x \pm s$), and comparisons between groups were made using the independent samples *t*-test. For data that did not follow a normal distribution, the median and interquartile range [M (P25, P75)] were used, with comparisons between groups made using the Mann-Whitney U-test. Categorical data were expressed as percentages (%), and intergroup comparisons were performed using the chi-square (χ^2) test. Pearson's correlation analysis was employed to evaluate the relationship between MMSE and MoCA scores and folate metabolic profiles in older adults. Statistical significance was set at $P < 0.05$. The variance in cognitive function explained by folate metabolic profiles was determined using stratified multiple regression, accounting for age and education. Due to the relatively small sample size, comorbidities and medication use were not included as covariates. However, individuals with neurological, psychiatric disorders or medications known to affect cognition were excluded at enrollment to minimize potential confounding. Given the exploratory nature of this study, adjustments for multiple comparisons were not performed.

3 Results

3.1 Comparison of the prevalence of cognitive impairment in different age groups

A total of 100 participants were included in this study, of whom 29 were younger than 65 years and 71 were 65 years or older. The prevalence of cognitive impairment was significantly higher in the elderly group (56.3%) compared to the non-elderly group (20.6%) ($\chi^2 = 10.534$, $P = 0.0025$).

3.2 Baseline characteristics of the two groups

A total of 31 cognitively normal (CN) participants and 40 ARCI participants were included in the study. The general and clinical characteristics of the elderly participants are presented in Table 1. Statistically significant differences were observed between the two groups in terms of age, years of education, total bilirubin, direct bilirubin, and total protein levels ($P < 0.05$). The MMSE and MoCA scores of the ARCI group were significantly lower than those of the CN group, and the differences were statistically significant ($P < 0.001$). There were no significant differences between the two groups in other baseline biochemical markers,

TABLE 1 Characteristics of the HC and ARCI participants in this study.

Characteristic	CN ($n = 31$)	ARCI ($n = 40$)	$Z/t/\chi^2$	P
Age (years)	70 (67, 72)	72 (68.25, 76)	−2.106	**0.035***
Sex			0.848	0.357
Male	15 (48.40%)	15 (37.50%)		
Female	16 (51.60%)	25 (62.50%)		
AST (U/L)	17 (14, 21)	19 (16.25, 22)	−1.633	0.102
ALT (U/L)	13 (10, 26)	13 (9.25, 18.75)	−0.627	0.53
GGT (U/L)	21 (14, 31)	14.5 (12, 22.75)	−1.532	0.125
Total bilirubin (μmol/L)	12.8 (10.2, 16.8)	9.95 (7.75, 13.23)	−2.435	**0.015***
Direct bilirubin (μmol/L)	4.7 (4, 6)	3.7 (3.05, 4.97)	−2.407	**0.016***
Total bile acids (μmol/L)	4.1 (2.1, 7.3)	5.9 (3.2, 9.23)	−1.618	0.106
Fasting glucose (mmol/L)	5.26 (4.7, 6.48)	5.36 (4.53, 6.28)	−0.157	0.876
Triglyceride (mmol/L)	1.08 (0.79, 1.41)	1.05 (0.77, 1.51)	−0.226	0.821
TSH (mIU/L)	2.09 (1.45, 3.57)	1.9 (1.46, 3.22)	−0.081	0.935
TAU-181 (ng/ml)	18.1 (14.4, 28.8)	28.7 (11.05, 72.58)	−1.676	0.094
Aβ1-42 (ng/ml)	31.1 (13.7, 85.3)	45.8 (26.88, 104.8)	−1.78	0.075
Glycated hemoglobin (%)	5.9 (5.5, 7.7)	6.1 (5.7, 7.78)	−1.01	0.313
Education level (years)	9 (6, 12)	6 (0, 9)	−2.348	**0.019***
BMI (kg/m^2)	24.03 ± 3.41	23.42 ± 3.82	0.701	0.486
ALP (U/L)	74.68 ± 16.81	76.63 ± 19.34	−0.445	0.658
Total protein (g/L)	65.74 ± 5.94	69.77 ± 6.53	−2.679	**0.009****
Albumin (g/L)	40.43 ± 3.33	41.8 ± 2.88	−1.862	0.067
Creatinine (μmol/L)	57.81 ± 15.25	61.9 ± 14.02	−1.174	0.244
uric acid (μmol/L)	272.87 ± 78.66	261.75 ± 68.6	0.635	0.527
Total cholesterol (mmol/L)	4.18 ± 0.91	4.49 ± 1.19	−1.173	0.245
HDL-C (mmol/L)	1.24 ± 0.33	1.29 ± 0.41	−0.576	0.566
LDL-C (mmol/L)	2.47 ± 0.8	2.72 ± 0.95	−1.177	0.243
MMSE	29.00 (28.00, 29.00)	24.50 (20.00, 26.00)	−7.263	**<0.001*****
MoCA	27.00 (27.00, 28.50)	20.00 (16.00, 25.00)	−7.244	**<0.001*****

The data are expressed as the mean ± standard deviation. For data that did not follow a normal distribution, the median and interquartile range [M (P25, P75)] were used. Categorical data were expressed as percentages (%). CN, cognitively normal; ARCI, age-related cognitive impairment; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; TSH, thyroid-stimulating hormone; BMI, body mass index; ALP, alkaline phosphatase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment. *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$. Bold values indicate statistically significant differences ($P < 0.05$).

including AST, ALT, GGT, lipid profiles, Tau-181, and Aβ1-42 (all $P > 0.05$).

3.3 Comparison of folate metabolic profiles of the two groups

The results showed that the levels of VB2 and VB9 in the ARCI group were significantly lower than those in the control group, while the levels of SAH and Hcy were significantly higher. These differences were statistically significant, as presented in Table 2 and Figure 1.

3.4 The correlation effects between MMSE and MoCA scores and folate metabolic profiles in older adults

To verify the value of folate metabolic profiling in clinical practice, we performed correlation analyses between folate metabolic profiling and cognitive scale scores. Serum VB2 (MMSE: $r = 0.354$, $P = 0.002$; MoCA: $r = 0.314$, $P = 0.008$), VB9 (MMSE: $r = 0.345$, $P = 0.003$; MoCA: $r = 0.354$, $P = 0.002$) and SAM (MMSE: $r = 0.424$, $P < 0.001$; MoCA: $r = 0.399$, $P < 0.001$) levels were positively correlated with MMSE and MoCA scores. In contrast, Hcy was negatively

correlated with MMSE ($r = -0.363$, $P = 0.002$) and MoCA scores ($r = -0.329$, $P = 0.006$), as shown in Table 3 and Figure 2.

3.5 Logistic regression analysis of folate metabolic profiles and their association with cognitive impairment

Logistic regression analysis indicated that education level and Hcy levels were significantly associated with cognitive impairment. Logistic regression was performed to ascertain the effects of education and Hcy variables on the likelihood that participants have a cognitive dysfunction. Higher education was correlated with a lower likelihood of cognitive impairment (OR = 0.84, 95% CI: 0.74–0.96, $P = 0.008$), while elevated Hcy levels were correlated with a higher likelihood (OR = 1.0003, 95% CI: 1.0000–1.0006, $P = 0.018$). The logistic regression model was statistically significant, χ^2 (2) = 13.33, $P = 0.001$, with a Nagelkerke's $R^2 = 0.229$, indicating a moderate model fit. Receiver operating characteristic (ROC) analysis showed an area under the curve (AUC) of 0.66 (95% CI: 0.54–0.78, $P = 0.024$) for education and 0.61 (95% CI: 0.48–0.74, $P = 0.047$) for Hcy. The combined model yielded an AUC of 0.73 (95% CI: 0.62–0.84, $P = 0.018$), indicating acceptable discrimination in distinguishing between cognitively impaired and normal participants (Figure 3).

TABLE 2 Comparison of the serum levels of folate of the HC and ARCI participants.

Biomarker (ng/ml)	CN ($n = 31$)	ARCI ($n = 40$)	Z/t	P
VB2 (ng/ml)	14.98 (10.89, 21.79)	9.59 (7.99, 14.07)	−3.107	**0.002****
VB6 (ng/ml)	4.06 (3.12, 8.43)	4.41 (2.85, 7.01)	−0.151	0.880
VB9 (ng/ml)	42.34 (22.63, 52.05)	29.75 (18.38, 45.51)	−1.994	**0.046***
SAM (ng/ml)	2561.58 ± 837.09	2360.46 ± 1139.46	0.825	0.412
SAH (ng/ml)	107.72 ± 34.41	129.5 ± 48.16	−2.13	**0.037***
Hcy (ng/ml)	13920.53 ± 4018.65	17662.54 ± 9163.16	−2.119	**0.038***

The data are expressed as the mean ± standard deviation. For data that did not follow a normal distribution, the median and interquartile range [M (P25, P75)] were used. CN, cognitively normal; ARCI, age-related cognitive impairment; VB2, vitamins b2; VB6, vitamins b6; VB9, vitamins b9 or folate; SAM, S-adenosylmethionine; SAH, S-adenosylhomocysteine; Hcy, homocysteine; $^*P < 0.05$, $^{**}P < 0.01$. Bold values indicate statistically significant differences ($P < 0.05$).

TABLE 3 The correlation effects between MMSE and MoCA scores and the serum levels of folate.

Biomarker	MMSE		MoCA	
	r	p	r	p
VB2	0.354**	0.002	0.314**	0.008
VB6	0.155	0.158	0.163	0.175
VB9	0.345**	0.003	0.355**	0.002
SAM	0.424**	<0.001	0.399***	<0.001
SAH	−0.107	0.375	−0.101	0.401
Hcy	−0.363**	0.002	−0.325**	0.006

MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; VB2, vitamins b2; VB6, vitamins b6; VB9, vitamins b9 or folate; SAM, S-adenosylmethionine; SAH, S-adenosylhomocysteine; Hcy, homocysteine. $^{**}P < 0.01$ and $^{***}P < 0.001$.

