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Effectiveness of exercise and nutrition interventions for cognitive function in older adults: A systematic review and meta-analysis

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ABSTRACT

Although life expectancy has increased, the proportion of years lived without disability has not improved at the same rate. This has contributed to the rising prevalence of dementia, which currently affects over 55 million people worldwide. In the absence of curative treatments, non-pharmacological strategies such as exercise and diet have attracted interest as a means of preserving cognitive function in older adults. This systematic review and meta-analysis evaluated the effectiveness of combined exercise and dietary or nutritional supplementation interventions on global cognitive function in healthy older adults or those with mild cognitive impairment. Following PRISMA guidelines (PROSPERO ID: CRD42024528600), we searched the following databases up to 1 May 2025: PubMed, Scopus, Web of Science and SportDiscus. Fourteen randomised controlled trials involving 4013 participants aged 65 years or over (mean age: 71.4) without diagnosed dementia were included. Global cognition was assessed using validated tools. The methodological quality was assessed using the PEDro scale and the risk of bias using Cochrane's RoB 2 tool. A random-effects meta-analysis was conducted using the DerSimonian-Laird method, with heterogeneity estimated via the I^2 statistic. A combined exercise and nutritional intervention significantly improved global cognitive function compared to the control group (SMD: 0.15; 95% CI: 0.07 to 0.24; I^2: 50%). A sensitivity analysis that excluded multi-domain interventions confirmed this effect (d = 0.12; 95% CI: 0.02 to 0.22; $I^2 = 0\%$). However, no significant improvements were found in specific domains, such as executive function or visual-perceptual ability. Variability in methodological protocols, follow-up durations, cognitive tools and adherence measurement limits comparability. While the observed effect size was modest, these findings, in the context of healthy ageing, suggest the potential for these combined interventions to attenuate cognitive decline and preserve functional autonomy, thereby highlighting their role in dementia prevention strategies.

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1. Introduction

Global ageing presents significant societal and healthcare challenges, driven primarily by the widening gap between total life expectancy and healthy life expectancy (Ministerio de Sanidad, 2022; Pérez Díaz et al., 2020). Consequently, populations are aging with a higher burden of multimorbidity and dependency, comparisons in which dementia is a leading contributor. Currently affecting over 55 million people worldwide, dementia has been designated a public health priority by the World Health Organization (World Health Organization, 2025, 2020). Given that curative or disease-modifying treatments remain elusive (Budd Haeberlein et al., 2022; van Dyck et al., 2023), there is an urgent need for preventive strategies capable of maintaining cognitive function and delaying clinical decline. This necessity has spurred growing interest in modifiable lifestyle factors, particularly diet and physical activity (Mandolesi et al., 2018; Poddar et al., 2019; Ungvari et al., 2023).

In isolation, both nutrition and exercise play critical roles in brain health. Specific dietary patterns, such as the Mediterranean and MIND diets, as well as targeted supplementation (e.g., omega-3 fatty acids, antioxidants, and vitamins), have demonstrated positive effects on cognitive function and neuronal integrity (Atmadja et al., 2020; Castle et al., 2020; Devranis et al., 2023; Dobreva et al., 2022; Fekete et al., 2023; Gensous et al., 2020; Jia et al., 2019; Key and Szabo-Reed, 2023; Kim et al., 2024; Nolan et al., 2022; Patan et al., 2021; Stavrinou et al., 2020). Similarly, numerous randomized controlled trials (RCTs) and neuroimaging studies have documented the beneficial impact of physical exercise on functional brain plasticity and cognitive performance (Bolandzadeh et al., 2015; Huang et al., 2022). However, evidence regarding the efficacy of these single-domain interventions remains inconsistent; notably, recent umbrella reviews have questioned their independent clinical significance across diverse age groups (Ciria et al., 2023).

In response to these inconsistencies, research focus has shifted toward multi-domain approaches that address several modifiable risk factors simultaneously (Hafdi et al., 2021). These interventions are predicated on the hypothesis that combining strategies, such as physical exercise, nutritional optimization, and cognitive stimulation, may exert a synergistic protective effect on brain health. Ideally, this synergy would surpass the benefits of single-domain interventions. For instance, the seminal FINGER study (Ngandu et al., 2015) reported significant improvements in global cognitive and executive functions compared to general health counselling. Conversely, other large-scale investigations, such as the three-year MAPT trial (Andrieu et al., 2017), failed to observe significant benefits in primary cognitive outcomes following combined exercise, dietary advice, and cognitive training.

Against this background of conflicting evidence, this systematic review and meta-analysis aimed to evaluate the effectiveness of combined interventions involving exercise and diet, or nutritional supplementation, on global cognitive function in healthy older adults or those with mild cognitive impairment.

2. Methods

This systematic review followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement (Page et al., 2021) (Checklist PRISMA; Supplementary Material: Table S1), and its review protocol was prospectively registered in the PROSPERO database (registration number CRD42024528600).

2.1. Data sources and search strategy

The electronic databases of PubMed, Sport Discus, Scopus and Web of Science were searched. The search was conducted on May 1, 2025. The strategy was devised according to the PICO framework, focusing on the following elements: Population: "older adult*" OR "elder*" OR "senior"; Intervention: exercise OR “physical activity” OR sport OR “strength training” OR “resistance training” AND “Nutritional Sciences" OR "Nutritional Status" OR "supplementat*"; Comparator: control; Outcome: Cognition OR "Cognition Disorders” OR comprehension OR memory. The complete search syntax is detailed in the Supplementary Material (Table S2). Two independent authors (SCB and GLB) were responsible for downloading all articles into a CSV document, independently removing duplicates between databases, identifying, screening and selecting studies. Any selection disagreements during the selection process were resolved by consensus.

2.2. Inclusion and exclusion criteria

The following inclusion criteria were applied: 1) RCTs; 2) studies including older adults with a mean age of ≥ 65 years at baseline, who were either cognitively healthy or diagnosed with mild cognitive impairment (MCI); 3) interventions combining exercise with dietary or supplementing intervention or, exercise and diet/supplementation in combination with other non-pharmacological strategies; 4) studies providing explicit descriptions of exercise and nutrition interventions protocols; 5) studies including control groups; and 6) studies reporting changes in global cognitive function, defined as the change in any validated measure of cognitive function from baseline to the end of the intervention period. Secondary outcomes related to cognitive subdomains were also considered.

We excluded studies focusing on clinical populations other than the target group, as well as trials exclusively involving patients diagnosed with malignant diseases, established neurological, metabolic, or cardiovascular diseases, or those including patients with dementia diagnosed at baseline. Additionally, we excluded studies conducted in hospitalized persons.

2.3. Quality assessment and risk of bias

The Physiotherapy Evidence Database (PEDro) scale was used to evaluate the methodological quality of each study. Based on their PEDro score, studies were classified as excellent (9–11), good (6–8), fair (4–5) or poor (<4). The PEDro scale has demonstrated validity and reliability for assessing the internal validity of RCTs (Maher et al., 2003).

Following the Cochrane Collaboration guidelines, the risk of bias for each included study was assessed using the Cochrane risk-of-bias tool for randomized trials (RoB 2) (Sterne et al., 2019). RoB 2 evaluates the following domains for randomized trials: 1) bias arising from the randomization process; 2) bias due to deviations from the intended interventions; 3) bias due to missing outcome data; 4) bias in the measurement of the outcome; 5) bias in the selection of the reported result. Overall, each study was classified as having a high risk of bias, some concerns or a low risk of bias.

The PEDro and RoB 2 tools were both applied by two independent researchers (SCB and GLB), and any disagreements were resolved by consensus.

2.4. Data extraction

Data from each study were collected for every variable presented in Table 1, including: 1) the first author, year and country; 2) cognitive status of the population and sample size; 3) characteristics of each group; 4) type of intervention; 5) characteristics of the control group; 6) educational level of both groups; 7) adherence to the intervention; and 8) method of adherence calculation.

The remaining data are presented in Table 2: 9) characteristics of the exercise intervention (frequency, intensity, type of exercise, duration, and volume); 10) characteristics of the nutrition intervention (timing and dosage of supplementation, and type of diet); 11) cognitive outcome; 12) outcome measure; and 13) results.

Table 1
Study and participant characteristics.

