Single-domain and multidomain lifestyle interventions for the prevention of cognitive decline in older adults who are cognitively unimpaired: a systematic review and network meta-analysis

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Summary

Background Preventing cognitive impairment in older adults is a public health priority. Although multidomain interventions have shown promise as preventive strategies, the optimal combination of interventions remains unclear. This network meta-analysis aimed to compare and rank the relative efficacy of single-domain and multidomain lifestyle interventions for the prevention of cognitive impairment in older adults who are cognitively unimpaired.

Methods We did a systematic review and network meta-analysis of randomised controlled trials (RCTs) published in PubMed and Embase from inception until the date of our search on May 7, 2024 following a preregistered protocol in PROSPERO (CRD42024601975). We included RCTs in older adults who are cognitively unimpaired evaluating lifestyle interventions targeting diet, physical exercise, cognitive training, social activity, and health education, either alone or in combination. The primary outcome was global cognition, analysed using random-effects network meta-analysis, reporting standardised mean differences (SMDs) and 95% CIs, and compared against health education, active control, or no intervention. Subgroup analyses explored potential age-related differences and the effect of intervention duration. Risk of bias was assessed using Cochrane Risk of Bias 2, and publication bias was evaluated by assessing funnel plot asymmetry.

Findings Of the 10 200 citations identified and 1183 full texts screened for eligibility, we identified 109 eligible RCTs, including 23 010 participants (median age 70·1 years [IQR 68·7–73·8], 14 957 [65%] female and 8053 [35%] male). Compared with health education, significant improvements in global cognition were found for physical exercise and cognitive training combined (SMD 0·26 [95% CI 0·10–0·42; p=0·0011); cognitive training alone (SMD 0·21 [0·08–0·33]; p=0·00092); diet, physical exercise, cognitive training, and health education combined (SMD 0·14 [0·02–0·27]; p=0·028); and physical exercise alone (SMD 0·14 [0·05–0·22]; p=0·0014). Random-effects models using active control and no intervention as comparators yielded similarly significant effects for the aforementioned interventions, with effect sizes in the same order. Risk of bias was high in 44 (40%) studies, and publication bias was suggested in studies comparing interventions with health education.

Interpretation Several single-domain and multidomain lifestyle interventions are efficacious at modulating global cognition in older adults who are cognitively unimpaired, with the combination of physical exercise and cognitive training demonstrating the strongest effect. Combining lifestyle interventions might enhance efficacy, but increased number of domains does not automatically translate into greater cognitive benefits. These findings support lifestyle interventions as key components of prevention strategies; however, their optimal combination requires further investigation.

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Introduction

Dementia represents one of the greatest public health challenges of the 21st century, affecting more than 55 million people worldwide, with cases projected to triple by 2050.[1] Traditionally, research and clinical practice have been guided by a diagnostic approach, focusing on identifying neurodegenerative changes once cognitive impairment is evident. However, as growing evidence suggests that pathological processes develop decades before clinical symptoms emerge, the focus is shifting towards a prediction and preventive approach aiming at early risk assessment, detection, and prevention.[2,3] This strategy is of particular interest because, despite recent advancements in disease-modifying treatments for Alzheimer's disease,[4,5] no pharmacological

Research in context

Evidence before this study

Preventing cognitive decline in older adults who are cognitively unimpaired has been a public health priority for decades. Existing evidence, including the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability trial, has demonstrated that multidomain interventions might be able to reduce cognitive decline in populations at risk of dementia. However, the comparative efficacy of different interventions and their combinations has remained uncertain. Previous meta-analyses have typically compared single-domain with control interventions or multidomain with control interventions, leaving a knowledge gap regarding the relative ranking of specific combinations and whether more complex multidomain interventions outperform simpler, more focused approaches in cognitively healthy populations.

Added value of this study

To our knowledge, this systematic review and network meta-analysis is the first to directly compare the efficacy of single-domain and multidomain lifestyle interventions in improving global cognition in older adults who are cognitively unimpaired. By simultaneously evaluating single interventions (eg, cognitive training, physical activity, diet, social activity, and health education) and their combinations, this study provides a comprehensive and comparative overview of their relative efficacies. Our findings indicate that cognitive training and physical activity are among the most efficacious single-domain strategies for enhancing global cognition. Certain multidomain interventions, particularly those combining physical exercise and cognitive training, demonstrated greater benefits than health education or no intervention.