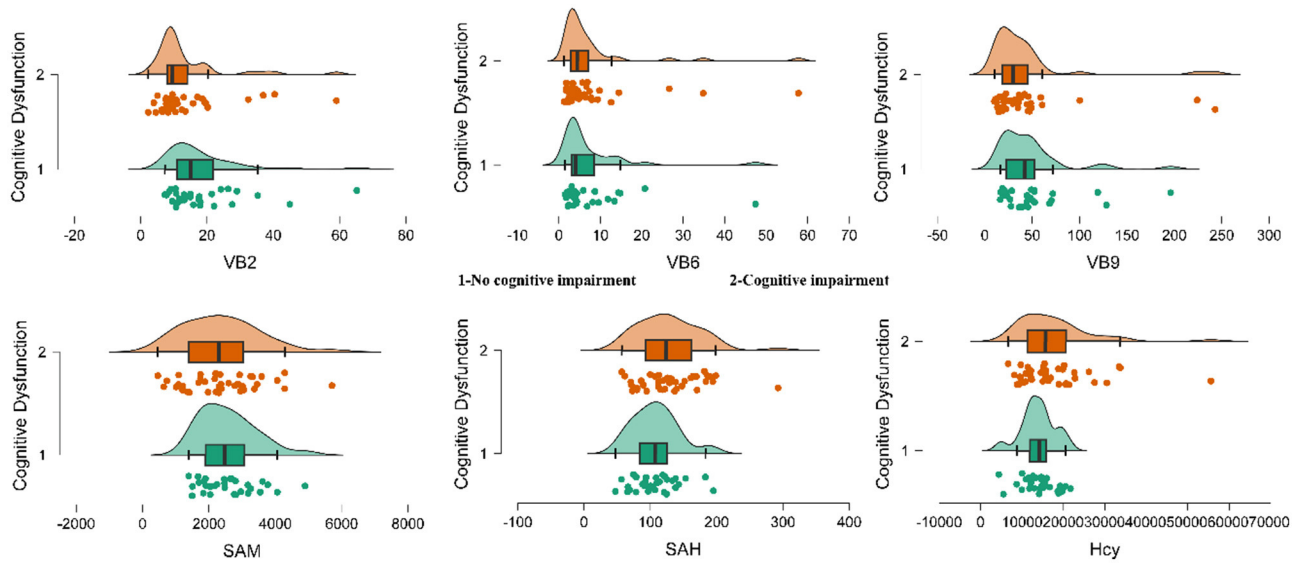

FIGURE 1
The rainbow plot of the descriptive statistics of the serum levels of folate of the two groups. Group 1 represents participants without cognitive impairment, while Group 2 represents participants with cognitive impairment. Significant differences were observed between the CN and ARCI groups in VB2, VB9, SAH, and HCY levels.

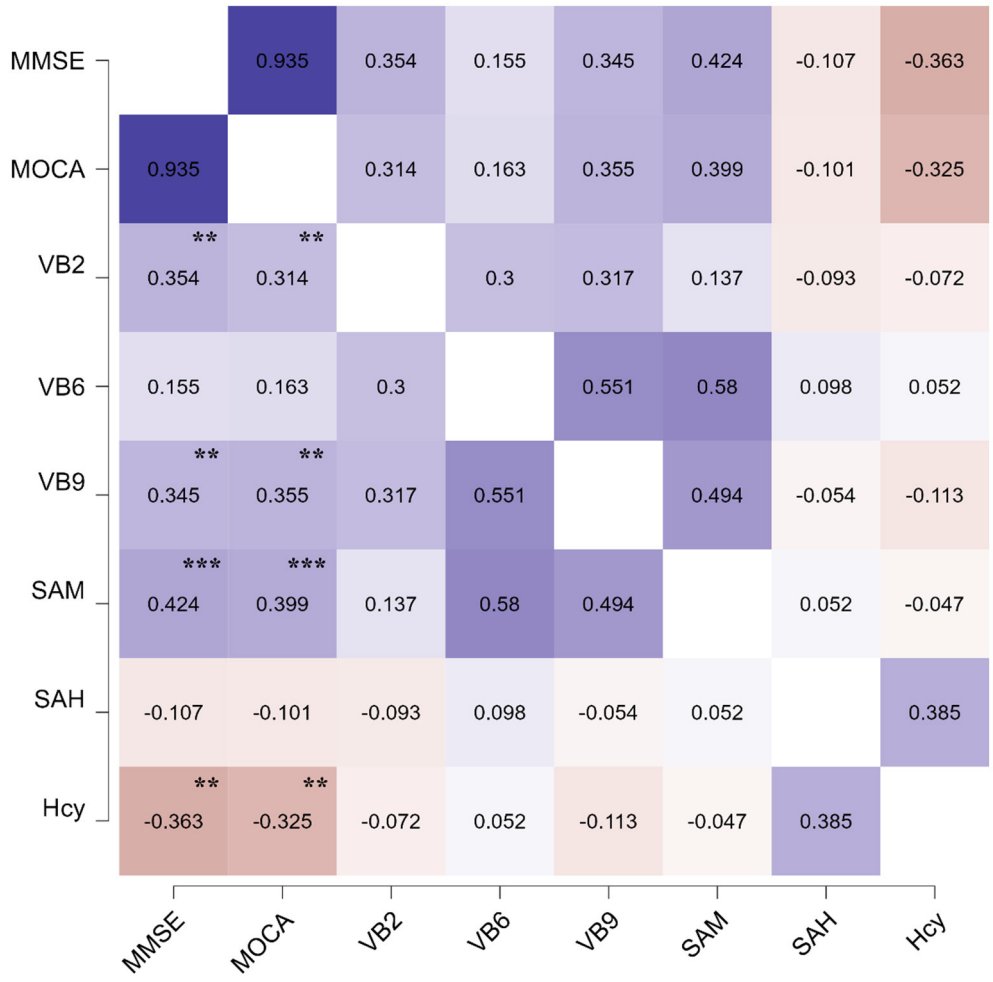

FIGURE 2
The pearson's heatmap of the correlation effects between the serum levels of folate and MMSE, MoCA scores. The significant of the correlation effects was shown in the figure. $^{**}P < 0.01$ and $^{***}P < 0.001$.

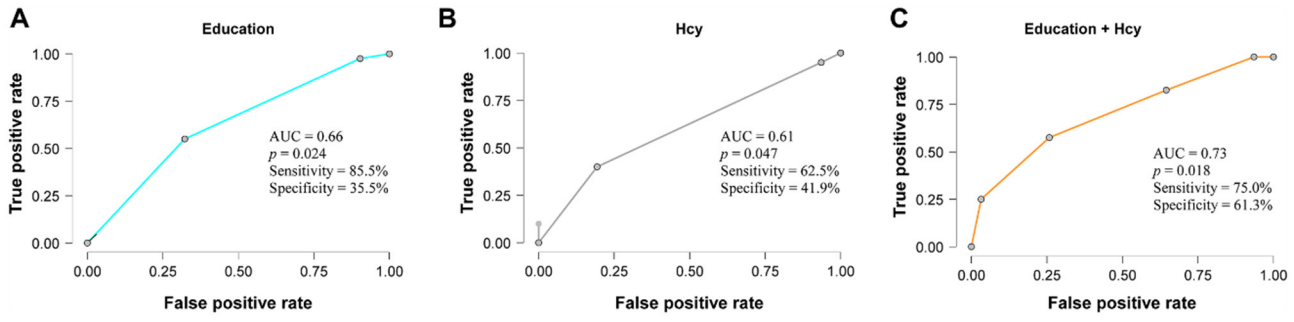

FIGURE 3
ROC curve plot of the discriminative performance of the Education and Hcy variables for cognitive impairment. **(A)** Education; **(B)** Hcy; **(C)** Combination of Education and Hcy.

3.6 Linear regression analysis of MMSE and MoCA scores and folate metabolic profiles

As shown in Tables 4, 5, multiple linear regression using the enter method was performed to assess the associations of continuous variables (age, education and folate metabolism-related products) with MMSE and MoCA scores. Previous studies have shown that age and education are associated with cognitive impairment (7, 21). Folate metabolic profile variables were included to evaluate whether they were also associated with MMSE and

TABLE 4 Linear regression for MMSE.

Model	Unstandardized	Standard error	Standardized	*t*	*p*
M_1					
(Intercept)	35.717	4.920		7.260	<0.001
Age	−0.194	0.071	−0.264	−2.724	0.008**
Education	0.125	0.076	0.157	1.642	0.106
VB2	0.078	0.031	0.249	2.471	0.016*
VB9	0.007	0.009	0.086	0.771	0.444
SAM	0.001	3.82×10^{-4}	0.354	3.336	0.001**
Hcy	-1.212×10^{-4}	4.69×10^{-5}	−0.250	−2.583	0.012**

MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; VB2, vitamins b2; VB9, vitamins b9 or folate; SAM, S-adenosylmethionine; Hcy, homocysteine. *$P < 0.05$ and **$P < 0.01$.

TABLE 5 Linear Regression for MOCA.

Model	Unstandardized	Standard error	Standardized	*t*	*p*
M_1					
(Intercept)	41.857	7.012		5.969	<0.001
Age	−0.328	0.102	−0.322	−3.226	0.002**
Education	0.154	0.109	0.139	1.411	0.163
VB2	0.092	0.045	0.212	2.045	0.045*
VB9	0.016	0.013	0.137	1.188	0.239
SAM	0.002	5.445×10^{-4}	0.317	2.908	0.005**
Hcy	-1.305×10^{-4}	6.688×10^{-5}	−0.195	−1.951	0.055

MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; VB2, vitamins b2; VB9, vitamins b9, or folate; SAM, S-adenosylmethionine; Hcy, homocysteine. *$P < 0.05$ and **$P < 0.01$.

MoCA scores. In the initial models, age and education explained 11.5 and 13% of the total variance in the MMSE and MoCA, respectively; the explanatory power of the MMSE and MOCA models was significantly improved with the addition of the folate metabolic profile indicator, which increased the variance explained by ∼45.9%, F (4, 66) = 9.051, $P < 0.001$, $R^2 = 0.459$, respectively; and 42.7%, F (4, 66) = 7.961, P <0.001, $R^2 = 0.427$, respectively. Each additional year of age was associated with decreases of 0.264 (95% CI: −0.337 to −0.052, $P = 0.008$) and 0.322 points (95% CI: −0.531 to −0.125, $P = 0.002$) in MMSE and MoCA scores, respectively. Higher levels of VB2 and SAM were associated with increases of 0.249 (95% CI: 0.015 to 0.14, $P = 0.016$) and 0.354 (95% CI: 0.001 to 0.002, $P = 0.001$) points in MMSE scores, and 0.212 (95% CI: 0.002 to 0.181, $P = 0.045$) and 0.317 (95% CI: 0.000495 to 0.003, $P = 0.005$) points in MoCA scores, respectively. Additionally, each 1-ng/ml increase in Hcy was associated with a decrease of 0.25 points in MMSE (95% CI: −0.000215 to −0.000027, $P = 0.012$).