Author, year (Country) (reference)	Population cognitive status; sample size		Sample size by group Age ± SD % women	Type of intervention	Educational level; People; %. Years ± SD.	Adherence; %±SD	Adherence calculation method; supervision
Alves et al. (2013) (Alves et al., 2013). (Brazil)	Cognitively healthy n = 24	**INT**	12 67.3 ± 5.6 100%W	RT and creatine supplementation	6.6 ± 3.5	Supplementation: 100 Training: 84.4 ± 8.0	Supplementation was self-reported; not supervised Training percentage of sessions attended; Supervised
		CG	12 66.4 ± 5.6 100%W	Placebo (dextrose same dosage than creatine)	7.3 ± 3.1		
Andrieu et al. (2017) (Andrieu et al., 2017). (France)	Cognitively healthy (MMSE>24) with memory complaints or limitations in one instrumental activity of daily living or slow gait speed n = 754	**INT**	374 75.4 ± 4.4 61%W	Group meetings for cognitive training (ACTIVE and MEMO ADAPT), individualised AE, encouraging nutritional advice, supplementation with DHA and EPA and management of cardiovascular risk factors.	PS: 75; 20% SS: 145; 39% HS: 52; 14% U: 100; 27%	55%	For supplementation counting the number of capsules returned by participants; partially supervised For the multi-domain intervention by sessions attended; supervised
		CG	380 75.1 ± 4.4 66%W	Placebo capsules contained flavoured paraffin oil	PS: 82; 22% SS: 117; 31% HS: 67; 18% U: 108; 29%	85%	
Gutiérrez-Reguero et al. (2024) (Gutiérrez-Reguero et al., 2024). (Spain)	Cognitively healthy (Institutionalized) n = 38	**INT**	19 78.2 ± 10.7 47%W	MCEP combined with B-hydroxy b-methylbutyrate (HMB) supplementation	N/R	Unless 80% of the sessions	By register to training program attended; supervised
		CG	19 86.2 ± 8.9 74%W	Maintain their usual routine			
Komulainen et al. (2021) (Komulainen et al., 2021). (Finland)	Cognitively healthy n = 698	**INT**	232 65.8 ± 5.4 54%W	RT with Finnish Nutrition Recommendations adapted to their usual diet.	RT+D: 10.7 ± 3.6	66% RT+D (47% for RT and 84% for D)	Participants deemed 100% adherent if they had at least 2 sessions/week of resistance training; not supervised
		INT	232 66.2 ± 5.3 54%W	AE with Finnish Nutrition Recommendations adapted to their usual diet.	AE+D: 11.4 ± 4.1	71% AE+D (57% for AE and 85% for D).	Participants deemed 100% adherent if they had at least 300 min/week of moderate intensity aerobic training; not supervised
		CG	234 66.2 ± 5.4 47%W	General recommendations on physical activity and diet.	11.2 ± 3.9		
MacPherson et al. (2022) (MacPherson et al., 2022). (Australia)	Subjective memory impairment n = 147	**INT**	73 70 ± 6.3 70%W	RT and AE and omega-3 fatty acid, vitamin D, and protein supplementation.	Incomplete HS: 11; 15% Complete HS: 11; 15% Trade/certificate. 14; 19% U: 37; 51%	Exercise sessions. 76.9 ± 23.4	Supplementation protocol was self-reported; not supervised Training, percentage of sessions attended; supervised
		CG	74 70.5 ± 5.9 70%W	Stretching/flexibility program and a placebo drink containing 16 g of whole milk power and maltodextrin.	Incomplete HS: 12; 16) Complete HS: 5; 7% Trade/certificate. 19; 26% U: 38; 51%	Exercise sessions. 76 ± 24	

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Table 1 (*continued*)

Author, year (Country) (reference)	Population cognitive status; sample size		Sample size by group Age ± SD % women	Type of intervention	Educational level; People; %. Years ± SD.	Adherence; %±SD	Adherence calculation method; supervision
Moon et al. (2021) (Moon et al., 2021). (Korea)	Cognitively healthy having at least one modifiable dementia risk factor n = 90	**INT**	48 71.6 ± 4.8 72.9%W	Multi-domain intervention: MCEP, nutritional guidance (MIND diet), management of vascular risk factors, cognitive training and social activity and motivational enhancement.	9.8 ± 4.7	Vascular and metabolic risk factor 98.0%, cognitive training 97.4%, social activity 95.9%, exercise 91.0%, nutritional 94.2%, and motivational enhancement 97.7%.	Exercise training was cross-checked their written self-report with the recorded Fitbit activity; supervised. Nutritional, cognition and motivational home sessions by examining the participants' homework; supervised.
		CG	42 70.1 ± 4.6 78.6%W	Providing a booklet of lifestyle guidelines to prevent dementia, and usual care.	10.3 ± 4.7		
Ngandu et al. (2015) (Ngandu et al., 2015). (Finland)	At high risk of dementia (CAIDE>6) plus performing at the mean level or slightly lower than expected for age in one out of three short cognitive tests: WLMT ≤ 19; WLT ≤ 75%; MMSE ≤ 26 n = 1190	**INT**	591 69.5 ± 4.6 45%W	Muti-domain intervention: MCEP, Finnish Nutrition Recommendations, cognitive training and vascular risk monitoring.	10.0 ± 3.4	Nutrition 100% Exercise 90%	In person session attendance percentage reported and diary completion by participants; partially supervised
		CG	599 69.2 ± 4.7 47%W	General health advice	10.0 ± 3.4		
Phoemsapthawee et al. (2022) (Phoemsapthawee et al., 2022). (Thailand)	MCI (MMSE ≤23) n = 38	**INT**	20 77.7 ± 7.7 80%W	MCEP and gotu Kola (Centella asiatica) supplementation.	Unable RW: 2; 10% Incomplete PS: 6; 30% Complete PS: 11; 55% HS or U: 1; 5%	100%	N/R
		CG	18 73.7 ± 8.3 83.3%W	Placebo	Unable RW: 1; 5.6% Incomplete PS: 6; 33.3% Complete PS: 10; 55.6% HS or U: 1; 5.6%		
Sakurai et al. (2024) (Sakurai et al., 2024). (Japan)	Cognitive decline SD of 1.0 or more from the reference threshold for one or more of the four cognitive domains n = 433	**INT**	215 74.3 ± 5.0 52%W	Multi-domain intervention; MCEP, dietary reference intakes for Japanese, management of vascular risk factors and cognitive training (Brain HQ).	12.6 ± 2.5	Exercise session 83% Cognitive training 18%	Exercise sessions: N/R Cognitive training: During the 4–6, 10–12 and 16–18 months (intensive training periods) of tablet use; supervised.
		CG	218 74.4 ± 4.8 52%W	General health-related information in writing every 2 months.	12.5 ± 2.4		
Tokuda et al. (2020) (Tokuda et al., 2020). (Japan)	MCI n = 49	**INT**	21 67.1 ± 1.1 52%W	RT and AE with LCPUFA	13.2 ± 0.6	N/R	Training, percentage of sessions attended; supervised.
		CG	28 67.4 ± 1.0 86%W	Placebo capsules	13.3 ± 0.4		
Ng et al. (2018) (Ng et al., 2018). (Singapore)	Cognitively healthy Frail and pre-frail n = 99	**INT**	49 70.4 ± 4.7 53,1%W	Multi-domain intervention; RT, with functional tasks and balance training, multi supplement and cognitive training	No education: 6; 12.2% 1–6 Years: 22; 44.9% 7 or more: 21; 44.9%	88%	By supplements consumed or training or home-based sessions completed; supervised

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Table 1 (*continued*)

Author, year (Country) (reference)	Population cognitive status; sample size		Sample size by group Age ± SD % women	Type of intervention	Educational level; People; %. Years ± SD.	Adherence; %±SD	Adherence calculation method; supervision
		CG	50 70.2 ± 5.0 57.1%W	Placebo liquid capsules and tablet formulations	No education: 10; 20.4% 1–6 Years: 29; 59.2% 7 or more: 10; 20.4%	94%	
Montero-Odasso et al. (2023) (Montero-Odasso et al., 2023). (Canada)	MCI MoCa 13–24/30 n = 68	**INT**	37 73.1 ± 7.6 54.1%W	AE and RT with Vit D supplementation, and sham cognitive training.	14.7 ± 2.6	Exercise regimes, cognitive training 87% Nutrition N/R	N/R
		CG	34 73.8 ± 6.2 50%W	Balance and toning exercise, sham cognitive training and placebo Vit D.	17.2 ± 4.9		
Chatterjee et al. (2022) (Chatterjee et al., 2022). (India)	Cognitively healthy n = 30	**INT**	15 65.2 ± 3.7 33.3%W	Multi-domain intervention; Exercise regime, Mediterranean diet, computer cognitive therapy.	Intervention Group: Below graduation: 0; 0% Graduation: 11; 73.3% Post graduation: 4; 26.7%	N/R	N/R
		CG	15 71.1 ± 6.9 40%W	Health awareness instructions for brain stimulating activities such as sudoku, mental maths, learning music and new skills	Control Group: Below graduation: 4; 26.7% Graduation: 9; 60.0% Post graduation: 2; 13.3%		
Romera-Liebana et al. (2018) (Romera-Liebana et al., 2018). (Spain)	Non severe cognitive impairment (MEC-35 Lobo) ≥ 18 points n = 352	**INT**	176 77.2 ± 6.8 76.1% W	Multi-domain intervention; Physical activity, high-protein nutritional shake, memory workshops and medication review following STOPP criteria.	US: 78; 44.3% PS: 60; 34.1% SS: 25; 14.2% U: 13; 7.4%	Intervention 54.2% Educational sessions 52.0%.	N/R
		CG	176 77.4 ± 7.7 74.4% W	Usual care. Both groups were also given counselling regarding dietary habits, lifestyle recommendations, and domestic hazards.	US: 67; 38.1% PS: 80; 45.5% SS: 25; 14.2% U: 4; 2.3%	Educational sessions 48.0%.	
van de Rest et al. 2014 (van de Rest et al., 2014). (Netherlands) OUT OF SYSTEMATIC REVIEW BUT INCLUDED IN THE META-ANALYSES.	Cognitively healthy. Frail and pre-frail n = 62	**INT**	31 77.7 ± 8.8 64%W	RT with protein supplementation	Low: 3; 10% Middle: 17; 55% High: 11; 36%	98%	By returned ticked calendars and non-consumed beverages; supervised.
		CG	31 81.2 ± 7.4 52%W	Placebo protein	Low: 0; 0% Middle: 17; 55% High: 14; 45%		