Implications of all the available evidence

Despite advances in research, disease-modifying treatments remain unavailable for most forms of dementia, emphasising the continued need for prevention strategies targeting modifiable risk factors. The available evidence, including the results of this network meta-analysis, support the implementation of lifestyle interventions for dementia prevention in older adults who are cognitively unimpaired. Multidomain interventions, especially those combining cognitive training and physical exercise, appear promising and might offer superior cognitive benefits compared with single-domain approaches. However, the addition of interventions to more domains did not consistently confer added cognitive benefits. This finding might reflect, as suggested by some behavioural research, that moderate-complexity interventions are more likely to be adhered to and achieve better clinical effects than more intensive protocols. Future research should focus on refining the optimal combination, intensity, and duration of interventions, and on identifying individual-level factors that might influence their effectiveness.

therapy has been shown to prevent cognitive decline in older adults who are cognitively unimpaired. As a result, increasing attention has turned towards lifestyle interventions that target modifiable risk factors, which account for up to 45% of dementia cases.[6]

Given the cumulative nature of these risk factors, interventions targeting multiple lifestyle modifications have become central to dementia-prevention strategies. Several single-domain lifestyle interventions, including physical exercise, dietary modifications, and cognitive training, have individually demonstrated benefits in older adults who are cognitively unimpaired.[7–9] These interventions are supposed to share common pathways to increase cognitive reserve,[10] implying direct changes in the brain volume[11] and in brain-derived neurotrophic factors.[12] Building on these findings, multidomain lifestyle interventions have gained increasing attention as potentially the most effective approaches to prevent cognitive impairment. The landmark Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) demonstrated that a multidomain intervention combining diet, physical exercise, cognitive training, and vascular risk management significantly prevented cognitive decline in older adults at risk of dementia.[13] However, subsequent large-scale trials such as the Multidomain Alzheimer Preventive Trial (MAPT)[14] and AgeWell.de[15] have yielded mixed results, raising questions about the optimal combination, intensity, and duration of multidomain interventions. Therefore, although multidomain interventions are conceptually attractive, their feasibility and real-world effectiveness remain unclear.[16] To address these gaps, we did a systematic review and network meta-analysis, a method that allows for the simultaneous comparison of multiple interventions, even when they have not been directly compared in individual trials, to compare the efficacy of single-domain and multidomain lifestyle interventions in preventing global cognition in older adults who are cognitively unimpaired.

See Online for appendix

Methods

Search strategy and selection criteria

This systematic review and network meta-analysis followed the recommendations of PRISMA-NMA (checklist in appendix p 2).[17] This project was preregistered with PROSPERO (CRD42024601975).

We did a literature search in PubMed and Embase from inception to our search date on May 7, 2024, using terms related to cognition in older adults, global cognition outcomes, and randomised controlled trials (RCTs), restricting to studies in humans. The detailed search strategy is presented in the appendix (p 6). The initial abstract screening was done in Rayyan[18] independently by pairs of researchers (AJM, OS, GK, RM, GV, GR, UN, and SG-L). No restrictions were placed on language or year of publication. The full-text

manuscripts were reviewed individually (AJM, OS, GK, RM, GV, GR, UN, and SG-L) thereafter. Any disagreements were resolved through discussion, and if a consensus was not reached, a third researcher (AJM) made the final decision. The accuracy of the search formula was confirmed through cross-verification with the results of previous systematic reviews (appendix p 7), and studies not discovered in previous stages were incorporated on the basis of this validation.