4 Discussion

The present study aimed to examine the associations between ARCI and levels of folate, vitamin B, SAM and Hcy. The findings revealed a high prevalence of cognitive impairment among older adults, with high levels of VB2, folate and SAM being strongly associated with better cognitive function in this population. Logistic regression suggested that education and Hcy levels were independently associated with the likelihood of cognitive impairment. Multiple linear regression analyses demonstrated that cognitive function scores (MMSE and MoCA) significantly declined with increasing age. Conversely, higher levels of VB2 and SAM were associated with significant improvements in cognitive function scores, whereas elevated Hcy levels were associated with decreased MMSE and MoCA scores. These results suggest that folate metabolic profiles are significantly associated with the presence of ARCI in older adults.

Aging is the strongest known risk factor for developing dementia, with the risk increasing significantly with age, particularly among individuals aged 65 years and older (22). The present study aligns with this finding, as we found a higher prevalence of cognitive impairment and lower cognitive function scores with advancing age. Our research found that lower education levels were significantly associated with an increased risk of cognitive impairment, which is consistent with previous studies suggesting that higher education levels may be associated with a protective effect (23) and contribute to greater "cognitive reserve" (24).

Several epidemiological studies have examined associations between folate metabolic profiles, which are believed to play a role in maintaining central nervous system function, and cognitive function or dementia (25). For example, higher intake of VB2

has been shown to improve cognitive performance across multiple domains in middle-aged and older adults (26) and is associated with better cognitive function in the elderly. Additionally, higher MoCA scores have been linked to elevated serum levels of VB9, VB6, and VB12 (27). Vitamin B supplementation has been found to reduce serum Hcy and plasma SAH levels while increasing plasma SAM levels and may lead to improvements in MoCA scores, particularly in naming and orientation (28). Hyperhomocysteinemia is recognized as a risk factor for cognitive decline, mild cognitive impairment, and Alzheimer's disease (29). Moreover, Hcy, folate, and VB12 levels have been associated with the degree of cognitive impairment in older adults (30, 31). Our study supports previous findings, confirming the positive correlation between VB2, VB9, and SAM levels and cognitive function, as well as the negative correlation between Hcy levels and cognitive function. However, not all studies have found consistent or linear associations. For instance, Ding et al. (32) reported inverse U-shaped relationships between folate or B12 status and cognitive scores in older adults, with no statistically significant associations observed across much of the biomarker distribution, and no evidence of interaction between the two vitamins.

Despite this, VB2, SAM, and Hcy were also significantly associated with the presence of age-related cognitive impairment in older adults. To better understand these associations, it is important to consider the underlying biochemical pathways through which folate-related metabolites influence neural function.

VB2, in its coenzyme forms flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD), is involved in numerous enzymatic reactions, including the conversion of tryptophan to nicotinic acid. A deficiency in VB2 decreases the efficiency of these reactions, thereby affecting neurotransmitter synthesis (33). Folate, in its active form 5-methyltetrahydrofolate, provides methyl groups that are transferred to Hcy to generate methionine, which is subsequently converted to SAM through an ATP-dependent reaction. SAM, as a methyl donor, plays a critical role in the methylation of DNA, RNA and proteins (11). These methylation processes are essential for regulating gene expression, DNA repair, and maintaining genome stability. Deficiencies in VB9 or SAM led to hypomethylation and impact nervous system function; however, these mechanisms remain hypothetical and require further investigation. Therefore, low levels of VB2, VB9, and SAM may be involved in neurological dysfunction by reducing DNA methylation and neurotransmitter synthesis, ultimately inducing cognitive decline.

In addition, elevated levels of Hcy, a neurotoxic substance, have been suggested to be associated with cognitive deficits through several proposed mechanisms, including activating the N-methyl-D-aspartate (NMDA) receptor (34) or through conversion to homocysteine thiolactone, leading to neuronal damage and apoptosis (35). While these pathways are well-supported by prior studies, in our cross-sectional data we observed an association between elevated Hcy and ARCI, which may reflect similar neurotoxic processes in this population. These findings suggest that maintaining optimal levels of folate, vitamin B and SAM may be associated with better cognitive health and a lower likelihood of ARCI.

In the present study, multiple linear regression showed that VB2 and SAM were significantly positively correlated with cognitive function scores and Hcy was negatively correlated. Logistic regression further indicated that Hcy was independently associated with a higher likelihood of cognitive impairment. This result may reflect that higher levels of VB2 and SAM are associated with better cognitive performance, possibly due to their roles in neuroprotection and metabolic support, although they may not be significantly associated with a lower likelihood of cognitive impairment. On the contrary, elevated Hcy levels may exert stronger effects once exceeding certain thresholds, potentially contributing more directly to the presence of impairment, as reflected in the logistic model. These observations highlight the possibility of differential associations between folate-related metabolites and various dimensions of cognitive health.

Our study also identified a significant difference in the baseline characteristics of total and direct bilirubin levels between the two groups of patients. It has been shown that gut microbial metabolites are strongly associated with cognitive function, especially the potential regulatory role of bile acid metabolism in neurological health (36–38). Building on this observation, we propose to further investigate the potential interplay between folate metabolic profiles and bile acid metabolic profiles in relation to cognitive function. This line of inquiry may help elucidate the complex mechanisms of the gut-brain axis in the regulation of cognitive function and could contribute to identifying candidate biomarkers for future research.

5 Limitation

While this study identifies significant associations between folate metabolic profiles and ARCI, several limitations must be acknowledged. The cross-sectional design precludes establishing causality, as the temporal relationship between folate metabolism biomarkers and cognitive outcomes remains unclear, and reverse causation cannot be ruled out. Additionally, due to financial and time constraints, the study was limited to a relatively small sample of elderly patients from a specific region, which may restrict the generalizability of findings to broader populations. The recruitment of participants from a hospital-based setting, rather than a community-based cohort, may introduce selection bias, as these individuals may differ systematically from the general older adult population. Furthermore, the lack of detailed data on dietary habits and vitamin supplement intake, which relied partly on self-reports, may have influenced the accuracy of folate metabolic profiles. Potential confounders, including physical activity, comorbidities, and medication use, were not fully controlled, potentially affecting the observed associations.

To address these limitations, future research should prioritize large-scale, prospective cohort studies involving diverse populations to enhance generalizability and clarify causal relationships. Comprehensive assessments of dietary habits, lifestyle factors, and repeated biomarker measurements over time would provide deeper insights into the dynamic interplay between folate metabolism and ARCI, enabling the development of targeted interventions.

6 Conclusion

In general, this study identified significant associations between VB2, SAM, Hcy levels and cognitive function in older adults, suggesting that folate metabolic profiles may serve as informative indicators of age-related cognitive status. These findings provide a foundation for future research into metabolic biomarkers of cognitive health by underscoring the importance of early metabolic screening in aging populations and its potential role in shaping preventive strategies for cognitive decline.

Data availability statement

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

Ethics statement

The studies involving humans were approved by Ethics Review Committee of the Affiliated Hospital of Xuzhou Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. The human samples used in this study were acquired from primarily isolated as part of your previous study for which ethical approval was obtained. 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. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

HLv: Writing – original draft. JL: Writing – original draft. LC: Writing – original draft. KL: Writing – original draft. XZ: Writing – review & editing. MG: Writing – review & editing. HLu: Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research and/or publication of this article. This study was supported by the Jiangsu Provincial Geriatric Health Research Project (Grant number: LKM2024016) and the Construction Project of High Level Hospital of Jiangsu Province (Grant number: LCZX202514).

Acknowledgments

We would like to thank all participants and the clinicians for their contribution to the study.

Conflict of interest

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

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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frontiers | Frontiers in Medicine

TYPE Study Protocol
PUBLISHED 01 September 2025
DOI 10.3389/fmed.2025.1505093

OPEN ACCESS

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RECEIVED 02 October 2024
ACCEPTED 21 July 2025
PUBLISHED 01 September 2025

CITATION
Whaikid P, Piaseu N and Souza A (2025) Protocol for a systematic review of sarcopenia in older adults with type 2 diabetes mellitus and its association with increased risk of mortality.
Front. Med. 12:1505093.
doi: 10.3389/fmed.2025.1505093

Protocol for a systematic review of sarcopenia in older adults with type 2 diabetes mellitus and its association with increased risk of mortality

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Background: Sarcopenia and type 2 diabetes mellitus (T2DM) are prevalent health conditions that significantly impact mortality risk, particularly among older adults. While both conditions have been individually associated with increased mortality, limited evidence exists regarding their combined effect, and no prior systematic review has synthesized this association specifically among older adults with T2DM. This study aims to examine the association between sarcopenia and all-cause mortality in older adults with T2DM. It seeks to evaluate whether this relationship varies by population characteristics, sarcopenia definitions, and follow-up duration.

Methods: We will conduct a comprehensive literature search using databases such as PubMed, Scopus, CINAHL, and Embase to identify studies exploring the relationship between sarcopenia and all-cause mortality in older adults with T2DM from January 1, 2014, to September 1, 2024. Two authors will independently screen all eligible clinical studies. Statistical analyses will be conducted using JBI SUMARI software.

Results: Preliminary findings will indicate the overall prevalence and mortality rate among older adults with sarcopenia and T2DM. By consolidating findings from diverse studies, this meta-analysis will provide clearer insights into how sarcopenia and T2DM interact to affect mortality risk.

Conclusion: Understanding the relationship between sarcopenia and T2DM is crucial leading to developing effective interventions to reduce mortality risk and improve the quality of life in older adults. Addressing this important research gap will contribute to better healthcare practices and outcomes.

KEYWORDS

sarcopenia, type 2 diabetes mellitus, mortality risk, systematic review, meta-analysis, protocol

1 Introduction

Sarcopenia is a condition characterized by the progressive loss of skeletal muscle mass and strength (1), which can lead to physical disability (2, 3), poor quality of life (4, 5), and increased mortality (6, 7). It is also associated with an increased risk of falls, which contributes substantially to healthcare costs, accounting for over $50 billion annually in medical expenses (8). In 2016, sarcopenia was officially recognized as a disease associated with aging by the World Health Organization and was assigned an ICD-10-CM code (M62.84) (9), reinforcing its clinical relevance and importance for public health (1). The prevalence varies between 10% and 27%, depending on the classification criteria used (10). Sarcopenia is particularly prevalent in older adults and can be exacerbated by chronic conditions such as type 2 diabetes mellitus (T2DM) (10). T2DM is one of the most commonly observed conditions and a significant contributor to sarcopenia among its various etiologies. T2DM is a metabolic disorder characterized by high blood sugar levels due to insulin resistance or insufficient insulin production (11, 12).