AE: Aerobic exercise; CG: Control group; INT: Intervention group; D: Diet; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; HMB: B-hydroxy b-methylbutyrate; HS: High school; IG: Intervention group; LCPUFA: Long chain polyunsaturated fatty acids; MCEP: Multicomponent exercise program; MCI: Mild cognitive impairment; MEC-35 Lobo: Lobo Mini Cognitive Test; MMSE: Mini Mental State Examination; MoCA: Montreal Cognitive Assessment. PS: Primary School; RT: Resistance training; RW: Read and Write; SS: Secondary school; U: University; W: Women; WLMT: Word List Memory Task; WLR: Word List Recall. N/R: —

Table 2
Intervention characteristics and results.

Author, year (Country)	Exercise intervention					Nutrition intervention	Cognitive outcome	Outcome measure	Results
	Session frequency (weekly)	Intensity	Type of exercise (supervised/ not supervised)	Intervention duration	Volume				
Alves et al. (2013) (Alves et al., 2013). (Brazil)	2 d/wk	12–15RM	RT (supervised)	24 weeks	3 sets of 7 exercises/ 1´rest between sets.	First five days 20 g (4 ×5 g/d), followed by 5 g daily dose of creatine monohydrate with any meal of the day.	Global cognition, executive function, memory function	MMSE Stroop (Color, non-color and color word) TMT (A) DST (Forward and backward) DRT BBCS	↔ ↔ ↔ ↔ ↔ ↔
Andrieu et al. (2017) (Andrieu et al., 2017). (France)	5 d/wk	Individualised every six months	AE (walking) (not supervised)	36 months	At least 150 min per week.	Two capsules with 400 mg DHA, 112.5 mg EPA for 3 years and nutritional advice (15 min per session, 2 s/w first month, 1 s/w second month and 1 s per month for third month) based on French National Nutrition and Health Programme	Global cognition, executive function and memory function	Composite Z score COWAT MMSE TMT (A and B) CNT CDR-SoB FCRST	↔ ↔ ↔ ↔ ↔ ↔ ↔
Gutiérrez-Reguero et al. (2024) (Gutiérrez-Reguero et al., 2024). (Spain)	5 d/wk	AE: be able to speak, talk test. RT: 50%RM	MCEP (Vivifrail) (supervised)	12 weeks	AE: ranging from 3 min to 20 min RT: (3 ×12)/2' 50%RM BE: (3 ×10'')/2'	3 g daily dose of free acid HMB dissolved freely into 250 mL of water. Consumed after training.	Global cognition	MMSE	↑
Komulainen et al. (2021) (Komulainen et al., 2021). (Finland)	RT: First 6 months, 1 d/wk, after 2 d/wk.	RT: First 6 months, 40% RM, after 60%RM	RT (supervised)	48 months	RT: First 6 months, 1 set and 10 reps for 10 exercises, after 2 sets, 15 reps.	11 individualized face-to-face counselling sessions, based in their usual diet and current health status and Finnish Nutrition	Global cognition	CERAD – TS	RT + D: ↔ AE + D: ↔
	AE: First 6 months, 2–4 times/wk, after 5 times/wk	AE: First 6 months 40–50% VO2max, after 60% VO2max	AE (not supervised)	48 months	AE: First 6 months, 30–60 min, after at least 60 min				
MacPherson, H et al. 2022 (MacPherson et al., 2022). (Australia)	2 d/wk	RT: 5–8 RPE AE: 5–8 RPE	RT and AE (Supervised)	6 months	RT: 2 sets (8–12 repetition) for 8 exercises AE: 10 min	5 g of nonmicroencapsulated omega-3 (900 mg EPA and 600 mg DHA per day), 1000 IU VitD3, and 25 g of whey protein concentrate 80% (20 g protein, 590 kJ) Consume 1–2 h before training session, and before the breakfast on rest day.	Global cognition, executive function	CogState battery 6 tests composite z score TMT (A, B, B-A) MoCA	↔ ↔ ↔
Moon et al. (2021) (Moon et al., 2021). (Korea)	3 d/wk	40–60% Percentage of maximum HR	AE, RT, balance, flexibility and finger-and-toe movements. (Partially supervised)	24 weeks	RT: 1–4 sets, 10–15 muscle groups. AE: 20–25' BE: 5' F: 5' FTM: 5'	Three individual counselling sessions (30 min) and seven group sessions (50 min), based in the MIND diet.	Global cognition	RBANS includes 12 subtests and evaluates five different cognitive domains Immediate memory Visuoconstruction Language Attention Delayed memory	↑ ↔ ↑ ↔ ↔ ↑
Ngandu et al. (2015) (Ngandu et al., 2015). (Finland)	RE: First 6 months, 1–2 d/wk, after, 2–3 d/wk AE: First 6 months, 2–4 d/	RE: First 6 months, 40–70% RM, after 70–80% RM.	RT, AE and balance exercises (Supervised)	24 months	RE: First 6 months, 8–10 sets, after 8–20 AE: First 6 months, 30–60 min, after 45–60 min	Nutritional counselling: 7 group and 3 individual sessions based in their usual diet and Finnish Nutrition	Global cognition	NTB total battery 14 tests Executive functioning (CFT, CST (C), TMT (B-A), Stroop (color word)) Memory (Immediate, delayed recall, word list	↑ ↑ ↔

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Table 2 (*continued*)

Author, year (Country)	Exercise intervention					Nutrition intervention	Cognitive outcome	Outcome measure	Results
	Session frequency (weekly)	Intensity	Type of exercise (supervised/ not supervised)	Intervention duration	Volume				
	wk, after, 3–5 d/wk							learning and delayed recall) Processing speed (CST (A), letter digit substitution test, Stroop (non-color))	 ↑
Phoemsapthawee et al. (2022) (Phoemsapthawee et al., 2022). (Thailand)	3 d/wk	AE: 65–75% Maximum HR	RT, AE, postural balance retraining and dual-task training (Supervised)	12 weeks	RT: 30 min AE: 40 min	500 mg twice a day of Gotu kola (Centella asiatica) extract	Global cognition, executive function and memory function	MMSE TMT (A and B) DSB DSF	↑ ↑ ↑ ↑
Sakurai et al. (2024) (Sakurai et al., 2024). (Japan)	1 d/wk	AE: 40–80% maximum HR.	AE, RT, stretching and dual task training and group meetings. (Supervised)	18 months	Two types of sessions FIRST: RT: 15–20’, AE: 20–30’, dual task 20–30’ and stretching: 10’. s: Stretching: 10’, AE: 20–30’, 20–30’ dual task, 15–20’ minutes of group meeting	Three face-to-face and 12 telephone counselling based on the Dietary Reference Intakes for Japanese	Global cognition, executive function, memory function and attention	Composite Z score MMSE WMS-R Logical memory I WMS-R Logical memory II FCSRT TMT (A and B) DSST Digit Span (Forward and Backward) Letter word fluency test	↔ ↔ ↔ ↔ ↔ ↔ ↔ ↔ ↔
Tokuda et al. (2020) (Tokuda et al., 2020). (Japan)	RT: 2 d/wk AE: 5 d/wk	RT: 10 RM AE: 12–13 RPE	RT and AE (supervised)	24 weeks	RT: 6 exercises, 5 sets for squat and 3 sets for the rest. AE: 30 min walking	1080 mg/day of LCPUFA with 300 mg of DHA, 100 mg of EPA, and 120 mg of ARA	Executive function, memory function	Stroop (Color, non-color and color word) TMT (A and B) Digit Span KWCST CA Verbal fluency WMS-R Logical memory I WMS-R Logical memory II ROCFT recall	↔ in non-color and color word ↑ in color ↔ ↑ ↔ ↔ ↔ ↔ ↔
Ng et al. (2018) (Ng et al., 2018). (Singapore)	N/R	60–80% RM	RT with functional tasks (12 weeks supervised and not supervised)	6 months	8–10 exercises	Fortisip Multi Fibre (200 mL). One capsule of Sangobion; one tablet of Neuroforte; one tablet of Caltrate (Vit D 200 IU; 600 mg of calcium).	Global cognition	RBANS total includes 12 subtests and evaluates five different cognitive domains Attention Language Visuospatial/ constructional Immediate memory Delayed memory	↔ ↔ ↔ ↑ ↔ ↔
Montero-Odasso et al. (2023) (Montero-Odasso	3 d/wk, 60 min	AE: Progression since RPE 5–6 until 7–8.	RT and AE (Supervised)	20 weeks	RT: progression until (2–3 sets x 6–8 reps)/60’’.	The dose of 10,000 IU of vitamin D three times per week.	Global cognition	ADAS – Cog 13 ADAS – Cog Plus	↔ ↔

