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Review

Multi-Domain Interventions for Dementia Prevention – A Systematic Review

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Abstract

OBJECTIVES: There is a growing incidence of cognitive decline and dementia associated with the ageing population. Lifestyle factors such as diet, physical activity, and cognitive activities may individually or collectively be undertaken to increase one's odds of preventing cognitive decline and future dementia. This study will examine whether clinical trials using multidomain lifestyle intervention can significantly decrease the risk of cognitive decline and therefore dementia.

DESIGN, SETTING AND PARTICIPANTS: This systematic literature review of multidomain lifestyle interventions for the prevention of cognitive decline and dementia followed the PRISMA guidelines. Clinical trials involving multidomain intervention (i.e., diet and physical activity, or without cognitive training) in older adults (≥ 49 years old) at higher risk of dementia were identified through 5 electronic databases (EMBASE, MEDLINE, CINAHL, Cochrane, and Scopus). A comprehensive search was performed to identify and retrieve publications until 15 November 2022. Trials were published in English.

RESULTS: The included studies (n=15) assessed change in cognition in response to a multidomain lifestyle intervention. However, the cognitive outcome measures used in these studies were heterogeneous. Despite this heterogeneity, two thirds of the studies showed improvement in cognition following a multidomain intervention (n=10 with a total of 9,439 participants). However, five studies reported no improvement in cognition following the multidomain intervention. The most common form of dietary intervention included higher amount of fruit and vegetable intake; whole-grain cereal products instead of refined; low fat options in milk and meat products; and limiting sucrose intake to less than 50 g/day. Most clinical trial studies were powered to examining the effects of multidomain interventions in cognition but were not designed to test the contribution of individual domains (i.e., dietary changes, increased physical activity, or increased cognitive stimulation alone).

CONCLUSION: This systematic review aimed to determine the effect of multimodal lifestyle interventions on cognitive outcomes in older adults at risk of dementia. We found that participants with conditions that may increase the risk of dementia, (e.g., hypertension, cardiovascular fragility) do benefit from multi-modal lifestyle changes including diet, physical activity, and cognitive training. Two thirds of studies using multidomain lifestyle interventions showed improvements in cognitive function. Trials with a focus on cognitive training, dietary improvement, and physical activity may prevent or delay cognitive decline in older adults including those at risk of developing dementia. Future studies should consider longer follow-up periods and adequate power to be able to examine the effects of each lifestyle component in the context of multimodal interventions.

Key words: Lifestyle intervention, nutrition, physical activity, cognitive training, dementia prevention.

Introduction

Continued growth in the number of older adults worldwide has been accompanied by increased rates of acute and chronic conditions, including dementia (1). The increased prevalence of dementia has become a central issue for public health globally and specifically in Australia, as it is the leading cause of disease burden among Australians aged 65 years and over (2-4). Dementia due to Alzheimer's disease (AD) accounts for ~70% of all diagnosed cases (1).

There is substantial evidence demonstrating that modifying lifestyle factors in isolation can improve cognition or delay cognitive decline. Studies have shown that moderate to vigorous physical exercise improves cognitive functions, including processing speed, memory, and executive function (5). Physical activity may enhance cognitive function due to an array of behavioral, cellular, and molecular mechanisms (6). In addition, evidence suggests that exercise plays a role in lowering brain levels of amyloid beta and tau, the pathological hallmarks of AD (5). Cognitive training may improve and maintain cognitive performance, resulting in the prevention or delay of dementia, potentially through stimulating neuroplasticity and task-dependent brain activation, as well as influencing brain metabolism. Several studies have demonstrated an association between foods or nutrients and cognitive outcomes (6). Current research suggests that following healthy dietary patterns, such as the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet, a combination of the Mediterranean Diet (MeDi) and the Dietary Approaches to Stop Hypertension (DASH) diet, improves cognitive function in older adults.

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The MIND diet may be superior to other plant-rich diets for improving cognition, including the MeDi (7, 8) partly due to the recommendation for consumption of berries in the MIND diet due to their antioxidant attributes (9-11). The MIND diet recommends consumption of several plant-based food components (nuts, olive oil, legumes, whole grains) which all have known benefits for health brain performance (12-17).

More recently, the development of multimodal interventions has expanded this field of research. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) (18), showed that a combination of aerobic and resistance training physical exercises, a healthy diet, computerized online cognitive training, and medical monitoring of cardiometabolic risk can improve the brain function in people at higher risk of developing dementia (19).

Multi-disciplinary lifestyle approaches to enhance cognitive health are crucial, since preventing dementia occurrence via lifestyle approaches is an important area of interest with minimal investment and significant cost savings for individuals at risk as well as health care providers (20). This review will investigate the effects of healthy dietary patterns in combination with a multidomain lifestyle intervention on reducing and/or preventing cognitive decline in older adults at risk of developing dementia.

Methods

A systematic literature review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Clinical trials involving multidomain lifestyle intervention (dietary intervention, physical activity, and cognitive training) in adults aged 49 years or older were identified through 5 electronic databases (EMBASE, MEDLINE, CINAHL, Cochrane, and Scopus). The protocol for this review was published on PROSPERO (www.crd.york.ac.uk/PROSPERO) under registration number CRD42021264292.