T2DM may also contribute to skeletal muscle degradation through extracellular matrix (ECM) remodeling, which disrupts insulin signaling and promotes muscle fibrosis and dysfunction, thereby accelerating sarcopenia progression (13). The combination of sarcopenia and T2DM in older adults poses significant health risks, including an increased likelihood of falls, fractures, and overall mortality (14). Currently, despite having a growing awareness of the impact of sarcopenia on health outcomes, significant gaps remain in understanding of sarcopenia affect mortality risk in older adults with T2DM. Although studies have investigated the link between sarcopenia and T2DM, comprehensive research examining their relationship in terms of increased mortality risk among older adults remains limited. To date, no systematic reviews or meta-analyses have been conducted on this topic. Understanding this relationship is crucial, as sarcopenia may not only worsen diabetes outcomes but also increase the risk of premature mortality. In fact, sarcopenia has been associated with up to a 45% higher risk of mortality in older adults compared to those without sarcopenia (15). This gap in knowledge underscores the need for an updated systematic review on the relationship between sarcopenia and mortality. This review aims to examine the association between sarcopenia and all-cause mortality in older adults with T2DM, while considering whether this relationship varies based on the population, the definition of sarcopenia, and the duration of follow-up. This will pave the way for developing effective treatment strategies to manage both conditions concurrently, ultimately improving health outcomes and survival rates.

2 Methods

2.1 Study registration

This meta-analysis was registered with PROSPERO on 14 September 2024 (Registration number: CRD42024586761) and will follow the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA- P).

2.2 The inclusion criteria

2.2.1 Types of studies

Cross-sectional, longitudinal, and prospective cohort studies will be considered for inclusion, while animal studies, randomized controlled trials (RCTs), quasi-experimental designs, case reports, and review articles will be excluded.

2.2.2 Types of participants

Participants will include individuals aged 60 years and above, as well as those diagnosed with type 2 diabetes mellitus.

2.2.3 Types of outcomes

This study will investigate the prevalence of all-cause mortality among older adults affected by both T2DM and sarcopenia. The main outcome focus will be on mortality rates within 1–2 years, with secondary outcomes examining mortality at 5 and 10 years. This comprehensive approach aims to shed light on how the interplay of these conditions impacts overall survival and health outcomes in older adults.

2.3 Collection and analysis of data

2.3.1 Search strategy

We will conduct a comprehensive literature search using databases such as PubMed, Scopus, CINAHL, and Embase to identify studies exploring the relationship between sarcopenia and all-cause mortality in older adults with type 2 diabetes mellitus. The following keywords were used to search the databases for relevant literature: “sarcopenia” OR “muscle mass” OR “muscle strength” OR “physical performance” AND “mortality” OR “death rate” OR “die” OR “died” OR “survival” AND “T2DM” OR “diabetes mellitus” OR “type 2 diabetes mellitus.” The search included studies published between January 1, 2014, and September 1, 2024. Titles and abstracts were screened for an initial extraction of all eligible studies.

2.3.2 Selection of studies

Two researchers will conduct a comprehensive search across all relevant databases, based on predefined inclusion and exclusion criteria to ensure the studies’ relevance and quality. Each study will be carefully cross-verified by both researchers to ensure that no pertinent studies are inadvertently excluded. This process will adhere to the PRISMA flow diagram (Figure 1), which provides a systematic framework for study selection and data extraction, ensuring a thorough and transparent review process.

2.3.3 Assessment of risk of bias and quality of evidence

To ensure the credibility of the empirical evidence, the researchers will utilize the Newcastle-Ottawa Scale Quality Assessment scale (NOS) (16) to assess the risk of bias. This checklist is designed to independently evaluate the quality and rigor of studies across various research designs, including cross-sectional, longitudinal, and prospective cohort studies.

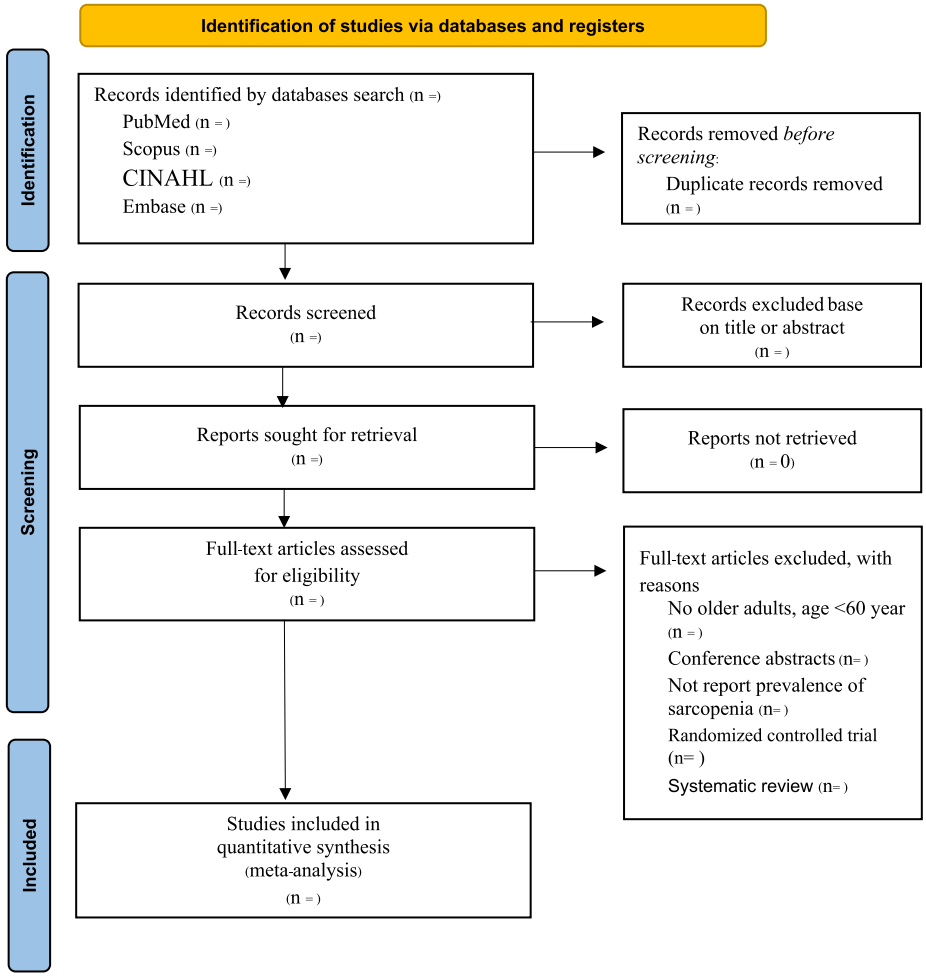

FIGURE 1
Flow diagram for Study Selection.

Three researchers will independently assess each study using the NOS, which involves evaluating factors such as selection of study groups, comparability of groups, and ascertainment of outcomes (or exposures). This independent assessment helps to mitigate bias and ensures that the studies included in the review meet high standards of quality and reliability. The use of the NOS checklist provides a structured and systematic approach to appraising empirical evidence, contributing to the overall validity and robustness of the research findings.

2.4 Statistical analysis

2.4.1 Synthesis of data

The synthesis of data will involve integrating and summarizing the results from the selected studies to provide a comprehensive understanding of the factors associated with mortality. This process will include examining various aspects such as participant characteristics (e.g., sample size, sex, age, and population), definitions of sarcopenia, its prevalence, and the causes of mortality.

2.4.2 Measures of effect

The authors will perform the statistical analysis using JBI SUMARI software. A meta-analysis will be conducted to investigate factors associated with the causes of mortality, utilizing a fixed-effect model through the inverse variance approach. The primary analysis will involve calculating effect sizes with 95% confidence intervals (CI) using a hazard ratio (HR) and odds ratios (OR) of mortality will be calculated.

2.4.3 Assessment of heterogeneity

Heterogeneity among studies will be assessed using I^2 statistics, with the following interpretations: (1) 0–24.9% indicating minimal heterogeneity, (2) 25.0–49.9% suggesting moderate heterogeneity, (3) 50.0–74.9% representing substantial heterogeneity, and (4) 75.0–100% indicating considerable heterogeneity. Additionally, the presence of heterogeneity will be evaluated using χ^2 (chi-square) p-values, with $p < 0.1$ signaling significant heterogeneity.

2.4.4 Assessment of reporting bias

To evaluate reporting bias, both a funnel plot and the Egger test will be employed. The funnel plot will visually represent the distribution of study results, helping us identify any potential

asymmetry that may indicate bias in reporting. By using both methods, we will enhance our ability to effectively identify and analyze the potential for reporting bias in the results.

2.4.5 Subgroup analysis

Subgroup analyses will be performed according to the primary analysis if sufficient data are available, focusing on populations with mortality, the definition of sarcopenia, and the duration of follow-up.

3 Discussion

Sarcopenia and T2DM are two health conditions that significantly impact mortality risk, particularly in older adults (17, 18). Investigating the relationship between these conditions can provide valuable insights into the associated risks and guide more effective management strategies. Older people diagnosed with T2DM experience a more pronounced and accelerated decline in both muscle mass (19, 20) and muscle strength (21, 22) compared to those without diabetes. T2DM is associated with a reduction in key components used to diagnose sarcopenia. Therefore, sarcopenia and T2DM coexist, the risk of mortality increases significantly. Individuals with both conditions tend to have poorer overall health and face a higher likelihood of severe complications and mortality (23, 24). This combination leads to a marked decline in physical health, further elevating the chances of serious complications and mortality.

Simultaneously studying sarcopenia and T2DM is essential for developing effective health management strategies that reduce mortality risk and improve the quality of life in older adults. A deeper understanding of the relationship between these conditions can drive more impactful research and enhance medical practices in caring for older adults. Current studies on sarcopenia and T2DM present mixed findings and fail to offer a clear understanding of the relationship between these conditions and mortality risk. A meta-analysis could integrate the available data, reduce heterogeneity, and enhance the precision of risk assessment. This approach would also provide greater insight into the combined effects of sarcopenia and T2DM on mortality, addressing an important research gap that requires further investigation.