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Table 2 (*continued*)

Author, year (Country)	Exercise intervention					Nutrition intervention	Cognitive outcome	Outcome measure	Results
	Session frequency (weekly)	Intensity	Type of exercise (supervised/ not supervised)	Intervention duration	Volume				
et al., 2023). (Canada)					AE: progression until (2 ×10')/1'				
Chatterjee et al. (2022) (Chatterjee et al., 2022). (India)	2 d/wk	RT: progression to 40% RM until 80% RM. AE: progression to 40% HR until 80% HR.	AE (Walking) and RT (supervised)	6 months	RT: 2 sets x (8–15 reps)/ 5' for each exercise AE: 20 min	FINGER diet. Supervised twice a week by dietician.	Memory function	PGI-MS total Mental balance Attention and Concentration Immediate Recall Visual retention Stroop.	↑ ↑ ↑ ↔ ↑ ↔
Romera-Liebana et al. (2018) (Romera-Liebana et al., 2018). (Spain)	2 d/w non-consecutive	N/R	AE (supervised)	3 months	60'	1 hyperproteic nutritional shake daily, 11.8 g protein, 17 g carbohydrate, 4.4 g fat, 156 kcal per bottle daily.	Memory function	Short-Term Medium-Term Verbal Memory Animal Naming Test, Evocation of words Designation of famous people's names Verbal designation of images Verbal Memory Verbal abstraction of word pairs	↑ ↑ ↑ ↑ ↑ ↑ ↑
van de Rest et al. 2014 (van de Rest et al., (2014). (Netherlands) OUT OF SYSTEMIC REVIEW	2 d/wk	50–75% RM	RT (supervised)	24 weeks	20 sets for all body per session	Twice daily, 250-mL protein supplemented beverage containing 15 g protein, 7.1 g lactose, 0.5 g fat.	Executive function	Composite score for executive function TMT	

↑: intervention improved performance; ↔: No effect; ADAS-Cog-13: Alzheimer Disease Assessment Scale Cognitive 13; AE: Aerobic exercises; ARA: arachidonic acid; CDR: Clinical Dementia Rating Scale; CNT: Category Naming Test; COWAT: Controlled Oral Word Association Test; D: Diet; DHA: docosahexaenoic acid; DRT: Delay Recall Test; DSST: Digit Symbol Substitution Test; DST: Digit Span Test; EPA: eicosapentenoic acid; FCRST: Free and Cued Selective Reminding test; g: grams; HMB: β-hidroxi-β-metilbutirato; HR: Heart Rate; kj: kilojoules; LCPUFA: Long chain polyunsaturated fatty acids; MCEP: Multicomponent training; MMSE: Mini-Mental State Examination; MoCa: Montreal Cognitive Assessment; NTB: Neuropsychological Test Battery; PGI-MS: Post Graduate Institute Memory Scale; RM: Maxima repetition; RPE: Rating of perceived exertion; RT: Resistance training; TMT: Trail Making Test; UI: international units; vitD: serum 25-hydroxyvitamin D; Vo_2max: maximal oxygen consumption; WAIS-III: Digit Span of the Wechsler Adult Intelligence Scale; wk: week.

2.5. Statistical analyses

The Standardized Mean Difference (SMD) was calculated as the individual effect size for each relevant variable. In cases where the necessary raw data were not available in the original reports, we contacted the corresponding authors to request the missing information. Subsequently, results were pooled using the DerSimonian–Laird method in a random-effects meta-analysis (easymeta). In the meta-analysis, a positive SMD in global cognitive function favoured the intervention group. Similarly, for the executive function and visual-perceptual ability variables measured over time, where lower values indicate better performance, the direction of the data was reversed. This transformation was performed to ensure that a positive SMD always represents an improvement, thus enabling a consistent interpretation of all forest plots.

A sensitivity analysis was performed to exclude trials that included additional interventions beyond exercise and diet.

Heterogeneity was assessed using the I^2 statistic (Higgins et al., 2003), which describes the variance between studies as a proportion of the total variance. I^2 values of 25–50% indicate low heterogeneity, 50–75% moderate heterogeneity and > 75% high heterogeneity.

The possible presence of publication bias was examined using funnel plot asymmetry and Egger and Begg correlation tests. Additionally, Duval and Tweedie's Trim and Fill method (Duval and Tweedie, 2000) was applied using JASP software (Version 0.95.4) to confirm the robustness of the results against possible unpublished studies.

Regarding the inclusion of the study by van de Rest et al., (2014) in the meta-analyses, it is important to clarify our approach. This study was a multi-arm randomized controlled trial. While the primary comparisons reported by the authors did not directly align with our specific contrast of interest, the trial included the exact intervention and control arms required for our meta-analysis. Because the authors provided complete raw descriptive data (means, standard deviations, and sample sizes) for these specific arms, we independently calculated the effect sizes for this comparison. To address any potential bias associated with this procedure, a sensitivity analysis will be conducted to assess the robustness of the findings and ensure that the inclusion of this study does not disproportionately influence the overall results.

3. Results

3.1. Main search

The initial search yielded 1361 records. After removing 190 duplicates and 1171 records through title and abstract screening, 48 full-text articles were assessed for eligibility by two independent reviewers (SCB and GLB). Finally, 14 articles were included in the review. Fig. 1 shows the PRISMA flowchart and the reasons for excluding articles from the final sample of selected studies.

3.2. Quality assessment and risk of bias

The individual PEDro quality scores ranged from 7 to 11, with eight studies classified as excellent and six as good (Supplementary Material: Table S3). Only three trials adequately blinded subjects, therapists and assessors (Alves et al., 2013; Andrieu et al., 2017; MacPherson et al., 2022) and four studies did not include dropouts in the analysis (Alves et al., 2013; Gutiérrez-Reguero et al., 2024; Phoemsapthawee et al.,