Search Strategy

The following Medical Subject Heading words and their combinations were searched: "Alzheimer's disease" OR "cognitive impairment" OR "dementia" OR "mild cognitive impairment" (MCI) OR "subjective cognitive decline" (SCD) OR "subjective memory complaints" (SMC) OR "prodromal Alzheimer's disease" AND cognition OR memory OR "neuropsychological assessment" OR "quality of life" OR "mental health" AND lifestyle OR "multidomain intervention" OR prevention OR World-Wide FINGERS OR "Multi-component intervention" OR "dietary intervention" AND "physical activity intervention" "randomized controlled trial" OR "intervention studies" OR "clinical trial" OR "clinical intervention" OR cohort OR "longitudinal cohort study". Stars were used to return results that contain the letters preceding the specific characters. The electronic database search was conducted from 15th January 2022 to 15th November 2022, with no restrictions on the date of publication. Limits included human only studies, peer-reviewed articles and published full-text articles. References of the retrieved publications were also examined to identify other potential papers for inclusion.

Eligibility Criteria

Publications were included if they were in English, had neuropsychological assessments investigating the effects of a multidomain approach (with diet and physical activity, with and without cognitive training) as a primary or secondary outcome measure in older adults at risk of developing dementia.

The inclusion criteria were adults and older adults (≥ 49 years) with risk of dementia including sedentary lifestyle with no or low level of moderate exercise (e.g., fast walking for 30 minutes) less than three times a week, or with a poor diet (malnutrition that is characterized by inadequate intake of protein, energy, and micronutrients) or at increased risk of vascular and /or metabolic risk factors.

Additionally, adults over 49 years of age presenting limitation in one of the instrumental activities of daily living (IADL, activities that allow an individual to live independently in a community), or slow gait speed, or Apolipoprotein E (APOE) ε4 carriers were also included. Studies were excluded if they did not report either cognition or neuropsychological assessments as an outcome or did not report multidomain intervention that included diet and physical activity. Since the target population was older adults at risk of developing dementia, participants with MCI and AD were excluded. Studies were also excluded if they were conducted in patients with cancer, HIV, chronic kidney disease, liver disease or any other condition that could affect cognitive function. Studies were also excluded if they were reviews, meta-analysis, conference abstracts, animal studies, in vitro studies, withdrawn or clinical trial registry with no associated publication.

Selection process and quality assessment

The titles and abstracts of all articles were independently screened by two reviewers (CBC and LMC) against the eligibility criteria. If there was insufficient information in the abstract to warrant exclusion of an article, the full text of the article was retrieved to determine eligibility. The full texts of all potentially relevant publications were retrieved, and a second selection assessment was undertaken. Any discrepancies in the assessment or disagreements in any article to be included were resolved after discussion with an independent investigator (CD, JC or HH). The methodological quality of the selected full texts was determined using the modified Cochrane Collaboration tool for crossover studies to assess risk of bias (21) and disagreements in methodological quality was resolved with a fourth reviewer (HH).

Using the Cochrane tool, we critically appraised the quality of each publication as well as to determine the relevance and validity of the selected publications. Biases were assessed as a judgment (high, low, or unclear risk) for individual elements from 7 domains [i.e., sequence generation, carryover effects, allocation concealment, blinding of the participants and study

personnel, blinding of outcome assessment, handling of missing data (intention-to-treat or per protocol analysis), and selective outcome reporting]. Then, each trial received an overall classification of risk of bias (22). The Physiotherapy Evidence Database (PEDro) score was also used to critically appraise the quality of the papers included. Using the PEDro scale, a score was calculated for each paper denoting high methodological quality if the score was higher than 6, moderate quality if the score was 5 to 6 and poor quality if the score was lower than 5 (23).

Data extraction

Publications were extracted by two authors (CBC, LMC) using a pretested data-extraction spreadsheet and assessed by a third collaborator (CD) for completeness. Disagreements were resolved by discussions among the two authors (CBC, LMC). The following data were extracted when available: study identification (author, year, and country), study design (crossover or parallel, and level of blinding), duration, sample size of each group, participant characteristics (age, gender, APOE ε4 status, body mass index, years of education, and ethnicity), type of exposure assessment, comparator characteristics (e.g., placebo), and measures and outcomes of interest.

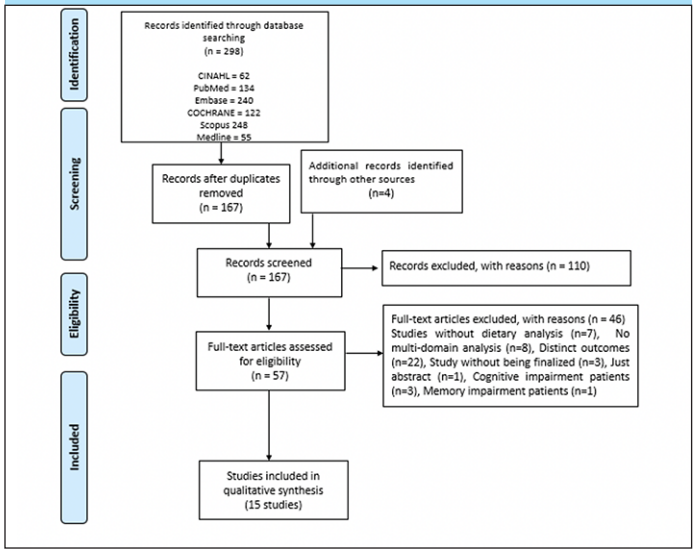
A meta-analysis has not been undertaken since our systematic review was better fitted with the aims of this manuscript in capturing all the available evidence in support of multi domain interventions to prevent dementia. In addition, a very limited number of publications in this field were available at the time resulting in significant heterogeneity in study designs, interventions, and outcome measures identified through the systematic literature review. The included studies vary in terms of study design (crossover or parallel), intervention components (dietary intervention, physical activity, cognitive training), and outcome assessments (cognitive tests). Additionally, the risk of bias and methodological quality across studies also varies. These differences make it challenging to pool the results statistically and derive meaningful conclusions through a meta-analysis. Therefore, a systematic narrative synthesis and critical evaluation of the included studies are deemed more appropriate for this review to provide a comprehensive understanding of the influence of multidomain lifestyle interventions for individuals at risk of dementia.