However, several limitations should be considered. First, variations in the diagnostic criteria for sarcopenia (e.g., EWGSOP2, and AWGS) across studies may introduce heterogeneity that could affect the comparability of results. Second, differences in population characteristics, such as ethnicity and healthcare settings, may limit the generalizability of the findings. Third, the inclusion of only English-language publications may lead to language bias. Lastly, publication bias and the inherent limitations of observational studies (e.g., residual confounding) may also influence the pooled estimates.

Author contributions

PW: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. NP: Conceptualization, Data curation, Investigation, Methodology, Funding acquisition, Supervision, Writing – review & editing. AS: Conceptualization, Data curation, Investigation, Methodology, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research and/or publication of this article. This study was supported by the Ramathibodi School of Nursing, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Thailand.

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

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frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 03 September 2025
DOI 10.3389/fmed.2025.1573384

OPEN ACCESS

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RECEIVED 09 February 2025
ACCEPTED 20 August 2025
PUBLISHED 03 September 2025

CITATION
Ji S, Lee E, Baek JY, Jang GY, Jung H-W and Jang I-Y (2025) Effect of a multicomponent intervention on institutionalization-free survival in older adults with sarcopenia: a *post-hoc* analysis.
Front. Med. 12:1573384.
doi: 10.3389/fmed.2025.1573384

Effect of a multicomponent intervention on institutionalization-free survival in older adults with sarcopenia: a *post-hoc* analysis

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Objectives: To assess the effect of a 24-week comprehensive multicomponent intervention on institutionalization-free survival, physical performance, and frailty among older adults with sarcopenia.
Design: A post-hoc analysis of a prospective, non-randomized intervention study with 1:1 propensity score matching.
Setting: Community-dwelling, socioeconomically vulnerable older adults.
Participants: A total of 283 older adults with sarcopenia were included, with 145 in the intervention group and 138 in the control group. After propensity score matching, 102 pairs were analyzed. The mean age was 77.57 years (intervention) and 77.64 years (control), with 82.4 and 81.4% females in each group, respectively.
Intervention: The multicomponent intervention consisted of exercise, nutritional support, depression management, deprescribing, and home hazard reduction, implemented over 24 weeks.
Measurements: The primary outcome was 30-month institutionalization-free survival. Secondary outcomes included changes in physical performance (Short Physical Performance Battery [SPPB] scores, gait speed) and frailty index over 6, 18, and 30 months.
Results: Following propensity score matching, mortality and institutionalization occurred in 13 (12.7%) and 35 (34.3%) participants in the intervention and control groups, respectively. A significant difference in 30-months institutionalization-free survival was observed between the intervention and control groups (63.4% vs. 87.2%). The intervention group had significantly higher SPPB scores and improved gait speed at 6 months, 18 months, and 30 months. The intervention group showed a significantly lower frailty index only at 6 months but similar scores at 18 and 30 months.
Conclusion: The multicomponent intervention significantly improved long-term institutionalization-free survival and physical function in older adults with sarcopenia, highlighting its potential to enhance independence and reduce frailty in vulnerable populations.

KEYWORDS

sarcopenia, multicomponent intervention, physical frailty, frailty, public health

1 Introduction

Sarcopenia, a progressive loss of skeletal muscle mass and function, is a highly prevalent geriatric syndrome linked to adverse outcomes such as falls, disability, hospitalization, institutionalization, and mortality (1–3). Its global prevalence is estimated to range from 10% to over 20% among community-dwelling older adults, depending on diagnostic criteria and population characteristics (2). Despite its clinical significance, intervention strategies are limited, with most guidelines only recommending exercise and nutritional support (4–7). Therefore, there is an urgent need to explore more effective interventions that can address needs of older adults with sarcopenia.

Frailty, another common aging-related syndrome, is characterized by increased vulnerability to stressors due to multisystem decline (8). Sarcopenia and frailty frequently coexist and share overlapping biological mechanisms—such as chronic inflammation, hormonal dysregulation, malnutrition, and physical inactivity—that contribute to impaired physical function and resilience (9, 10). Numerous longitudinal studies have demonstrated that both conditions are similarly associated with adverse outcomes, including, institutionalization, and mortality (11–13). A recent systematic review and meta-analysis further showed that several biomarkers, such as serum albumin and hemoglobin, are commonly implicated in both frailty and sarcopenia, reinforcing their biological convergence (14). In fact, some researchers suggest that sarcopenia and frailty may be difficult to disentangle, as they often coexist and manifest through similar clinical pathways (15, 16). Therefore, management strategies developed for frailty—particularly multicomponent geriatric interventions—may also be effective for sarcopenia.

Frailty management involves patient-centered multicomponent geriatric intervention, addressing unmet needs comprehensively (17, 18). These interventions extend beyond exercise and nutritional support to include deprescribing, mental health management, and environmental modifications—emphasizing the underlying causes of inactivity and anorexia in older adults (17). The World Health Organization's Integrated Care for Older People (ICOPE) framework exemplifies these principles (19), and several geriatric care guidelines have incorporated this holistic approach (20, 21). Although sarcopenia and physical frailty substantially overlap, the specific effectiveness of multicomponent geriatric interventions on sarcopenia outcomes remains insufficiently established. This challenge arises from the very nature of geriatric care, which is inherently individualized and multifactorial—making it difficult to evaluate with traditional disease-specific trial designs (22). In this context, conducting a post-hoc analysis of sarcopenic subgroups within previously conducted frailty intervention trials is a meaningful and justified approach to explore potential benefits in this high-risk population.

The Aging Study of Pyeongchang Rural Area-Intervention Study (ASPRA-IS) study, a non-randomized clinical trial, was designed to assess the effectiveness of a 24-week multicomponent intervention in socially vulnerable older adults living in the community, with the results detailed in a prior study. In summary, prior studies demonstrated that the program reduced the risk of disability (23), institutionalization-free survival over 30 months (24), by improvements in physical performance (25). The intervention included various components, including exercise, nutrition, depression management, deprescribing, and home hazard reduction (25). In this study, we conducted a *post hoc* analysis specifically examining participants with sarcopenia within the ASPRA-IS to determine whether the multicomponent intervention is effective in older adults with sarcopenia. Furthermore, we examined its effectiveness across multiple operational definitions of sarcopenia—including those defined by the Asian Working Group for Sarcopenia (AWGS) (4), the Korean Working Group on Sarcopenia (KWGS) (26), as well as subtypes such as severe sarcopenia and functional sarcopenia.

2 Methods

2.1 Study design

This study was a *post hoc* analysis of the ASPRA-IS, a prospective, single-arm intervention study that conducted a 24-week multicomponent intervention in Pyeongchang County, Gangwon Province, South Korea. Details of the ASPRA-IS study are described in previous studies (24, 25). In summary, ASPRA-IS enrolled participants who lived alone or received medical aid from the ASPRA cohort, an ongoing prospective cohort study of community-dwelling older adults (27). Exclusion criteria included inability to walk 100 m, recent admission to long-term care facilities, diagnoses of end-stage heart failure, end-stage renal disease, metastatic cancer, cognitive impairment (Mini-Mental State Examination score $\leq$ 18 points), and plans to relocate outside the study area within the next 6 months (27).

From the ASPRA cohort, 383 eligible individuals were identified, with 187 opting for the multicomponent intervention and 196 choosing not to participate. Since those who declined intervention underwent the same comprehensive geriatric assessment as part of the observational cohort (ASPRA cohort), information was collected for both the intervention and control groups. The study protocol received approval from the Institutional Review Boards of Asan Medical Center and was registered in 2015 (NCT02554994). Informed consent was obtained from all participants before the entry. This study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

2.2 Study population and assessment of sarcopenia

Among 383 participants of the ASPRA-IS study, participants with sarcopenia were the focus of this investigation. Sarcopenia was defined in accordance with the AWGS (4) and KWGS guidelines (26). Bioelectrical impedance analysis (BIA) was employed to measure muscle mass at frequencies of 5, 50, and 500 kHz. Appendicular skeletal mass (ASM) was calculated by summation of the lean mass of both arms and legs, adjusted by height squared (ASM/h^2). Low muscle mass was identified as ASM/h^2 below 7.0 kg/m^2 in men and below 5.7 kg/m^2 in women, measured after an overnight fast. Grip strength was assessed using a handgrip dynamometer (T. K. K 5401 Grip-D; Takei, Tokyo, Japan), with low grip strength defined as <28 kg for men and <18 kg for women. Usual gait speed was determined by instructing participants to walk 7 m at their regular pace on a flat indoor surface. Trained nurses measured the 4 m transit time with a digital stopwatch, excluding the acceleration and deceleration interval of 1.5 m. Slow gait speed was defined as <1 m/s.

TABLE 1 Overview of the multicomponent intervention program.

Focus	Description of intervention
Exercise	• Intervention: 60-min group exercise session led by licensed trainers focusing on the following types. The intensity started with low-intensity exercises and increased intensity every month 1. Resistance (20 min): squat, plank, side plank, straight leg raises 2. Balance (20 min): one-leg standing, shifting from side to side, heel-to-toe walk 3. Aerobic/endurance (20 min): step up and down, quick pace, dancing 4. The exercise trainer was given instructions not to exceed 60–70% of the maximal exercise capacity based on the perceived exertion scale • Target: all participants • Frequency: twice a week
Nutrition	• Intervention: administration of 125 mL commercial liquid formula containing 200 kcal of energy, 24.5 g carbohydrate, 13 g protein, 5.63 g essential amino acid, and 7 g fat • Target: all participants • Frequency: twice a day
Depression	• Intervention: evaluation by a geriatrician or a psychiatrist and administration of supportive psychotherapy or antidepressant medication as clinically indicated • Target: participants with a CES-D score > 20 points at baseline • Frequency: monthly
Polypharmacy	• Intervention: medication review by a geriatrician, and dose reduction or discontinuation of potentially inappropriate medications according to the 2012 Beer's criteria • Target: participants taking five prescription medications at baseline • Frequency: monthly
Home hazards	• Intervention: evaluation of home environment by a visiting nurse and a social worker using the Home Fall Prevention Checklist by the Centers for Disease Control and Prevention and modification of the environment to eliminate any identified hazard • Target: all participants with any identified home hazard at baseline • Frequency: trimonthly

CES-D, center for epidemiologic studies depression.
Source: Oh G, Lee H, Park CM, Jung H-W, Lee E, Jang I-Y, et al. Long-term effect of a 24-week multicomponent intervention on physical performance and frailty in community-dwelling older adults. Age and Ageing. 2021; 50: 2157–66.