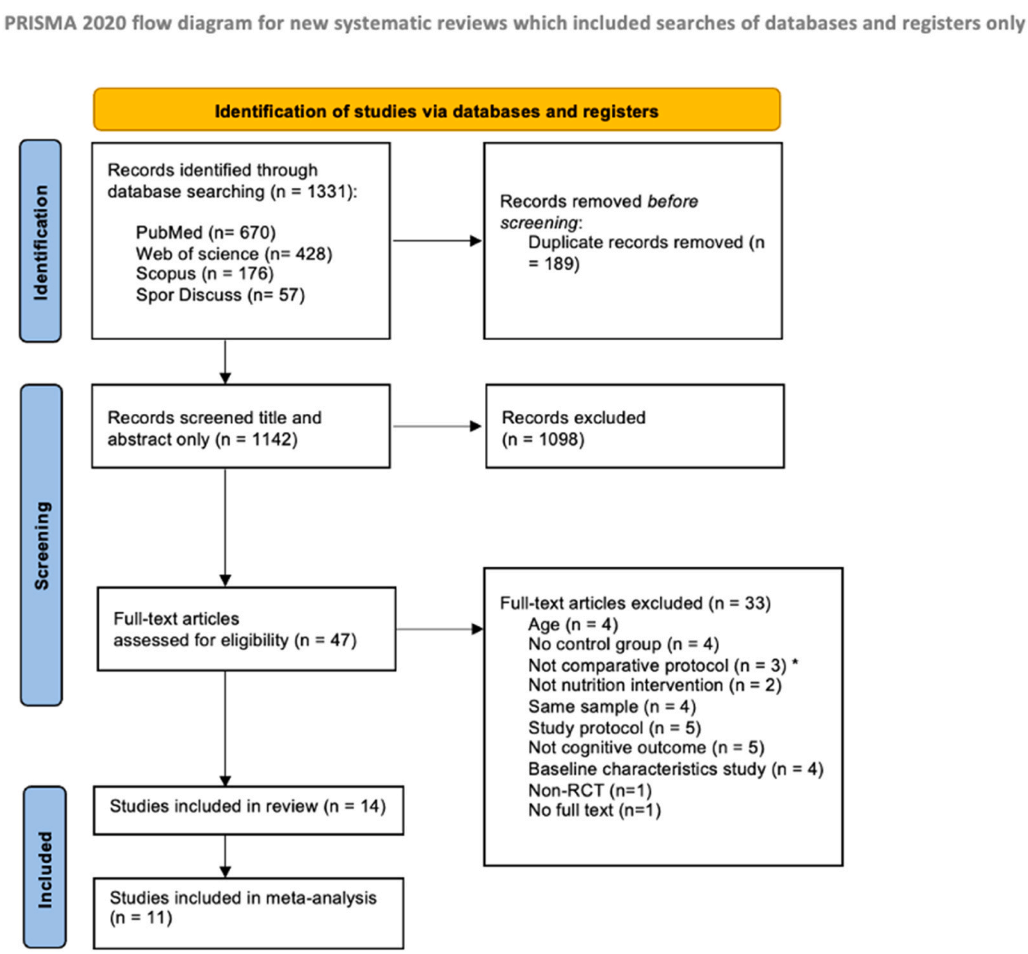

Fig. 1. PRISMA flow-chart diagram.

2022; Tokuda et al., 2020).

According to the results of the RoB 2 tool, eight studies had a low risk of bias across all domains (Alves et al., 2013; Andrieu et al., 2017; Komulainen et al., 2021; MacPherson et al., 2022; Montero-Odasso et al., 2023; Ngandu et al., 2015; Romera-Liebana et al., 2018; Sakurai et al., 2024). Three studies raised some concerns for domain 2 (Bias due to deviations from intended intervention) (Chatterjee et al., 2022; Gutiérrez-Reguero et al., 2024; Moon et al., 2021), while two studies raised some concerns for domains 1 (Bias arising from the randomization process) (Ng et al., 2018; Phoemsapthawee et al., 2022), 4 (Bias in measurement of the outcome) (Chatterjee et al., 2022; Phoemsapthawee et al., 2022) and 5 (Bias in selection of the reported result) (Chatterjee et al., 2022; Moon et al., 2021). One study showed high risk of bias for domain 2 (Tokuda et al., 2020), and all of them had low risk of bias for domain 3 (Bias due to missing outcome data) (Supplementary Material: Figure S4). Thus, the overall biases were low in eight studies, with some concerns in five studies, and a high risk in one.

Due to the nature of the intervention, blinding of participants is a major difficulty, and therefore the positive point on the PEDro and RoB 2 scales was awarded if at least one of the two main interventions in this review (exercise or diet) was blinded, in the case of exercise performing a sham intervention as in Montero-Odasso et al. (Montero-Odasso et al., 2023) and Macpherson et al. (MacPherson et al., 2022), where they performed stretching and flexibility exercises, or blinding in the case of dietary supplementation, as is the case in several articles (Alves et al., 2013; Andrieu et al., 2017; Ng et al., 2018; Phoemsapthawee et al., 2022; Tokuda et al., 2020).

3.3. Description of participants and studies

Two studies were performed in each of the following countries: Spain, Finland and Japan. Brazil, Francia, Portugal, Australia, Korea, Thailand, Singapore, Canada, China and India contributed one study each. The origin of each individual study is presented in the first column of Table 1.

The mean age of the study population was 71.4 ± 6.4 years. Educational level was reported in eight studies as the number of years of education, with a mean 10.9 ± 3.7 years (Alves et al., 2013; Komulainen et al., 2021; Montero-Odasso et al., 2023; Moon et al., 2021; Ngandu et al., 2015; Sakurai et al., 2024; Tokuda et al., 2020), whereas other studies utilized categories of varying orders (Table 1), and one study did not report this data (Gutiérrez-Reguero et al., 2024). Regarding sex distribution, the studies included more women than men (56.4% women), with one trial enrolling only women (Alves et al., 2013). The included participants were cognitively healthy (Alves et al., 2013; Chatterjee et al., 2022; Gutiérrez-Reguero et al., 2024; Komulainen et al., 2021; Ng et al., 2018), had subjective memory complaints and/or were considered at high risk for dementia (Andrieu et al., 2017; MacPherson et al., 2022; Moon et al., 2021; Ngandu et al., 2015), had non-severe impairment (Romera-Liebana et al., 2018), or were diagnosed with MCI (Montero-Odasso et al., 2023; Phoemsapthawee et al., 2022; Sakurai et al., 2024; Tokuda et al., 2020) at baseline.

The study sample size in each study ranged from 24 to 1190 participants. The 14 trials included a total of 4013 randomized participants: 2114 participants in the intervention groups and 1899 in the control groups. The exercise and diet alone intervention included a total of 646 participants (Alves et al., 2013; Gutiérrez-Reguero et al., 2024; Komulainen et al., 2021; MacPherson et al., 2022; Montero-Odasso et al., 2023; Phoemsapthawee et al., 2022; Tokuda et al., 2020), while the exercise and diet combined with other non-pharmacological intervention groups included 1468 participants (Andrieu et al., 2017; Chatterjee et al., 2022; Moon et al., 2021; Ngandu et al., 2015; Sakurai et al., 2024).

3.4. Exercise and diet intervention characteristics

The duration of the intervention in the included trials varied considerably, ranging from 12 weeks (Gutiérrez-Reguero et al., 2024; Romera-Liebana et al., 2018), to 36 months (Andrieu et al., 2017) and even 48 months (Komulainen et al., 2021).

The exercise intervention can be divided into three main groups: strength or aerobic training only, a combination of both, or multicomponent programs (strength, aerobic, balance, flexibility or dual tasks exercises). The specific characteristics of each intervention (frequency, intensity, type of exercise, duration and volume) are shown in Table 2. Furthermore, it was noted whether the training was supervised by an exercise specialist or performed at home/independently.

On the other hand, the nutritional interventions included in this review can be classified into two categories: those that utilize different supplements and those that provide dietary recommendations or guidelines. The supplement-based interventions utilized various types of supplements: creatine monohydrate (Alves et al., 2013), docosahexaenoic acid (DHA) and eicosapentenoic acid (EPA) (Andrieu et al., 2017; MacPherson et al., 2022; Tokuda et al., 2020), β-hidroxi-β-metilbutirato (HMB) (Gutiérrez-Reguero et al., 2024), vitamin D (MacPherson et al., 2022; Montero-Odasso et al., 2023; Romera-Liebana et al., 2018), protein (MacPherson et al., 2022; Ng et al., 2018), gotu kola (Phoemsapthawee et al., 2022), and multivitamins (Ng et al., 2018). The dosage and frequency of each supplement are described in Table 2. The nutritional advice and dietary guidelines were based on the Finnish Nutrition Recommendations (Ngandu et al., 2015), Mind Diet (Moon et al., 2021), Japanese recommendations (Sakurai et al., 2024) and FINGER diet (Chatterjee et al., 2022). Typical recommendations include a high intake of fruit, vegetables, berries, legumes, whole grains and fish (two to three times per week), adequate hydration and limited intake of high-fat products, red meat, soft drinks and juices. These interventions were delivered through group meetings or individual interviews, with some adaptations made to participants' usual diets.

3.5. Multi-domain intervention characteristics

The multi-domain intervention trials included several lifestyle modification components that were added to the exercise and diet intervention. In particular, several articles included cognitive training, which was delivered in small group sessions and focused on different areas of memory using different tasks and strategies for remembering verbal and visual information. Some examples of these tasks included 'spot the differences', categorizing and encoding (to improve attention and processing speed), and matrix reasoning exercises, mazes, and tangram games (to improve reasoning and problem-solving skills) (Andrieu et al., 2017; Ng et al., 2018). Dual tasks have also been used to discriminate sets of items (Montero-Odasso et al., 2023). In a different way from the rest, Chatterjee et al. (Chatterjee et al., 2022) used the Rehacom software, a tool that provided a variety of tasks to work on attention, memory, visuospatial abilities and executive functions. Ngandu et al. (Ngandu et al., 2015) used both small group and computer-based sessions. In addition to cognitive training, two studies included vascular risk factor management (Ngandu et al., 2015; Sakurai et al., 2024). On the other hand, Romera-Liebana et al. (Romera-Liebana et al., 2018) included memory workshops and medication review according to stopping criteria in their intervention.