Results

Studies and participants' characteristics

A total of 171 publications were identified, from which 15 publications matched the inclusion criteria (Figure 1). All included publications were randomized clinical trial studies, using either double (n=2) or single (n=6) blinded design or were unblinded (n=7), and all except 2 of the publications were placebo-controlled (n=13). One of the latter two studies used a parallel design and the other used an open label design. The general characteristics of the studies are described in Table 1.

Figure 1. PRISMA flow chart containing an overview of the study-selection process (25)



PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analysis; n= number of publications.

Included studies were published between 2010 and 2021. The studies had a total of 13,339 participants from both sexes, aged 49 to 77 years old. Sample sizes ranged from 32 to 2724 participants and, in 12 of 15 studies, 50% or more of the participants were women. The study cohorts included one or multiple countries and were from North America (n=1 USA), Asia (n=2 Korea, n=1 China and n=1 Singapore), Europe (n=1 The Netherlands, n=4 Finland, n=2 France, n=1 France and Monaco, n=1 The Netherlands, Finland, and France) and Oceania (n=1 Australia).

Studies were heterogeneous in duration (4 months to approximately 9 years), placebo used, and population studied (participants with dementia risk, including only one sex or both sexes). Studies were completed with (n=8) or without (n=7) industry support. Industry support included staff payments with no additional support or industry involvement (n=1), industry funding with no industry involvement in data collection or analyses (n=1), or industry funding with very limited description of the role of the industry partners (n=6).

The primary outcome measure was the Mini-Mental State Examination (MMSE; n=9), the Cardiovascular Risk Factors, the CAIDE (Cardiovascular Risk Factors, Aging, and Incidence of Dementia) Dementia Risk Score (n=4) and cognitive performance measured with the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) (n=2). Secondary outcome measures included quality of life (QoL), verbal fluency (included in cognitive outcomes) and self-reports on cognition including Memory Assessment Clinic – Questionnaire (MAC-Q).

Dietary interventions

In terms of dietary interventions, studies were also heterogenous. Studies used general nutritional counselling and dietary education and advice (n=5), the National Nutrition

Table 1. Characteristics of included studies that examined the impact of a multidomain intervention on cognitive outcomes in older adults at risk of dementia