Severe sarcopenia was identified in individuals exhibiting low muscle mass, low muscle strength, and slow gait speed. Sarcopenia (not severe) was defined as low muscle mass with either low muscle strength or slow gait speed, not meeting the criteria for severe sarcopenia. Functional sarcopenia was defined as having low muscle strength and slow gait speed without low muscle mass. This definition was introduced in the KWGS guidelines (26) and has been validated in previous studies regarding its comparable prognosis with earlier sarcopenia definitions (13) and its response to exercise and nutritional interventions (28). Among the 285 participants with sarcopenia, 2 with missing variables [Center for Epidemiologic Studies Depression (CES-D) scale] were excluded, resulting in 283 participants for propensity score matching. Of these, 138, 42, and 103 participants were classified as having severe sarcopenia, sarcopenia (not severe), and functional sarcopenia, respectively. Additionally, 145 and 138 participants were assigned to the intervention and control groups, respectively. The study flow chart is outlined in Supplementary Figure S1.

2.3 A multicomponent intervention

The 24-week multicomponent intervention program comprised group exercise, nutritional supplementation, depression management, medication review, and home hazard reduction. A detailed description of the intervention is available in a prior study (24, 25). In brief, all participants received group exercise sessions lasting 60 min twice a week, along with commercial nutritional supplements (125 mL liquid formula containing 200 kcal, 24.5 g carbohydrate, 13 g protein, 5.63 g essential amino acid, and 7 g fat) twice daily (29–31). The depression management program (32), deprescribing for potentially inappropriate medications for older adults (33), and home hazard evaluation and reduction were selectively administered to eligible participants based on predefined criteria (Table 1).

The 24-week multicomponent intervention was implemented 6 months after the baseline assessment (−6 months). Throughout the 6-month pre-intervention period, participants received routine care from local public health centers. After completing the 24-week multicomponent program, the intervention group transitioned to receiving routine care, serving as the comparison group. Adherence rates ranged from 83.7 to 91.3% across each subtype of the intervention program (23). Meanwhile, the control group continued to receive routine care throughout the entire study period.

2.4 Comprehensive geriatric assessment

Comprehensive geriatric assessment was performed every year: at baseline (6 months before the start of the intervention program), 6 months (at the end of the intervention), 18 and 30 months. Trained nurses who were unaware of the intervention status performed comprehensive geriatric assessment. For the intervention group, additional comprehensive geriatric assessment was performed at the start of the intervention program (0 months).

Data were collected on demographic characteristics, years of completed education, and identification of individuals with low socioeconomic status (those receiving medical aid due to a monthly income of <500 USD). Chronic conditions were collected, including 11 physician-diagnosed clinical conditions (angina, arthritis, asthma, cancer, chronic lung disease, congestive heart failure, diabetes, heart attack, hypertension, kidney disease, and stroke). Depressive symptoms were evaluated using the Korean version of the CES-D Scale (34). Cognitive status was assessed using the Mini-Mental State Examination for Dementia Screening (35). The risk of malnutrition was determined using the Mini-Nutritional Assessment Short Form score, with a score of ≤ 11 indicating malnutrition risk (36).

2.5 Outcome assessment

Institutionalization-free survival served as the outcome measure, assessed at 3-month intervals by nursing staff. The occurrence month and reasons for loss to follow-up were obtained directly from study participants or their family members. Changes in the Short Physical Performance Battery (SPPB) score (ranging from 0 to 12 points and encompassing usual gait speed, standing balance, and completion of five chair stands), usual gait speed, and a 47-item Frailty Index were also evaluated. The 47-item Frailty Index was calculated based on the deficit-accumulation theory using 47 specified items (Supplementary Table 1) (37).

2.6 Statistical analysis

We conducted 1:1 propensity score matching using a nearest-neighbor method with a caliper width of 0.2 standard deviation of the logit propensity score. The propensity score model was developed using logistic regression, with intervention status specified as the dependent variable. Baseline characteristics, including age, sex, enrolled year, living alone, CES-D score, number of chronic diseases, number of falls in the last year, emergency room or admission in the previous year, frailty phenotype, frailty index, gait speed, and sarcopenia phenotype, were used as independent variables. The balance in baseline characteristics between the two groups was assessed using standardized mean difference (SMD).

The SPPB score of 70 participants in this investigation was not measured due to a protocol update after the baseline assessment of participants enrolled in 2014. The SPPB score was imputed in the pre-matching cohort using mice R package with baseline gait speed, SPPB score at baseline and 0 months (intervention group) and 6 months (control group) among participants enrolled excluding 2014.

We summarized the mean and standard deviation or proportions of baseline characteristics for both groups before and after propensity score matching. A linear mixed model with random intercept was used to determine the effect of the intervention on the SPPB score, gait speed, and frailty index at 6, 18, and 30 months. This model included independent variables for intervention status, times as categorical variables, and their interaction terms. The mean differences (MDs) in SPPB score, gait speed, and frailty index between the two groups at 6, 18, and 30 months and their 95% confidence intervals (CI) were calculated from a linear mixed model.

Institutionalization-free survival was determined using Kaplan–Meier estimates. To examine the statistical differences in survival and hazard between the intervention and comparison groups, we employed the log-rank test and Cox proportional hazard model. Additionally, a subgroup analysis was performed by categorizing participants into two groups based on the presence or absence of low muscle mass, classified as sarcopenia (AWGS) and functional sarcopenia.

To underscore the robustness of the association between intervention status and institutionalization-free survival, a sensitivity analysis was conducted after categorizing participants into four groups: (A) individuals with low muscle mass, slow gait speed, and low grip strength (severe sarcopenia); (B) individuals with low muscle mass and slow gait speed but preserved grip strength; (C) individuals with low muscle mass and low grip strength but preserved gait speed; and (D) individuals with slow gait speed and low grip strength but preserved muscle mass (functional sarcopenia). We compared the institutionalization-free survival of the intervention and control groups across various combinations of A, B, C, and D.

A two-sided p-value <0.05 significance threshold was applied for all analyses to determine statistical significance. Statistical analyses were performed with R Software (version 4.1.1; R Foundation for Statistical Computing, Vienna, Austria).

3 Results

3.1 Baseline characteristics

In comparing the intervention ($N = 145$) and control ($N = 138$) groups, the intervention group had a higher mean age (77.8 years) than the control group (76.9 years). The percentage of females was higher in the intervention group (77.2%) than in the control group (75.4%). Grip strength was lower in the intervention group (15.2 kg) than in the control group (16.7 kg). Additionally, the intervention group had a lower risk of depression (mean CES-D score 10.3 versus 11.5). The prevalence of falls in the last year was higher in the intervention group (22.1%) compared to the control group (15.2%). Furthermore, the intervention group showed a higher number of chronic conditions (1.7 versus 1.5), slower gait speed (0.62 versus 0.66 m/s), worse SPPB score (6.97 versus 7.56), and greater frailty, as indicated by higher scores on both the frailty phenotype scale (2.6 versus 2.2) and frailty index (0.28 versus 0.26) than the control group.

Propensity score matching yielded 102 pairs, achieving effective balance in baseline characteristics between the two groups, as evidenced by absolute values consistently <0.1. Key variables, such as age (77.57 versus 77.64), percentage of females (82.4% versus 81.4%), and frailty index (0.27 versus 0.28), demonstrated appropriate balances (Table 2). Furthermore, variables related to the multicomponent intervention, such as the number of medications (2.91 versus 3.01), CES-D score (10.76 versus 10.90), and the percentage of individuals with fall event for the last year (17.6% versus 15.7%) also demonstrated appropriate balances.

3.2 Outcomes

In the matched cohort, mortality and institutionalization incidence were 6 (5.9%) and 7 (6.9%) in the intervention group and

TABLE 2 Comparison of baseline characteristics before and after propensity score matching.

Baseline characteristics	Before matching			After matching		
	Intervention (*N* = 145)	Control (*N* = 138)	SMD	Intervention (*N* = 102)	Control (*N* = 102)	SMD
Age, mean (SD)	77.78 (4.76)	76.91 (6.60)	0.151	77.57 (4.76)	77.64 (6.77)	0.012
Female, *n* (%)	112 (77.2)	104 (75.4)	0.044	84 (82.4)	83 (81.4)	0.025
Enrolled year, *n* (%)			0.197			0.027
2014	39 (28.3)	29 (20.0)		19 (18.6)	20 (19.6)	
2015	50 (36.2)	61 (42.1)		42 (41.2)	42 (41.2)	
2016	49 (35.5)	55 (37.9)		41 (40.2)	40 (39.2)	
Sarcopenia phenotype, *n* (%)			0.199			0.064
Severe sarcopenia	76 (52.4)	62 (44.9)		56 (54.9)	54 (52.9)	
Sarcopenia (not severe)	17 (11.7)	25 (18.1)		13 (12.7)	12 (11.8)	
Functional sarcopenia	52 (35.9)	51 (37.0)		33 (32.4)	36 (35.3)	
Medical aid, *n* (%)	31 (21.4)	27 (19.6)	0.045	19 (18.6)	21 (20.6)	0.049
Living alone, *n* (%)	120 (87.0)	117 (80.7)	0.171	87 (85.3)	87 (85.3)	<0.001
ASM/height^2, kg/m^2, mean (SD)	5.70 (1.15)	5.73 (1.00)	0.029	5.67 (1.06)	5.58 (1.00)	0.084
Grip strength, kg, mean (SD)	15.22 (5.79)	16.69 (6.90)	0.232	15.36 (5.63)	15.33 (6.13)	0.005
No. chronic conditions, mean (SD)	1.66 (1.08)	1.46 (1.05)	0.186	1.48 (1.11)	1.55 (1.07)	0.063
No. medications, mean(SD)	3.48 (3.52)	2.95 (3.11)	0.158	2.91 (2.66)	3.01 (3.16)	0.034
CES-D score, mean (SD)	10.26 (9.83)	11.48 (10.50)	0.120	10.76 (10.26)	10.90 (10.07)	0.014
MMSE-DS score, mean (SD)	23.67 (4.02)	23.76 (4.70)	0.022	23.30 (4.16)	23.27 (5.12)	0.008
Emergency room visit or admission in the last year, *n* (%)	27 (18.6)	22 (15.9)	0.071	13 (12.7)	15 (14.7)	0.057
Fall in the last year, *n* (%)	32 (22.1)	21 (15.2)	0.177	18 (17.6)	16 (15.7)	0.053
SPPB total score, mean (SD)	6.97 (2.56)	7.56 (2.76)	0.220	7.11 (2.42)	7.14 (2.80)	0.011
Gait speed, m/s, mean (SD)	0.62 (0.20)	0.66 (0.21)	0.205	0.63 (0.19)	0.62 (0.20)	0.020
Frailty phenotype, mean (SD)	2.57 (1.08)	2.24 (1.09)	0.301	2.42 (1.04)	2.45 (0.99)	0.029
Frailty index, mean (SD)	0.28 (0.09)	0.26 (0.11)	0.161	0.27 (0.09)	0.27 (0.11)	0.054

ASM, appendicular skeletal mass; CES-D, center for epidemiologic studies depression; SMD, standardized mean difference; SPPB, short physical performance battery; MMSE-DS, mini-mental state examination for dementia screening.