3.6. Adherence

Adherence data were reported in 12 of the 14 trials (Table 1) (Alves et al., 2013; Andrieu et al., 2017; Gutiérrez-Reguero et al., 2024; Komulainen et al., 2021; MacPherson et al., 2022; Montero-Odasso et al., 2023; Moon et al., 2021; Ng et al., 2018; Ngandu et al., 2015; Phoemsapthawee et al., 2022; Romera-Liebana et al., 2018; Sakurai et al., 2024). The methods used to collect and report adherence data varied considerably between studies, depending on factors such as setting, monitoring and individual criteria for adequate adherence.

3.7. Main outcomes

To assess the effect of interventions on global cognitive function, 11 out of the 14 trials investigated this outcome (Alves et al., 2013; Andrieu et al., 2017; Gutiérrez-Reguero et al., 2024; Komulainen et al., 2021; MacPherson et al., 2022; Montero-Odasso et al., 2023; Moon et al., 2021; Ng et al., 2018; Ngandu et al., 2015; Phoemsapthawee et al., 2022; Sakurai et al., 2024).The primary outcome measures used to assess global cognitive function were highly variable. For instance, one study employed the Consortium to Establish a Registry for Alzheimer's Disease total score (CERAD-TS) (Komulainen et al., 2021); two studies calculated a Composite Z-score from various cognitive tests (Andrieu et al., 2017; Phoemsapthawee et al., 2022); others used Composite Z-scores based on the Neuropsychological Test Battery (NTB) (Ngandu et al., 2015); one study included the Clinical Dementia Rating sum of boxes (CDR-SoB) (Andrieu et al., 2017); one study used MoCa (MacPherson et al., 2022); four studies used the MMSE (Alves et al., 2013; Gutiérrez-Reguero et al., 2024; Phoemsapthawee et al., 2022; Sakurai et al., 2024); two studies used the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Moon et al., 2021; Ng et al., 2018); one study calculated composite Z-scores based on the CogState Brief Battery (MacPherson et al., 2022); one study used Alzheimer disease assessment scale-cognitive (ADAS-COG) (Montero-Odasso et al., 2023); and one study used The Post Graduate Institute Memory Scale (PGI-MS) (Chatterjee et al., 2022).

3.8. Secondary outcomes

3.8.1. Concerning cognitive subdomains

3.8.1.1. Executive and visual-perceptual ability cognitive function. Several trials included the Trail Making Test (TMT) in their assessment of executive function and motor speed. It has two conditions (e.g., "A" and "B"), where condition "A" reflects both motor and visual control and condition "B" reflects the additional executive control needed to switch between number and letter sequences. All studies using the TMT evaluated both conditions (A and B) (Andrieu et al., 2017; MacPherson et al., 2022; Ngandu et al., 2015; Phoemsapthawee et al., 2022; Sakurai et al., 2024; Tokuda et al., 2020), with the exception of Alves et al. (Alves et al., 2013) who only evaluated the condition "A". In addition, three trials included the Stroop Test with its three conditions (Alves et al., 2013; Ngandu et al., 2015; Tokuda et al., 2020).

3.9. Meta-analyses results

3.9.1. Global cognitive function

The intervention generally improved global cognitive function (SMD: 0.15; 95% CI: 0.07 to 0.24; Fig. 2). The heterogeneity between studies was moderate (I^2 50%; p = 0.023; Fig. 2). The funnel plot was used to assess publication bias in the meta-analysis studies. The symmetric distribution of the points suggests the absence of visual bias, although a slight asymmetry in studies with small samples could be due to methodological variation or selection bias. This was statistically confirmed by Begg's test (p = 0.731) and Egger's test (p = 0.533) (Supplementary Material: Figure S5). Furthermore, a sensitivity analysis using Duval and Tweedie's Trim and Fill method imputed zero missing studies, which reinforced the robustness of the original findings (Adjusted SMD = 0.130; p = 0.006) (Supplementary Material: Figure S5).

The sensitivity analysis excluding trials that included more types of interventions other than exercise and diet/ supplementation, also revealed significant improvements (SMD: 0.12; 95% CI: 0.02 to 0.22; Fig. 2), with low heterogeneity (I^2 0%; p = 0.001; Fig. 2). As for the multi-domain interventions, a significant improvement was also observed (SMD: 0.18; 95% CI: 0.05 to 0.32; Fig. 2), with high heterogeneity (I^2 78%; p = 0.666; Fig. 2).

3.9.2. Executive cognitive function

Eight studies assessed executive cognitive function: five used the TMT, condition B (Andrieu et al., 2017; MacPherson et al., 2022; Phoemsapthawee et al., 2022; Sakurai et al., 2024; Tokuda et al., 2020); two calculated a combined Z-score from several tests (Ngandu et al., (2015); van de Rest et al., (2014) and one used the Stroop test in the colour-word condition (Chatterjee et al., 2022). As shown in Fig. 3, no significant improvements in executive cognitive function were observed (SMD = 0.05; 95% CI: −0.06 to 0.17). The heterogeneity between studies was moderate (I^2 = 46%; p = 0.073). The sensitivity analysis carried out only with the multi-domain interventions also revealed no

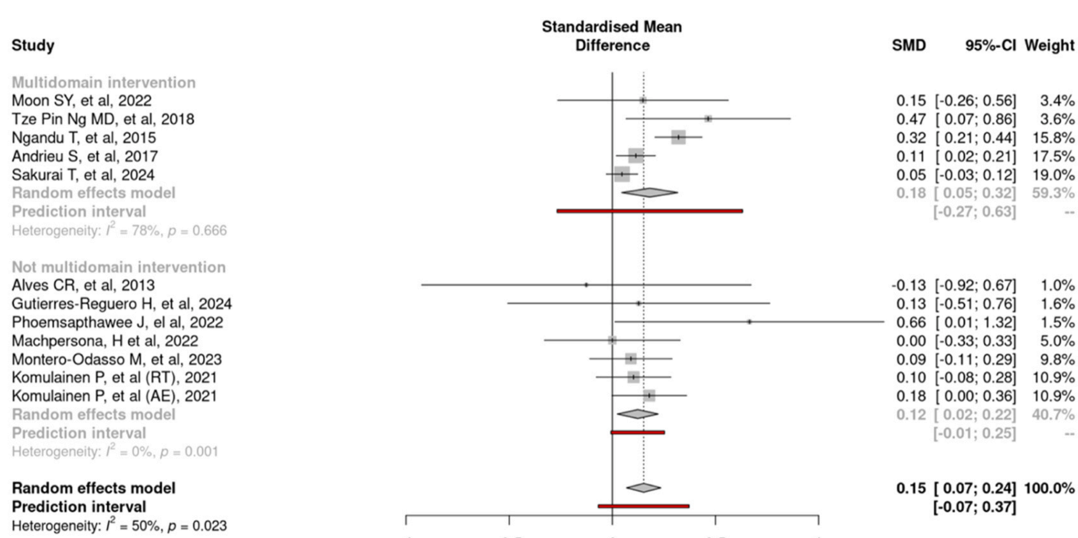

Fig. 2. Forest plot (random-effects model) showing the effect of exercise and nutrition interventions, differentiating between those that have and have not taken a multi-domain intervention, on global cognitive function. SMD: standardized mean difference; CI: confidence interval; Red line: Prediction interval. Studies on the right favour the intervention group.

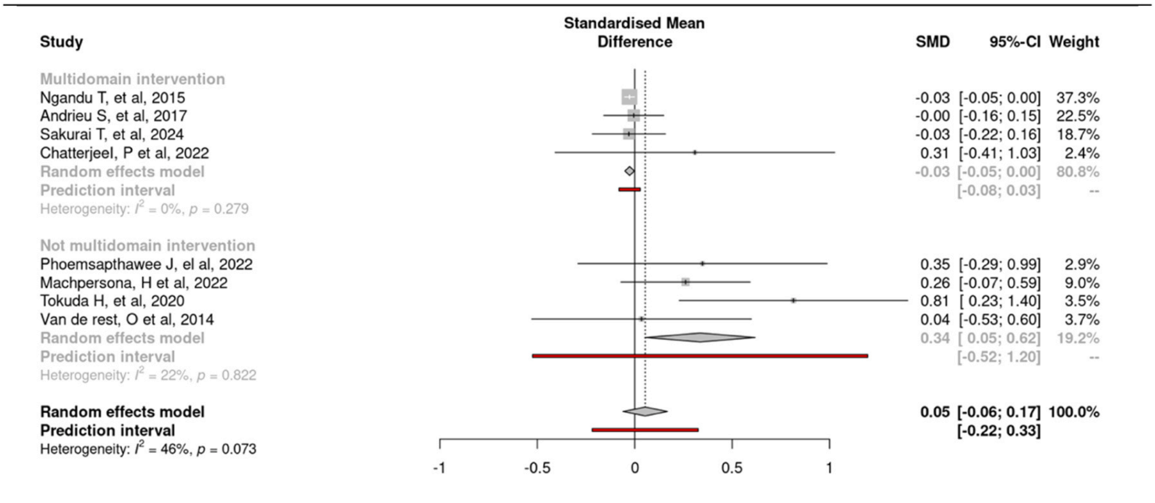

Fig. 3. Forest plot (random effects model) showing the effect of exercise and nutrition interventions on executive cognitive function. SMD: standardized mean difference; CI: confidence interval; Red line: Prediction interval. Studies on the right favour the intervention group.