Author, year, location (reference)	Participant characteristics [a]	Study Design	Intervention	Study duration	Outcome	Limitations
Andrieu et al, 2017, France and Monaco (29)	N= 1525 Age = 75.3 (4.4) Male = 547 (36%) APOE4(+) = 287 (23%)	Randomized, Placebo-Controlled Trial	Intervention: Multidomain (cognitive stimulation, physical activity, and nutrition) + 2 capsules of PUFAS daily. Control: Multidomain + 2 capsules of either placebo daily. The placebo capsules contained flavored paraffin oil.	3 years	Cognitive improvement in polyunsaturated fatty acid + multidomain intervention or the multidomain intervention alone. Improvement in those with a CAIDE dementia risk score of 6 or greater at baseline, and those with a positive amyloid PET scan.	Single blinded. Did not use a food frequency questionnaire. Funded by industry.
Anstey et al, 2020, AUS (20)	N= 128 Age = 51.1 (14.2) Male = 39 (31.2%)	Randomized, Controlled Trial	Intervention: Learning modules on dementia literacy, physical activity, nutrition, health monitoring, cognitive and social activities. Control: Generic information on basic nutrition, meal planning, physical activity, health conditions and sleep.	62-weeks	The multidomain BBL-GP lifestyle intervention was effective in reducing the risk of dementia for a period of at least 15 months. Participants aged 60 to 64 years with a one-point lower ANU-ADRI at baseline have an 8% lower chance of developing MCI or dementia over a 12-year period.	Small sample. High attrition. The study was not resourced for vigilant follow-up of participant. Funded by industry.
Chhetri et al, 2018, France (30)	N= 1680 Age= 75.4 (±4.3) Male= 473 (36.6%)	Randomized Controlled Trial	Intervention: Isolated n-3 PUFA or multidomain (nutritional counselling, physical exercise advice, cognitive stimulation) plus placebo, or multidomain in combination with n-3 PUFA. Control: Control on cognitive function of community dwelling older adults aged 70 or above.	3 years	High-risk participants for dementia screened with CAIDE dementia score might benefit from multi-domain intervention strategies as in the MAPT study, particularly in the orientation and delayed recall domain.	Post-hoc analysis of a larger RCT. Funded by industry
Koekkoek et al, 2012 Netherlands (26)	N= 258 Age= 59.3±5.6 Male= I: 147 (57.7%) RC: 165 (64.3%)	Cluster-Randomized Trial	Intervention: Multidomain (diet, physical activity, and promotion of protocol-driven strict regulation of metabolic parameters). Control: General practitioners were only informed about diagnostic test results.	6 years	Six years of IT in screen-detected type 2 diabetes had no benefit on cognitive functioning over RC.	NPA was not performed at the beginning of the study. No cognitive training part of inter-vention. Selection bias and selective attrition during follow-up. Funded by industry.
Lee, et al, 2014, South Korea (31)	N: 460 Age = 77.1 ± 2.5 Male = 98 (21.4%)	Cluster Randomized Controlled Trial	Intervention: Physical, cognitive, and social activities, antismoking, alcohol drinking in moderation and healthy diet. Control: Usual Care.	18 months	Cognitive activities + positive health behaviors, may be most beneficial in preserving cognitive abilities. Health worker-visit care group showed superior cognitive function (MMSE).	Short follow-up period. Low rate of retention. Participants didn't fully identify clini-cal information.
Lehtisalo, et al, 2019, Finland (24)	N= 1260 Age= I: 69.5 (4.6) Control: 69.1 (4.7) Male: I: 308 (54%) Control: 306 (52%)	Randomized Controlled Trials	Intervention: Dietary counselling, physical exercise program, cognitive training, and management of metabolic and vascular risk factors. Control: Regular health advice and feedback on vascular risk factors.	2 years	The cognitive performance among all participants improved. IG, improvement was significantly greater in global cognition and in executive function and processing speed domains. Dietary quality improved in the intervention group.	Guideline-based diet score used in analyses may not be optimal for brain health.
Lehtisalo, et al, 2016, Finland (32)	N= 522 Age= 61.1 ± 6.7 Male= 114 (31%)	Randomized Controlled Trials	Intervention: Individualized dietary, physical activity, and weight reduction counselling. Control: General information about lifestyle and diabetes risk.	9 years	Long-term dietary fat intake, BMI, and waist circumference have an inverse association with cognitive function. Decreases in BMI and waist prior to cognitive assessment are associated with worse cognitive performance.	No cognitive training part of intervention. Focused only on fats. Lack of statistical power. Funded by Industry.
Ngandu et al, 2015, Finland (19)	N= 1260 Age= IG: 69.5 (4.6) CG: 69.2 (4.7) Male= 639	Randomized Controlled Trial	Intervention: Diet, exercise, cognitive training, and vascular risk monitoring. Control: Regular health advice.	2 years	A multidomain intervention could improve or maintain cognitive functioning in at-risk older adults from the general population.	Methodological limitations.

Table 1. Characteristics of included studies that examined the impact of a multidomain intervention on cognitive outcomes in older adults at risk of dementia