12 (11.8%) and 23 (22.5%) in the control group, respectively (Detailed reasons for follow-up loss are described in Supplementary Figure S1). The 30-month institutionalization-free survival was 63.4% (95% CI, 54.4–73.9%) in the intervention group and 87.2% (81.0–94.0%) in the control group. A significant difference in institutionalization-free survival was observed between the intervention and control groups (log-rank $p < 0.001$), with a hazard ratio of 0.30 (95% CI, 0.16–0.56) (Figure 1a).

Additionally, a subgroup analysis was conducted by dividing the participants into two subgroups: those with and without low muscle mass (classified as sarcopenia (AWGS) and functional sarcopenia) (Figure 1b). In both subgroups, institutionalization-free survival maintained a noticeable difference between the intervention and control groups, although statistical significance was not reached in the functional sarcopenia group (log-rank $p < 0.001$ and $p = 0.09$, respectively). The hazard ratios for these comparisons were 0.28 and 0.34 (95% CI, 0.13–0.57, and 0.09–1.30), respectively.

Furthermore, when examining specific outcomes, the intervention group demonstrated significantly higher SPPB scores than the control group at 6 months (MD 3.8; 95% CI, 3.0–4.6; $p < 0.001$), 18 months (1.4; 95% CI, 0.6–2.2; $p = 0.001$), and 30 months (0.8; 95% CI, 0.1–1.6; $p = 0.035$) (Figure 2a). Moreover, the intervention group showed faster gait speed than the control group at 6 months (MD 0.42; 95% CI, 0.33–0.51; $p < 0.001$), 18 months (0.24; 95% CI, 0.15–0.33; $p < 0.001$), and 30 months (0.28; 95% CI, 0.21–0.36; $p < 0.001$) (Figure 2b). Lastly, the intervention group had a significantly lower frailty index only at 6 months (MD -0.05; 95% CI, −0.08 to −0.02; $p < 0.001$) and lower but without statistical significance at 18 months (MD -0.03; 95% CI, −0.06 to 0.00; $p = 0.09$) and 30 months (MD -0.01; 95% CI, −0.04 to 0.03; $p = 0.65$) (Figure 2c).

In addition, we categorized participants into four groups (A, B, C, and D) based on muscle mass, gait speed, and grip strength (Figure 3a). The distribution of participants in each group was as follows: 110 in Group A, 20 in Group B, 5 in Group C, and 69 in Group D. Institutionalization-free survival across all combinations of these four groups was then compared. Notably, the results remained consistent regardless of the combinations, with hazard ratios ranging from 0.27 to 0.34 (Figure 3b).

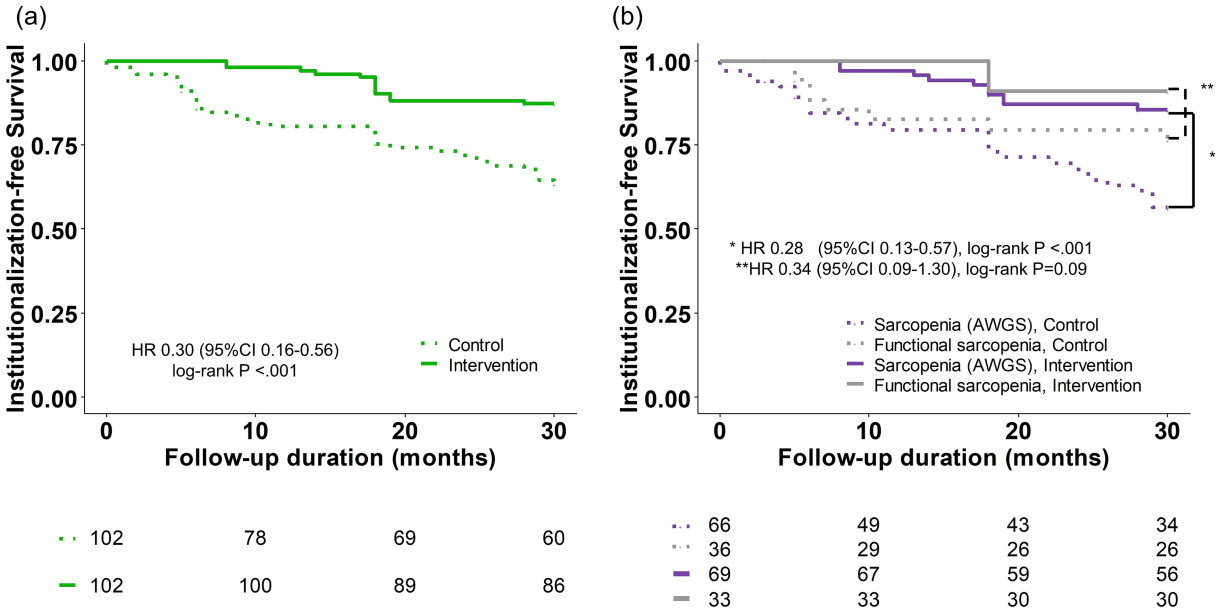

FIGURE 1
Kaplan–Meier estimate of institutionalization-free survival. **(a)** Total population. **(b)** Subgroup analysis according to Sarcopenia (AWGS) and functional sarcopenia. AWGS, Asian Working Group for Sarcopenia; CI, confidence interval; HR, hazard ratio.

4 Discussion

We found that a 24-week multicomponent intervention, including group exercise, nutritional supplementation, depression management, medication review, and home hazard reduction, was associated with a lower risk of institutionalization and mortality in socioeconomically vulnerable community-living older adults with sarcopenia. Furthermore, the SPPB score and gait speed improved after the intervention and persisted for up to 30 months. The frailty index showed improvement immediately after the intervention but gradually diminished over time. Remarkably, the positive association with institutionalization-free survival persisted irrespective of the combinations of different sarcopenia components. These results suggest that a multicomponent geriatric intervention, as a strategy for addressing frailty, may be effective in managing sarcopenia, regardless of how its components are combined.

The initial definition of sarcopenia focused on the loss of muscle mass associated with aging (38). However, it is now recognized as a systemic and complex condition lacking a single or clear pathophysiology, and no single intervention can completely restore its conditions (2, 39). Furthermore, the consequences of sarcopenia correspond with those of geriatric syndromes and frailty, such as disability, poor quality of life, and increased mortality (16). Therefore, there is a growing perspective that sarcopenia should be considered a geriatric syndrome or physical frailty (13, 15, 16, 26, 40, 41). Recommendations from the World Health Organization (WHO) Guidelines on Integrated Care for Older People (ICOPE), which not only emphasize exercise or nutrition but also polypharmacy, home hazard reduction, or pain management to improve mobility, align with this perspective. Guidelines on sarcopenia from KWGS and Australia and New Zealand highlight the assessment of various components, including falls, cognition, social support, or pain, among others (7, 26). Current approaches extend beyond focusing solely on mobility or muscle, addressing other systemic conditions and patient-centered unmet needs. Our study supports this viewpoint, reinforcing the conceptual alignment between sarcopenia and physical frailty.

Regarding functional sarcopenia, defined as low grip strength and low physical performance with preserved muscle mass according to the KWGS guidelines, our results are noteworthy (26). Functional sarcopenia was previously associated with greater frailty and comparable prognosis compared with sarcopenia (not severe) (13). We demonstrated that a multicomponent intervention is associated with improved outcomes in functional sarcopenia and sarcopenia (AWGS), defined according to the most popular guidelines in the Asian population (Figure 1b) (4). These results suggest that functional sarcopenia should be incorporated into the spectrum of sarcopenia, even with preserved muscle mass. Additional reasons supporting the inclusion of functional sarcopenia into sarcopenia are detailed in the discussion section of our previous study (13).

Our results reinforce the concept that sarcopenia and physical frailty have large similarities and suggest managing sarcopenia in terms of physical frailty, emphasizing a patient-centered and comprehensive approach. First, our results suggest that sarcopenia may benefit from the same intervention strategy with frailty. Second, as mentioned in the previous paragraph, by integrating functional sarcopenia into the sarcopenia spectrum, the operational definition of sarcopenia and physical frailty becomes very similar. Third, characteristics of a continuous concept for sarcopenia, rather than a binary, are suggested by a previous study (42) and our results as described in Figure 3. Fourth, both concepts share similar risk factors and consequences (15, 16). Furthermore, at least in clinical settings, distinguishing between these two concepts and their causal relationship may be impractical and of little importance (15, 16). Further detailed discussions on this topic have been published by various authors (15, 16).