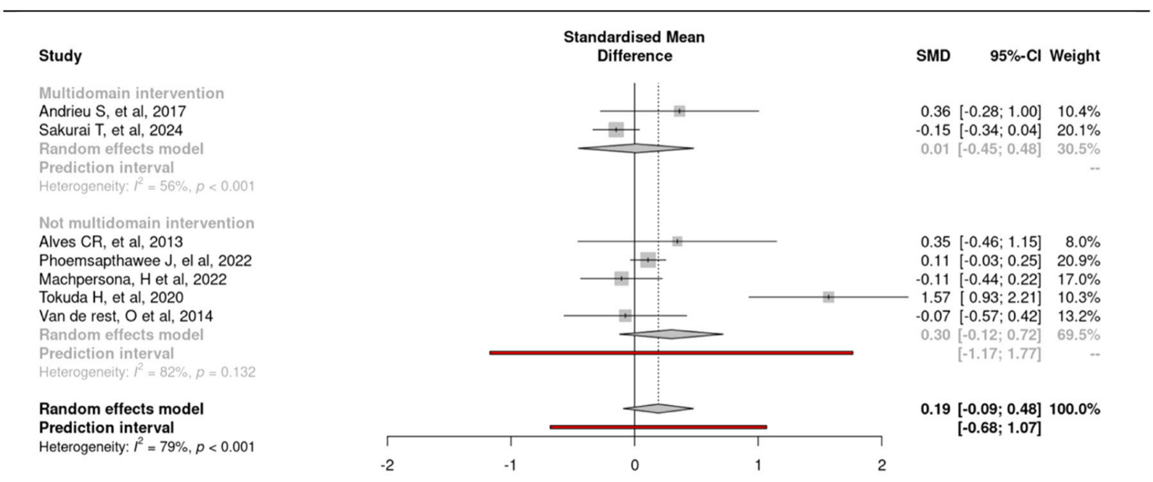

Fig. 4. Forest plot (random effects model) showing the effect of exercise and nutrition interventions on visual-perceptual ability cognitive function. SMD: standardized mean difference; CI: confidence interval; Red line: Prediction interval. Studies on the right favour the intervention group.

significant differences (SMD = 0.03; 95% CI: −0.05 to 0.00), on the other hand, trials that only including exercise and diet/supplementation showed significant improvements (SMD = 0.34; 95% CI: 0.05 to 0.62; Fig. 3), however another sensitivity analysis was developed taking out the Tokuda et al., 2020 (Tokuda et al., 2020) study as a possible outlier (see Fig. 3) and show an overall with high risk of bias in the RoB2 tool (Supplementary Material: Figure S4), obtaining no significant differences in both, overall effect size (SMD = −0.02; 95% CI: −0.05 to 0.00) and taking into account only trials including exercise and diet/supplementation (SMD = 0.23; 95% CI: −0.03 to 0.49) (Supplementary Material: Figure S6), similarly, without the article by van de Rest et al., (2014), we performed sensitivity analyses due to its potential source of bias, but no significant differences were found (SMD = 0.06; 95% CI: −0.06 to 0.19) (Supplementary Material: Figure S7).

3.9.3. *Visual-perceptual ability cognitive function*

Eight studies assessed this variable and all of them used the TMT (condition A). As shown in Fig. 4, no significant improvements in visual-perceptual ability cognitive function were observed (SMD = 0.19; 95% CI: −0.09 to 0.48). The heterogeneity between studies was high (I^2 = 79%; $p < 0.001$). A sensitivity analysis was developed taking out the Tokuda et al., 2020 (Tokuda et al., 2020) study as a possible outlier (see Fig. 4) and show an overall with high risk of bias in the RoB2 tool (Supplementary Material: Figure S4), obtaining no significant differences in both, overall effect size (SMD = 0.00; 95% CI: −0.14 to 0.15) and taking into account only trials including exercise and diet/supplementation (SMD = 0.07; 95% CI: −0.05 to 0.20) (Supplementary Material: Figure S8), similarly, without the article by van de Rest et al., (2014), we performed sensitivity analyses due to its potential source of bias, but no significant differences were found (SMD = 0.24; 95% CI: −0.08 to 0.56) (Supplementary Material: Figure S9).

4. Discussion

The primary finding of this systematic review and meta-analysis indicates that combined interventions comprising physical exercise and nutritional strategies (dietary advice or supplementation) significantly improve global cognitive function in older adults. Conversely, these interventions failed to yield significant benefits for domain-specific outcomes, namely executive function or visual-perceptual ability.

Notably, this positive effect on global cognition was observed despite substantial heterogeneity in the intervention protocols. Exercise regimens varied widely in frequency (1–5 days/week), duration (10–60 min), and modality (ranging from aerobic-only to MCEP). Similarly, the nutritional components were diverse, spanning from broad dietary counselling to specific supplementation. Notwithstanding this methodological variability, our analysis provides consistent evidence for the efficacy of these combined strategies on global cognitive health, aligning with previous meta-analyses (Reparaz-Escudero et al., 2024). Mechanistically, this may be attributed to the synergistic effects of aerobic exercise—known to enhance neuroplasticity and cerebral blood flow (Voss et al., 2011), and dietary factors rich in antioxidants and omega-3 fatty acids, which mitigate inflammation and support neuronal function (Gómez-Pinilla, 2008). This is further supported by landmark multi-domain studies like the FINGER trial, which demonstrated that simultaneously targeting diet, exercise, and cognitive training can effectively delay cognitive decline (Ngandu et al., 2015).

While the magnitude of the observed effect size is statistically modest, it must be interpreted within the trajectory of biological ageing, where cognitive function naturally declines over time (López-Otín et al., 2013). In this context, even a small positive effect, signalling maintenance or attenuation of decline, represents a clinically meaningful outcome relative to the expected deterioration in control groups. Given that some interventions spanned up to four years (Komulainen et al., 2021), the cumulative impact of stabilizing cognitive trajectories could have profound implications for preserving functional autonomy and potentially delaying dementia onset at the population level. To elucidate the biological underpinnings of these effects, it is essential to examine the underlying neurobiology.

Mechanistically, physical exercise acts as a potent modulator of brain health by promoting neurogenesis, synaptic plasticity, and the expression of neurotrophic factors, most notably brain-derived neurotrophic factor (BDNF) (Gomez-Pinilla and Hillman, 2013; Key and Szabo-Reed, 2023). BDNF is critical for neuronal survival and plasticity, with elevated levels consistently linked to improved memory and cognitive performance (Vaynman et al., 2004). While moderate-intensity aerobic exercise reliably upregulates BDNF (Farrukh et al., 2023), and even acute bouts can rapidly elevate circulating BDNF (Hung et al., 2018; Nicastri et al., 2022), acute elevations may not be sustained long-term without complementary stimuli (Kim et al., 2024; Kurdi and Flora, 2019). Here, the synergistic potential of combined interventions becomes evident: nutritional strategies, particularly those rich in omega-3 fatty acids and antioxidants (e.g., the Mediterranean diet), can potentiate BDNF expression and extend its neuroprotective window (Dinoff et al., 2016; Janssen and Kiliaan, 2014; Liu et al., 2023; Sohouli et al., 2023; Ziaei et al., 2024). Furthermore, individual genetic variability, such as the BDNF Val66Met polymorphism, may modulate responsiveness to these lifestyle interventions (Brown et al., 2019; Chang et al., 2024), highlighting the future importance of personalized precision medicine.

Beyond BDNF, the 'muscle-brain axis' offers further explanatory power. Muscle-derived signalling proteins, or myokines, such as Cathepsin B (CatB), are released during exercise, cross the blood-brain barrier, and stimulate hippocampal BDNF expression, thereby supporting memory and neurogenesis (Rai and Demontis, 2022). Research has also implicated CatB in biochemical pathways facilitating beta-amyloid degradation (Gökçe and Gün, 2023; Kim and Kang, 2020; Mueller-Steiner et al., 2006), linking muscle function directly to Alzheimer's pathology prevention. Crucially, since skeletal muscle is the primary source of CatB, the preservation of muscle mass is fundamental. This underscores the biological rationale for combining resistance training with adequate dietary protein intake (Moradell et al., 2025), by maintaining muscle integrity, these interventions ensure the sustained release of neuroprotective myokines, reinforcing the coordinated action of diet and exercise on cognitive resilience (Gokce et al., 2021; Gökçe and Gün, 2023).