Author, year, location (reference)	Participant characteristics [a]	Study Design	Intervention	Study duration	Outcome	Limitations
Park et al, 2019 South Korea (33)	N= 32 Age: AC: 76.1 (4.1) Int. + Main: 77.4 (4.8) Int. P: 76.6 (5.7) Male: 3 (9.4%)	Single-Blinded Randomized Controlled	Intervention: Physical activity, modifying vascular risk factors, diet, cognitive and social activities. Control: Personalized advice on lifestyle modifications to prevent dementia and the usual regular 3-month health check-ups.	24 weeks	The findings support the feasibility and efficacy of a multidomain intervention with maintenance program in terms of reducing the dementia risk in community-dwelling older adults at risk.	Short follow-up period. Reporting bias. Single blinded. Small sample. Funded by industry.
Ng et al, 2018 Singapore (35)	N= 246 Age: Control: 70.2 ± 5.0 Nutrition: 69.6 ± 4.3 Cognitive: 69.7 ± 4.3 Physical: 70.2 ± 5.2 Combination: 70.4 ± 4.7 Male= 95 (38.6%)	Randomized Controlled Trial	Intervention: Nutritional, physical, and cognitive training plus supplements (Fortisip Multi Fibre, iron and folate, vitamin B6 and vitamin B12, calcium and vitamin D Control: Community based social, recreational and day care rehabilitation services + placebo liquid capsules and tablet formulations.	1 year	Among frail older persons, cognitive training conferred the greatest cognitive benefits. Nutritional and physical interventions singly were associated with modest short-term or no cognitive benefits, but their combined effects on visuospatial construction should be further investigated.	Study sample size was based on physical frailty, not cognitive function. Findings are related to frail and pre-frail older individuals. Short intervention.
Richard et a, 2019 Netherlands, Finland, and France (36)	N= 2724 Age= 69 (67–73) Male=1427 (52.4%)	Randomized Controlled Trial	Intervention: Health priorities are physical activity, nutrition, coach advice and education (videos and games) Control: Advice and education - general static information on cardiovascular risk.	18 months	Primary outcome improved in the intervention group versus the control group. Coach-supported self-management of cardiovascular risk factors using an interactive internet intervention leads to a modest improvement of CRP.	Difficulty to establish its clinical relevance. It was not embedded in, or aligned with, the local primary care systems. Short intervention.
Smith et al, 2010, USA (38)	N= 124 Age= 52.3 (9.6) Male= 45 (36%	Randomized controlled trial	Intervention: Aerobic exercise combined with dietary modification. Control: Usual care control group maintained their usual dietary habits and did not lose weight or exercise for 4 months	4 months	DASH diet, especially + caloric restriction and aerobic exercise, improves neurocognitive performance and psychomotor functions among individuals with HBP.	Short intervention. No cognitive training part of intervention. Small sample size. Did not use an exercise control group without dietary modification or a weight loss control group
Stephen et al, 2020, Finland (25)	N= 1260 Age: Intervention: 70.0 (4.2) Control: 69.5 (3.9) Male= 33	Randomized Controlled Trial	Intervention: Dietary counselling, physical exercise program, cognitive training, and management of metabolic and vascular risk factors. Control: Regular health advice and feedback on their vascular risk factors.	2 years	Improving neurocognitive function among older adults with HBP, at greater risk for cognitive decline and AD. Decrease in fractional anisotropy and significant cognitive improvement. 2-year multidomain lifestyle intervention may modulate microstructural alterations.	Not specifically design to detect a significant difference between frailty status and the definition of frailty. · Participants with a subjective memory complaint included.
Tabue-Teguo et al, 2018, France (27)	N= 1680 Age= 5.2(±4.4) Male= 524 (35.8%)	Randomized Controlled Trial	Intervention: Isolated n-3 PUFA or multidomain (nutritional counselling, physical exercise advice, cognitive stimulation) plus placebo, or multidomain in combination with n-3 PUFA. Control: Multidomain + identical capsules comprising liquid paraffin oil.	3 years	PUFA supplementation has not significant effects on cognitive function change in frail older adults with memory complaints. The beneficial effect of multidomain intervention and n3 PUFA supplementation on cognitive function did not differ between frail and nonfragile participants.	Not specifically design to detect a significant difference between frailty status and the definition of frailty. Participants with a subjective memory complaint included.
Woo et al, 2019, China (55)	N= 180 Age= LMP group = 51.41 (11.69) Male= 78; 47,85%	Randomized, Controlled Trial	Intervention: Healthy lifestyle kit = balanced diet + daily physical activity + 24-week exercise program and + 2 glasses of fortified milk supplement (OPTIMEL 60þ Diamond powder). Control: Usual physical activities and dietary habits during the 24-week study period and received the same measurements as the intervention group.	24 weeks	24-week exercise and nutrition program improved self-rated health and moderate physical activity level among. No difference in the primary outcome of gait speed or other outcomes consisting of measures of physical performance, cognitive function, and cardiorespiratory fitness.	Short intervention. No cognitive training part of intervention. Because of resource limitations, a 2-group design instead of 4-group was used. Funded by industry.

*PUFAS (Polyunsaturated Fatty Acids), CAIDE (Cardiovascular Risk Factors, Aging, and Dementia), Amyloid PET Scan (Amyloid Positron Emission Tomography), MCI (Mild Cognitive Impairment), BMI (Body Mass Index), MMSE (Mini-Mental State Examination), CRP (C-Reactive Protein).

Table 2. Characteristics of the dietary components of the multidomain interventions

Author, year, location (reference)	Dietary Intervention
Andrieu et al, 2017, France and Monaco (29)	Nutritional advice (based on guidelines established by Program National Nutrition Santé, the French National Nutrition and Health Programme).
Anstey et al, 2020, AUS (20)	Dietary education and advice to assist the participant in adapting their diet to a healthy diet in areas that were identified as unhealthy in the dietary questionnaire (Australian Recommended Food Score).
Chhetri et al, 2018, France (30)	Isolated supplementation with n-3 PUFA + nutritional counselling (based on guidelines established by Program National Nutrition Santé, the French National Nutrition and Health Programme).
Koekkoek et al, 2012, Netherlands (26)	Lifestyle advice regarding diet.
Lee, et al, 2014, Suwon, Republic of Korea (31)	The healthy-diet recommendation consisted of encouraging participants to consume high quantities of fruit and vegetables, control their weight, and consume at least 2 portions of fish per week.
Lehtisalo, et al, 2019, Finland (24)	Fruits and vegetables above 400 g/d; whole-grain cereal products instead of refined ones; low fat options in milk and meat products; sucrose intake to less than 50 g/day; vegetable margarine and rapeseed oil instead of butter or butter-oil mixtures; and fish consumption of at least two portions per week. Minimum of 10 mg supplemental vitamin D was recommended daily throughout the year for all participants.
Lehtisalo, et al, 2016, Finland (32)	Individualized dietary and weight reduction counselling by the study nutritionist.
Ngandu, et al, 2015, Finland (19)	Nutritional intervention was based on the Finnish Nutrition Recommendations. Diet with 10–20% of daily energy from proteins, 25–35% daily energy from fat (<10% from saturated plus trans fatty acids, 10–20% from monounsaturated fatty acids, and 5–10% from polyunsaturated fatty acids [including 2·5–3 g/day of omega-3 fatty acids]), 45–55% daily energy from carbohydrates (<10% from refined sugar), 25–35 g/day of dietary fiber, less than 5 g/day of salt, and less than 5% daily energy from alcohol. Energy intake facilitating 5–10% reduction in bodyweight.
Park et a, 2019, South Korea (33)	The study nurse performed education and training aimed at modifying vascular risk factors and diet.
Pin Ng, et al, 2018, Singapore (35)	Commercial formula (Fortisip Multi Fibre, Nutricia), iron and folate supplement (Sangobion, Merck), vitamin B6 and vitamin B12 supplement (Neuroforte), calcium and vitamin D supplement (Caltrate).
Richard, et al, 2019, Netherlands, Finland, and France (36)	Mediterranean Diet Adherence
Smith, et al, 2010, USA (38)	DASH dietary intervention.
Stephen, et al, 2020, Finland (25)	Fruits and vegetables above 400 g/d; whole-grain cereal products instead of refined ones; low fat options in milk and meat products; sucrose intake to less than 50 g/day; vegetable margarine and rapeseed oil instead of butter or butter-oil mixtures; and fish consumption of at least two portions per week. Minimum of 10 mg supplemental vitamin D was recommended daily throughout the year for all participants.
Tabue-Teguo, et al, 2018, France (34)	Dietary guidelines established by the French National Nutrition and Health Program for the older adults, which is considered as the official reference in France.
Woo, et al, 2019, China (35)	2 glasses of fortified milk supplement [i.e., 2 sachets of 30 g each of unbranded OPTIMEL 60þ Diamond powder (Friesland-Campina, the Netherlands)] daily for 24 weeks. The milk supplement contains multivitamins and provides 13.6 g protein and 212 kcal for 60 g powder. During the 24-week intervention, they were asked to maintain their usual physical activities and dietary habits.