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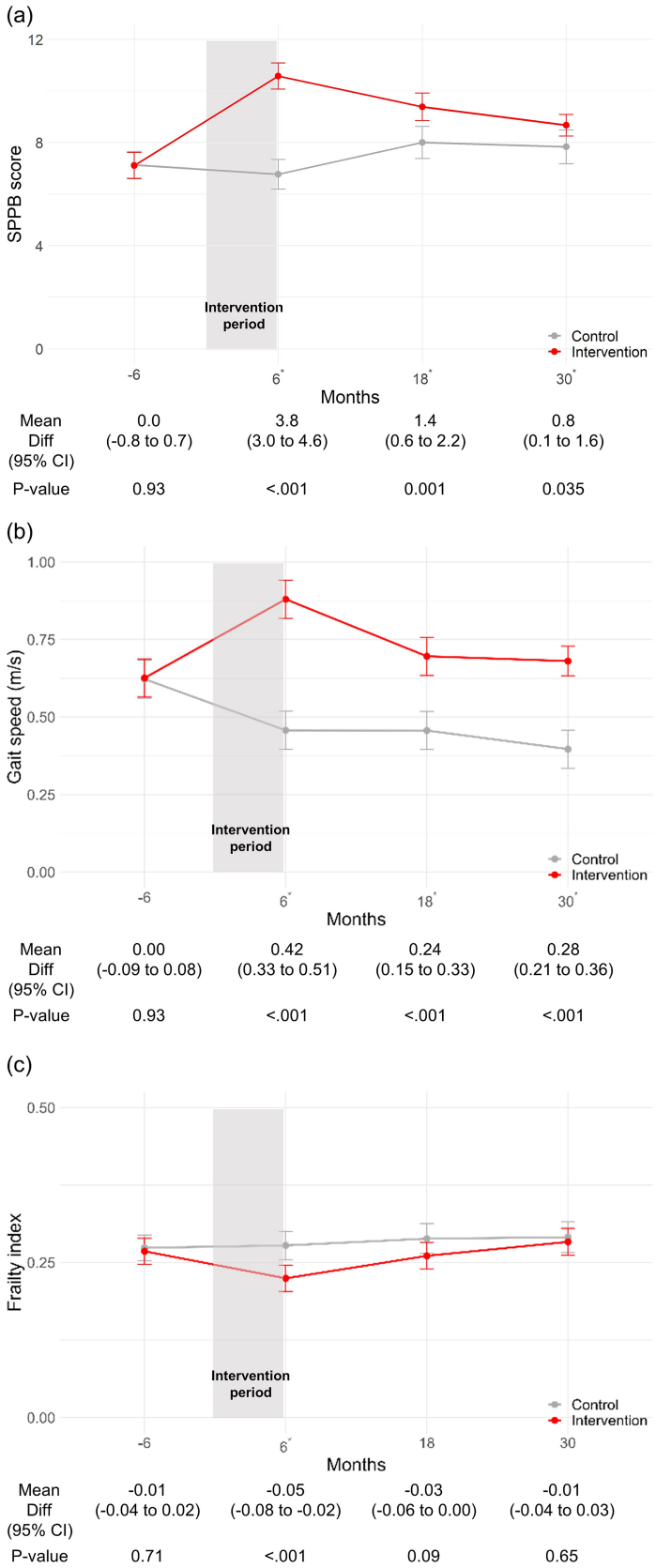
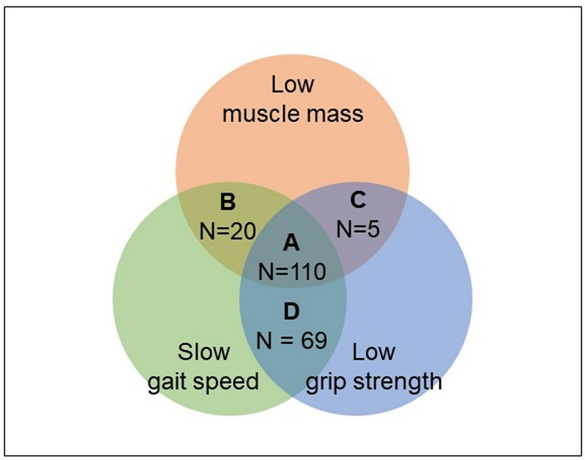


FIGURE 2
Change in SPPB score, gait speed, and frailty index stratified by intervention status. **(a)** Change in SPPB score. **(b)** Change in gait speed (m/s). **(c)** Change in frailty index. *p-value <0.05. CI, confidence interval; SPPB, short physical performance battery.

(a)



A = severe sarcopenia
B+C = sarcopenia (not severe)
A+B+C = sarcopenia (AWGS)
D = functional sarcopenia
A+B+C+D = sarcopenia (total population)

(b)

Groups	Intervention	Control	HR (95% CI)
A	10 / 56	24 / 54	0.33 (0.16—0.68)
D	3 / 33	8 / 36	0.34 (0.09—1.30)
A+B	10 / 67	27 / 63	0.27 (0.13—0.56)
A+C	10 / 58	24 / 57	0.33 (0.16—0.69)
A+D	13 / 89	32 / 90	0.34 (0.18—0.64)
A+B+C	10 / 69	27 / 66	0.28 (0.13—0.57)
A+B+D	13 / 100	35 / 99	0.30 (0.16—0.56)
A+C+D	13 / 91	32 / 93	0.34 (0.18—0.65)
A+B+C+D	13 / 102	35 / 102	0.30 (0.16—0.56)

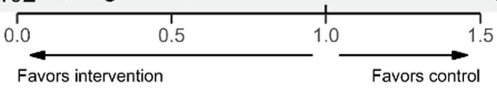


FIGURE 3
Impact of multicomponent intervention on institutionalization-free survival based on different sarcopenia component combinations (Analysis of Group B or C alone could not be performed due to insufficient data.). **(a)** Venn diagram illustrating study populations and Groups A, B, C, and D. **(b)** Sensitivity analysis examining the effect of multicomponent intervention on institutionalization-free survival across various combinations of Groups A, B, C, and D. AWGS, Asian Working Group for Sarcopenia; CI, confidence interval; SPPB, short physical performance battery.

To our knowledge, this study is the first to suggest multicomponent intervention, encompassing various geriatric interventions, such as nutrition, exercise, and deprescribing, can be effective in patients with sarcopenia. Previous studies have shown exercise and nutritional support can be effective in sarcopenia, and well described in a review article (43). A notable example is the result of The Sarcopenia and Physical fRailty IN older people: multi-componenT Treatment strategies (SPRINTT) project, which showed a multicomponent intervention including physical activity and nutritional counseling was associated with a reduction of mobility disability in a multicenter randomized controlled trial with older adults with SPPB score of 3 to 9 points and low appendicular lean mass (44). In addition to nutrition and physical activity, factors such as depression, polypharmacy, and falls have been shown to be associated with sarcopenia (16, 45). However, the effects of psychotherapy or antidepressants, deprescribing, or home hazard reduction have not been well validated. One example is a study indicating that deprescribing was associated with functional recovery

and home discharge among older adults with sarcopenia after a stroke (46, 47). We showed that encompassing those approaches with nutrition and exercise was associated with improved outcomes in patients with sarcopenia.

As a post-hoc analysis, this study has inherent limitations, including an increased risk of type I error due to multiple testing, as well as the potential for selection bias and residual confounding (48). While post-hoc subgroup analyses should be interpreted with caution, they can still yield valuable insights—particularly when supported by biological plausibility and a clear clinical rationale, as in our study involving a long-term, comprehensive intervention (49). To address these concerns, we conducted sensitivity analyses, which demonstrated consistent trends across different sarcopenia phenotypes, reinforcing the robustness of our findings. Although exploratory in nature, our results offer meaningful preliminary evidence that may inform the design of future prospective trials targeting this high-risk population.

This study has strength in its long-term follow-up with various geriatric outcomes, and the participants demonstrated higher adherence to the intervention, ranging from 83.7 to 91.3% (25). In addition to the above mentioned limitations of post-hoc analysis, several other limitations should be noted. Firstly, this study was a secondary analysis of a non-randomized trial, and the results should be interpreted with caution. It was conducted in rural areas with limited resources and infrastructure to conduct a randomized controlled trial, a known challenge in community-based interventions for older populations (50). While we attempted to minimize bias using propensity score matching, we acknowledge that these results do not ensure the methodological rigor of a randomized controlled trial. Secondly, generalization is limited since our results were derived from socioeconomically vulnerable older adults in rural areas in Korea. In previous work, we compared the ASPRA cohort with the nationally representative cohort to support external validity (27). Thirdly, since all participants in the intervention group received every aspect of the treatment according to each indication, isolating each component's impact is impossible. Consequently, we cannot pinpoint which specific element or duration of the program was most effective. Additionally, the multicomponent intervention's observed benefits could be attributed solely to the nutrition and exercise components, which are already established as effective treatments for sarcopenia (43, 44). Therefore, we believe a randomized controlled trial with a diverse population and various components, intensities, and durations of multicomponent intervention is warranted to validate the effect of such interventions on patients with sarcopenia and implement them in guidelines and public health policy. Finally, approximately 25% of SPPB scores were imputed due to a protocol change early in the study period. While the possibility of bias remains, we used a validated multiple imputation approach incorporating baseline gait speed and available SPPB data from other time points, based on observed longitudinal trends in SPPB (25).

In conclusion, our results demonstrated that a 24-week multicomponent intervention program was associated with a lower incidence of institutionalization and mortality, as well as sustained improvement of physical performance in socioeconomically vulnerable older adults with sarcopenia. Furthermore, this association with institutionalization and mortality rates remained robust across diverse groups, defined by different combinations of sarcopenia components. These results support the perspective of managing sarcopenia as a state of physical frailty, emphasizing a comprehensive geriatric approach as a potential solution for patients with sarcopenia.

Data availability statement

The datasets presented in this article are not readily available because the raw data supporting the conclusions of this article will be made available by the authors upon reasonable request, subject to review. Requests to access the datasets should be directed to onezero2@gmail.com.

Ethics statement

The studies involving humans were approved by the Institutional Review Boards of Asan Medical Center. 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

SJ: Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft. EL: Funding acquisition, Investigation, Project administration, Writing – review & editing. JB: Data curation, Project administration, Resources, Software, Writing – review & editing. GJ: Writing – review & editing, Methodology, Conceptualization, Validation. H-WJ: Conceptualization, Investigation, Methodology, Project administration, Writing – review & editing. I-YJ: Conceptualization, Funding acquisition, Investigation, Methodology, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research and/or publication of this article. This study was supported by a grant [2023IF0005] from the Asan Institute for Life Sciences, Asan Medical Center, Seoul, Korea; by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HR20C0026); and by a grant from the MD-PhD/Medical Scientist Training Program through KHIDI, funded by the Ministry of Health & Welfare, Republic of Korea.

Acknowledgments

Statistical advice for this study was offered by Hwa Jung Kim, who specializes in Clinical Epidemiology and Biostatistics at Asan Medical Center. We also like to acknowledge Editage (www.editage.co.kr) for providing English language editing services.

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 Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2025.1573384/full#supplementary-material

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