The interplay between physical activity and nutrition also exerts a profound influence on inflammatory regulation, mediated centrally by the interleukin-6 (IL-6) pathway. This cytokine exhibits a pleiotropic nature: while chronically elevated systemic levels drive low-grade inflammation, acute pulses released from contracting skeletal muscle act as 'myokines,' stimulating the production of anti-inflammatory mediators such as IL-10 and IL-1 receptor antagonist (Friedenreich et al., 2016). Crucially, exercise-induced IL-6 can cross the blood-brain barrier (Banks et al., 1994), where it promotes neurogenesis (Valliéres et al., 2002), and supports neuronal survival (Pervaiz, Hoffman-Goetz n.d.), a response dependent on exercise intensity and duration (Brown et al., 2023). Complementing this, nutritional strategies—specifically caloric restriction or omega-3 supplementation—can lower baseline pro-inflammatory IL-6 levels, thereby amplifying the anti-inflammatory milieu created by physical activity (Imayama et al., 2012; Pence et al., 2015; Van Gemert et al., 2016; Wu et al., 2013). These integrated effects are particularly vital for older populations, who are disproportionately at risk for chronic systemic inflammation and neurodegeneration.

Beyond inflammation, the combination of exercise and a nutrient-dense diet directly modulates key biomarkers of cognitive decline (Szabo-Reed and Key, 2025). Emerging evidence indicates that dietary diversity correlates with preserved hippocampal integrity, underscoring the link between nutritional status and structural brain health (Drouka et al., 2022; Otsuka et al., 2021). Furthermore, specific bioactive compounds, such as flavonoids, have been shown to facilitate angiogenesis and enhance memory function (Gomez-Pinilla and Gomez, 2011; Van Praag et al., 2007). These molecular mechanisms reinforce the necessity of a holistic approach, where physical exertion and nutritional intake work in concert to maintain cognitive resilience.

Collectively, these findings highlight the multifaceted impact of combined lifestyle interventions as a synergistic, non-invasive strategy for brain health. By simultaneously targeting the signalling cascades of BDNF, CatB, and IL-6, these interventions may enhance neuroplastic adaptations, optimize cognitive performance, and effectively mitigate the trajectory of cognitive decline throughout the lifespan (Gomez-Pinilla and Gomez, 2011; Schättin et al., 2016).

On the other hand, the lack of significant effects on executive function and visual-perceptual function compared to the impact on global cognitive function could be explained by several factors. First, the measure of global cognitive function reflects an average of performance across multiple domains, so it is possible that small, distributed improvements in several domains contribute to a significant increase in the global score, without necessarily implying a substantial improvement in specific domains, such as executive or visual-perceptual. It is therefore possible that these domains are less sensitive to change after interventions of this type, as has been observed in previous studies where no significant improvements in either memory or executive function were found after six months of exercise intervention (Lenze et al., 2022). One possible explanation is that the brain areas responsible for these functions show less neuroplasticity (Burke and Barnes, 2006), which would limit their ability to respond to intervention stimuli.

Due to the wide variety of methods employed, the current evidence is inconclusive regarding which supplements are most effective for specific outcomes, at what doses and in combination with which types of exercise. Additionally, the timing of supplementation and its interaction with exercise regimens is unclear, and these factors may be critical in maximising benefits. For example, creatine supplementation has been shown to enhance cognitive function in older adults (Xu et al., 2024), and its effectiveness may depend on the timing of its intake in relation to muscle mass gain (Candow et al., 2015). Given the emerging evidence on creatine's cognitive effects, it is increasingly being considered a key supplement for neuroprotective strategies in ageing populations. Its dual role, supporting both cognitive and muscular improvements suggests that future studies should explore its synergistic potential when combined with exercise interventions. These findings highlight the importance of considering not only the type of supplement, but also when it is taken, to optimise outcomes. Our review emphasises the need for further research to clarify how individual factors, such as health status, comorbidities and baseline nutritional levels, affect the effectiveness of these interventions. Ultimately, developing personalised strategies that optimise the combination of supplements and exercise based on individual characteristics, including the precise timing of supplementation, is essential to improving the quality of life of this population.

An important aspect is the rate of adherence to the different interventions, which should be more accurate and consistent. In this review, not all articles reported this, and among those that did, the form of data collection varied. As pointed out by Reparaz-Escudero et al. (Reparaz-Escudero et al., 2024), it may be crucial to reach specific thresholds in terms of work volume and intensity, and to perform exercise with sufficient frequency over time, to achieve sufficient exposure to the exercises and their potential benefits for brain health. Therefore, we emphasise the need to standardise adherence thresholds in future exercise trials.

We also found significant methodological differences in the assessment of global cognitive function, as some studies employed screening tools designed to detect dementia, such as the MMSE (Alves et al., 2013; Gutiérrez-Reguero et al., 2024; Moon et al., 2021; Phoemsapthawee et al., 2022). This may be considered of lower quality due to the lack of applicability of the MMSE, as this screening tool was not specifically designed to detect changes over time (Arevalo-Rodriguez et al., 2015; Tombaugh and McIntyre, 1992). Furthermore, it may not be suitable for detecting subtle changes in individuals (Hensel et al., 2007). Additionally, this test presents a ceiling effect in individuals with preserved cognitive function, which may mask potential improvements. In this review, studies that used comprehensive test batteries or composite measures to assess cognitive function tended to report larger and more robust effects compared to those relying solely on the MMSE (Andrieu et al., 2017; Komulainen et al., 2021; Ng et al., 2018; Ngandu et al., 2015; Sakurai et al., 2024). Similarly, the systematic review and meta-analysis by Reparaz-Escudero et al. (Reparaz-Escudero et al., 2024) also found more and greater changes in those studies that used test batteries or test compositions. Furthermore, this variability is presented as a limitation because it makes comparisons between studies difficult and limits the ability to accurately determine the true effect of exercise on cognition.

The present meta-analysis has several strengths, including the specific analysis of cognitive domains that have been poorly addressed in previous reviews, such as executive function and visual-perceptual function, as well as its focus on multicomponent interventions with clinical relevance in the older population. However, the wide variability of exercise programmes - in terms of frequency, intensity, type of exercise, duration and volume - is an important source of heterogeneity. This is compounded by the diversity of nutritional approaches used, including differences in type of diet or supplement, dosage, frequency of administration and adherence, which may also influence the results obtained.

5. Conclusions

Our analysis suggests that interventions combining exercise and diet positively influence global cognitive function in older adults. Importantly, rather than acute cognitive enhancement, these findings highlight a preventive potential to preserve functional autonomy and attenuate age-related decline. Future research should employ rigorous methods for exercise programming, monitoring, and dietary follow-up to better understand the combined effects of these interventions. Additionally, it is crucial to use sensitive tools to evaluate global cognitive function. The evidence supports incorporating multi-domain strategies, with exercise and diet as key elements, into interventions aimed at preventing cognitive decline in older adults. These results emphasize the importance of a comprehensive approach to lifestyle changes to support mental health in the aging population.

6. Limitations

Finally, a potential methodological limitation concerns the inclusion of the multi-arm trial by van de Rest et al., (2014), in the meta-analyses of executive and visual-perceptual functions as we calculated the effect size from the raw data. To mitigate any selection bias, we performed a sensitivity analysis that excluded this study, confirming that the overall results remained consistent, demonstrating that its inclusion contributes to the accuracy of the estimate without biasing the conclusions.

Institutional review board statement

Not applicable.

CRediT authorship contribution statement

Gabriel Lozano-Berges: Writing – original draft, Methodology, Conceptualization. **Germán Vicente-Rodríguez:** Writing – original draft, Funding acquisition, Conceptualization. **Casajús José A:** Writing – review & editing, Funding acquisition. **Alba Gómez-Cabello:** Writing – review & editing, Resources. **Ángel Matute-Llorente:** Writing – review & editing, Formal analysis. **Alejandro González-Agüero:** Writing – review & editing, Methodology. **Alejandro Gómez-Bruton:** Writing – review & editing, Formal analysis. **Sergio Castillo-Bernad:** Writing – original draft, Methodology, Formal analysis, Conceptualization. **Ana Moradell:** Writing – review & editing, Methodology.

Informed consent statement

Not applicable.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this paper, the author, SCB, used Chat GPT to improve the readability and language of the manuscript. After using this tool, the authors reviewed and edited the content as necessary and assume full responsibility for the content of the published article.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mad.2026.112183.

Data Availability

Data will be made available on request.

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