Santé, the French National Nutrition and Health Program (n=3), the Finnish Nutrition Recommendations (n=1), the Australian Recommended Food Score (n=1), commercial formula either Fortisip Multi Fibre or Nutricia (n=2), isolated supplementation with n-3 PUFA + nutritional counselling (n=1), Mediterranean Diet intervention (n=1), or the DASH intervention (n=1). The following study-specific advice was used in two of the studies (24, 25), fruits and vegetables (≥400 g/d); whole-grain cereal products instead of refined; low fat options for milk and meat products; sucrose (<50 g/day); vegetable margarine and rapeseed oil instead of butter or butter-oil mixtures; at least two portions of fish per week; and minimum of 10 mg/d vitamin D supplement. The majority of studies used nurses or health coaches (n=10) for the dietary education counselling, and only four out of fifteen studies had dietitians or nutritionists providing dietary counselling, which could provide better adherence to the dietary advice. The details of dietary interventions and characteristics are described in Table 2.

Most of the nutritional guidelines and dietary advice used in the included studies recommended increased consumption of fruits, vegetables, legumes, nuts, and whole grain food and decreased salt, processed food, red meat, saturated fatty acids, and alcohol intake. However, the guidelines had some differences regarding the consumption of dairy, seafood, and fiber. Some studies recommended an increase in the intake of dairy while others advised consumption of skim milk. Some trials recommended up to 3 servings a week of seafood and up to 15g/day of fiber.

Physical activity intervention

Studies focused mainly on aerobic exercises including walking, running, hiking, plus advice on the benefits of such physical exercise (n=5); followed by muscle strengthening plus aerobic exercises (n=4); muscle strengthening and stretching (n=2); Community Health Activities Model Program for Seniors (n=1) and American College of Sports Medicine (n=1); moderate to intense physical activity for 30 minutes per day (n=1). One study listed general physical activity, with no further specification.

Cognitive training intervention

Studies differed in their cognitive training modality. Four studies did not use commercial cognitive training interventions, four used web-based cognitive activities, and two reported adherences to daily home-based cognitive tasks (e.g., reading, learning a new language or course, watching TV, poetry classes) and one study practiced cognitive games and block puzzles. Four studies did not include cognitive training in their multimodal lifestyle intervention.

Table 3. Risk of bias [a] of studies included in this review and quality [b] of the publications

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Carryover effect	Blinding of outcome assessment	Incomplete outcome data	Selective outcome report	Other bias	Overall effect	PEDro score [b]
Cognitive outcomes										
Andrieu et al	Low risk	Unclear risk	High risk	Low risk	High risk	Low risk	Low risk	High risk	High risk	5
Anstey et al	Low risk	Low risk	High risk	Low risk	High risk	Low risk	Low risk	High risk	High risk	6
Chhetria et al	Low risk	Low risk	High risk	Low risk	High risk	Low risk	High risk	High risk	High risk	6
Koekkoek et al	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk	High risk	High risk	8
Lee K et al	Low risk	Unclear risk	High risk	Low risk	Low risk	Low risk	Low risk	High risk	High risk	6
Lehtisalo et al 2016	Low risk	Low risk	High risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	High risk	7
Lehtisalo et al 2019	Low risk	Low risk	High risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	High risk	7
Ngandu et al	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	10
Park et al	Low risk	High risk	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	8
Pin Ng et al	High risk	Unclear risk	High risk	Low risk	High risk	Low risk	Low risk	High risk	High risk	4
Richard et al	High risk	High risk	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	7
Smith et al	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	High risk	High risk	8
Stephen et al	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	High risk	9
Tabue-Teguo et al	High risk	High risk	High risk	Low risk	High risk	High risk	High risk	High risk	High risk	4
Woo et al	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	9

Note. Citations are displayed in chronological order. a. Cochrane assessment tool (22). b. PEDro (Physiotherapy Evidence Database) score: >6 = high; 5–6 = moderate and <5 = poor methodological quality (23).

General effects of lifestyle intervention on cognition

The impact of the lifestyle interventions on cognitive outcomes measures were heterogeneous, as three studies reported no improvement (26-28), ten studies reported improvement (19, 20, 24, 25, 29-34), and one study reported modest short-term improvement in the cognitive outcomes (35). In the studies that reported cognitive improvements, the dietary interventions were the DASH intervention or similar, with consumption of high quantities of fruit and vegetables, whole-grain cereal products instead of refined ones, control their weight, low-fat options in milk and meat products; sucralose intake to less than 50 g/day; vegetable margarine and rapeseed oil instead of butter or butter-oil mixtures; and fish consumption of at least two portions per week.

Assessment of risk of bias

All fifteen studies were included in the analysis (Table 3). From the nine studies reporting improvements in the MMSE as their primary cognitive outcome measure, eight presented a high risk of bias overall (20, 27, 29-31, 33, 35, 36) and one reported low risk (37). The main sources of bias among these fifteen studies were blinding of participants and personnel. Eleven of the studies presented high risk for blinding of participants and personnel, as the intervention type required that the participants were aware of their allocated groups. Nine of the fifteen publications had high methodological quality (19, 24-26, 28, 32, 33, 36, 38) according to the PEDro scale (Table 3).

Discussion

This systematic review aimed to determine the effect of multimodal lifestyle interventions on cognition in older adults at risk of developing dementia. This review supports the hypothesis that participants with conditions that may increase dementia risk, such as hypertension, or cardiovascular fragility, may benefit from lifestyle changes including diet, physical activity, and cognitive training. Despite the heterogeneity in outcome measures, more than two thirds of the clinical trials studies showed significant improvement in cognition following the multidomain intervention (n=10).

Observed improvements in cognition in the included studies may be due to these studies' interventions including a high consumption of fruits, vegetables, and whole grains cereals. These types of foods are rich in antioxidants and anti-inflammatory components. The nutrient antioxidants can decrease brain cellular damage and inflammation and possibly reduce the accumulation of amyloid beta plaques, the neuropathological hallmark of AD (39). However, the studies were not designed to test the individual contributions or effect of dietary changes, increased physical activity, and increased cognitive stimulation for the prevention of cognitive decline, given their context within a multidomain lifestyle intervention. Future multidomain lifestyle interventions designed to assess the impact of each domain of a healthy lifestyle and the optimal dosage of these components to improve cognition are required.

Although none of the studies specifically recommended the MIND diet, the majority focused on healthy dietary changes including promotion of components of the MIND diet, such as increasing fruits, vegetables, whole-grain cereal, and fish. The MIND diet has been associated with reduced odds of cognitive impairment in a longitudinal study with an Australian cohort (40). Currently there is enough evidence that adherence to MIND diet is slowing cognitive decline, and this is independent of brain pathology (41, 42). The MIND diet has also been linked to lower blood pressure, better blood lipid profiles, better blood glucose control and weight loss, all of which would reduce risk of cardiovascular disease, type 2 diabetes and hypertension, conditions that are considered risk factors for dementia, including AD (39). Adherence to the MIND diet is expected to contribute to maintaining brain health and is

expected to support cardiovascular health and management of type 2 diabetes (39). Since AD is related to impaired brain glucose metabolism, glucose control becomes crucial for dementia prevention (43).

The DASH diet intervention was also applied in some of the studies reviewed here. The DASH dietary intervention was originally developed to lower blood pressure without medication and is now widely considered to be one of the healthiest eating patterns. The DASH diet is anti-inflammatory and can help fight inflammation in those at risk of dementia. In addition, some studies used supplements of omega-3 polyunsaturated fatty acids, vitamin D and fortified milk supplement enriched with vitamins and minerals. In preclinical AD, insulin resistance leads to energy deficiency in the brain. Medium chain triglycerides (MCT) are metabolized into ketone bodies, thus dietary MCT may partially resolve the energy deficit in the glucose-deprived brain and subsequently improve brain energy metabolism (44).

Although the ten studies included in this review that used nurses or health coaches to administer the dietary education counselling found significant results, similar to the four studies that used dietitians or nutritionists, it is a limitation of those studies, particularly since dietitians can play a more informed role in the delivery of evidence-based dietary counselling to facilitate dietary behavioural changes. Individual and group level consultations provided exclusively by dietitians are effective in improving diet quality, weight outcomes (weight, waist circumference, body mass index), diabetes outcomes (including fasting blood glucose and hemoglobin A1c) and indicators related to cardiovascular disease (including triglycerides and total and low density lipoprotein cholesterol) (44-46).

The majority of the studies used aerobic exercise interventions, which are linked to increased brain oxygenation, increased anterior white matter integrity and grey matter volume. Previous randomized trials have demonstrated that aerobic exercise improves neurocognitive functioning (38). Furthermore, another possible mechanism partially explaining the lifestyle changes and cognitive enhancement is the increase in the brain derived neurotrophic factor (BDNF) levels following physical exercise. The increased BDNF level may stimulate neuroplasticity (the brain's lifelong neuronal ability to adapt to external stimuli), and thereby may increase cognitive reserve (the maintenance of cognitive function throughout ageing, despite injury or pathophysiological changes in the brain) and reduce the risk of developing dementia (2, 47, 48). Eleven of the studies used some form of cognitive training including computer-based, home-based, or face-to-face. Results from a meta-analysis of 52 randomized controlled trials revealed that computer-based cognitive training significantly improved memory, processing speed and visuospatial skills. In addition, computer-based cognitive intervention provided superior evidence of enhanced cognition in cognitively healthy older adults (49, 50). Out of the four studies that did not incorporate cognitive training as part of their intervention, only one demonstrated a notable enhancement in neurocognitive performance and psychomotor functions in individuals with high blood pressure (HBP) (38).

A limitation of this review was that only participants at risk of dementia were included as the focus of the review was on dementia prevention. Publications with participants who were diagnosed with any neurological condition, including prodromal (MCI) and dementia stages were excluded. Also, some of the exclusion criteria may have influenced findings. For example, studies were excluded if they were not published in English, and during the time of conducting the systematic review, no multidomain intervention trials were found that met the inclusion criteria in countries across South America, Central America, and Africa. In addition, we did not include any studies without dietary intervention, which could have excluded some multidomain lifestyle intervention articles, that focused on physical activity or cognitive training together for example.

Limitations of the included studies include their reliance on self-reported adherence, which may reduce the reliability and reproducibility of their findings. Although few studies did report low dropout rates, they failed to explain how they have assessed adherence (17, 37). The primary dropout reasons reported by one of the studies included health-related reasons, lack of time or motivation, and difficulties in participation (17). Another study reported higher dropout rates amongst intervention participants, suggesting further investigation is necessary to determine if the active intervention groups withdraw due to the demanding nature of such interventions (35). Studies included in our systematic review did not clarify how intervention adherence affected cognitive outcomes, and further failed to address the potential of practice effects on cognitive testing and what, if any, steps were taken to minimize this risk. Furthermore, studies have heterogeneous durations, varying from 4 months to 9 years, which should be considered as a confounder. To demonstrate positive effects of multidomain lifestyle interventions, the length of the study is crucial as long-term interventions may have more positive effects on cognition. Additionally, the ethnicity and cultural differences in terms of dietary guidelines may also affect intervention outcomes and limit generalizability of findings.

Future research should also focus on those living with dementia to have a better understating of the effects of tailored multimodal lifestyle interventions on improving cognitive functions and/or decreasing the rates of behavioral and motor symptoms related to dementia, such as gait speed and verbal communication. Furthermore, different cognitive test batteries have been used in various studies and there is a need to use standardized cognitive batteries and cognitive training methods.

Additional initiatives in multidomain interventions

As outlined above, this review focuses on articles with multidomain interventions including diet and physical activity, and some interventions specifically designed to reduce metabolic and vascular risk factors without both dietary and physical exercise interventions, whilst important to dementia research, would not have been included in our search terms. There are numerous ongoing initiatives in terms of multidomain interventions and cognitive prevention that will

advance dementia prevention in the near future, for example the Japan-Multidomain Intervention Trial for Prevention of Dementia in Older Adults with Diabetes (J-MIND-Diabetes) [51], the metabolic and vascular aspects of the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) trial (52), and the Systematic Multi-Domain Alzheimer's Risk Reduction Trial (SMARRT) (53). The SMARRT intervention included secondary outcomes such as improvement in targeted risk factors, functional ability, and incidence of MCI, AD, or other dementias.

Emerging research is examining the concept of dose effect that suggests the extent or intensity of an intervention may have a proportional impact on its outcomes. In the context of cognitive enhancement interventions, this implies that the quantity and frequency of engagement in various domains, such as physical activity, cognitive training, and dietary modifications, may influence the degree of cognitive improvement observed in older adults. The study by Belleville et al. (62) explores the nuances of dose effects in multidomain interventions to assess whether there is an optimal balance between the intensity of interventions and their cognitive benefits (54). The authors report that dose-response models were non-linear functions and the analysis highlights diminishing returns in multidomain interventions, with peak benefits observed at 12-14 training hours or 15-20 sessions over three years, particularly for specific demographics like women, younger individuals, and those with lower education or dementia risk (54). This suggests caution in overloading interventions and potential adverse effects associated with excessive engagement, revealing the unexpected finding that optimal outcomes can be achieved with approximately half of the available sessions. Therefore, understanding the dose effect is pivotal for designing evidence-based interventions that balance between efficacy and feasibility. Such findings may have practical implications for healthcare providers and policymakers in designing intervention programs that can be realistically implemented in real-world settings. By considering the dose effect, interventions that are not only effective but also sustainable over time can be ensured, aligning with the broader goal of promoting healthy aging and preventing cognitive decline and dementia in older adults. Further research will lead the way to develop more effective and tailored interventions for older adults, ultimately contributing to improved quality of life for this population.

Implications for research and practice

This systematic review critically assessed relevant studies to offer a comprehensive overview of the role of effects in multidomain interventions for the prevention of cognitive decline and dementia in older populations. It highlights the importance of dementia prevention through promoting a healthier lifestyle as a promising method for reducing dementia and its associated social, financial and health burden on people living with dementia worldwide. Within the World-Wide FINGERS (WW-FINGERS) initiative, a further wealth of data is expected on the effects of multidomain interventions on prevention of dementia following the completion of studies that are part of this international consortium.

Ten out of fifteen articles reviewed here with approximately 9,440 participants, showed improvement in cognition following a multidomain intervention. This systematic review supports evidence that dietary counselling and lifestyle interventions, including physical activity and cognitive training, may contribute to overall improvement in cognition.

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