Inclusion criteria were: RCTs; older adults (age ≥50 years) who are cognitively unimpaired; global cognition as an outcome (eg, Mini-Mental State Examination [MMSE], Montreal Cognitive Assessment [MoCA], or composite scores comprising two or more tests evaluating different cognitive functions); and single-domain or multidomain interventions aligned with those tested in the FINGER RCT[13]—namely, diet, physical exercise, cognitive training, social activity, and health education (further details on each intervention are in appendix p 8). The exclusion criteria were: observational studies, cognitive impairment (either diagnosis of mild cognitive impairment [MCI] or dementia), younger adults (age <50 years), other outcomes (eg, depression or biomarkers), interventions combined with drugs or supplements, other publication types (eg, reviews), participants with life-threatening diseases or severe disability, participants with severe or major psychiatric disorders, and participants with a diagnosis of neurological diseases associated with cognition. For studies that did not specify the cognitive stage of the participants, we assessed baseline MMSE or MoCA to validate the results of the test in the country of origin (with different countries having different thresholds for detecting mild cognitive impairment) or we included studies in which more than 90% of participants were cognitively unimpaired, with the remainder having MCI. In the case of several publications related to one cohort, we included the most recent publication or the study with the largest sample size.

Data extraction and statistical analysis

Data were extracted from each study, including study design, intervention, control group, intervention duration, sample size, baseline age, sex, and global cognition assessment (eg, MMSE or MoCA), by eight researchers (AJM, OS, GK, RM, GV, GR, UN, and SG-L). The mean and SD of the global cognitive outcome before and after the intervention, or the change between these two timepoints, were used to obtain the descriptive statistics. In the absence of means and SDs, we used alternative metrics (eg, IQR, SE, or CI) to derive them, then used these to calculate the standardised mean difference (SMD; formulas in appendix p 9). If this information was solely accessible through graphs, WebPlotDigitizer was used to retrieve the data,[19] or, in case of missing data, we contacted the corresponding author. For RCTs with several global cognition outcomes or several groups testing the same intervention, we averaged the effect estimates.[20]

We did a direct evidence plot to visualise both direct comparisons from trials and indirect evidence through a common comparator across the network. We also calculated minimal parallelism and mean path length for each comparison.[21] Consistency of the network (ie, the agreement between direct and indirect evidence) was measured through Cochran's Q statistic for inconsistency,[22] the node-splitting method,[23] and net heat plots[24] (appendix p 10). To improve consistency, we excluded interventions that were tested in fewer than three studies. Lastly, we analysed the distributions of sample size, age, and sex across study groups to evaluate the transitivity assumption of indirect comparisons.

We did a random-effects network meta-analysis to compare the effects of various interventions on global cognition, using SMD and 95% CI from both direct and indirect evidence. We used the generalised inverse function to handle multigroup studies, with health education, no intervention, and active control groups (appendix p 8) serving as reference treatments. Forest plots, effect estimate tables, and league tables of the relative treatment effects were constructed to evaluate the comparisons within the network. Interventions were ranked based on P-scores, which represent the average certainty that one intervention outperforms another on the basis of point estimates and SEs.[25] We did subgroup analyses to assess the influence of potential effect modifiers, including the duration of the intervention and baseline age. Additionally, we did pairwise random-effects meta-analyses for each direct comparison to assess treatment effects solely on the basis of direct evidence.

We evaluated the risk of bias using the Cochrane Risk of Bias tool version 2, which evaluated bias in five domains: bias arising from the randomisation process; bias due to deviations from intended interventions; bias due to missing outcome data; bias in measurement of the outcome; and bias in the selection of the reported result.[26] These criteria were adjusted to the specificities of our interventions and outcomes (appendix pp 11–15). Each domain was classified as high risk, having some concerns, or low risk by two independent raters among eight researchers (AJM, OS, GK, RM, GV, GR, UN, and SG-L). A third researcher resolved the conflict in case of any mismatch between raters. We did a sensitivity analysis of the network meta-analysis by excluding studies with a high risk of bias in the first domain, followed by those with a high risk in the second domain. Lastly, to evaluate potential small-study effects and publication bias across different control interventions, we constructed comparison-adjusted funnel plots for the three main control groups: health education, no intervention, and active control.[27] Statistical analyses were done with R using the *netmeta*, *metafor,* and *robvis* package.[28,29]

Role of the funding source

There was no funding source for this study.

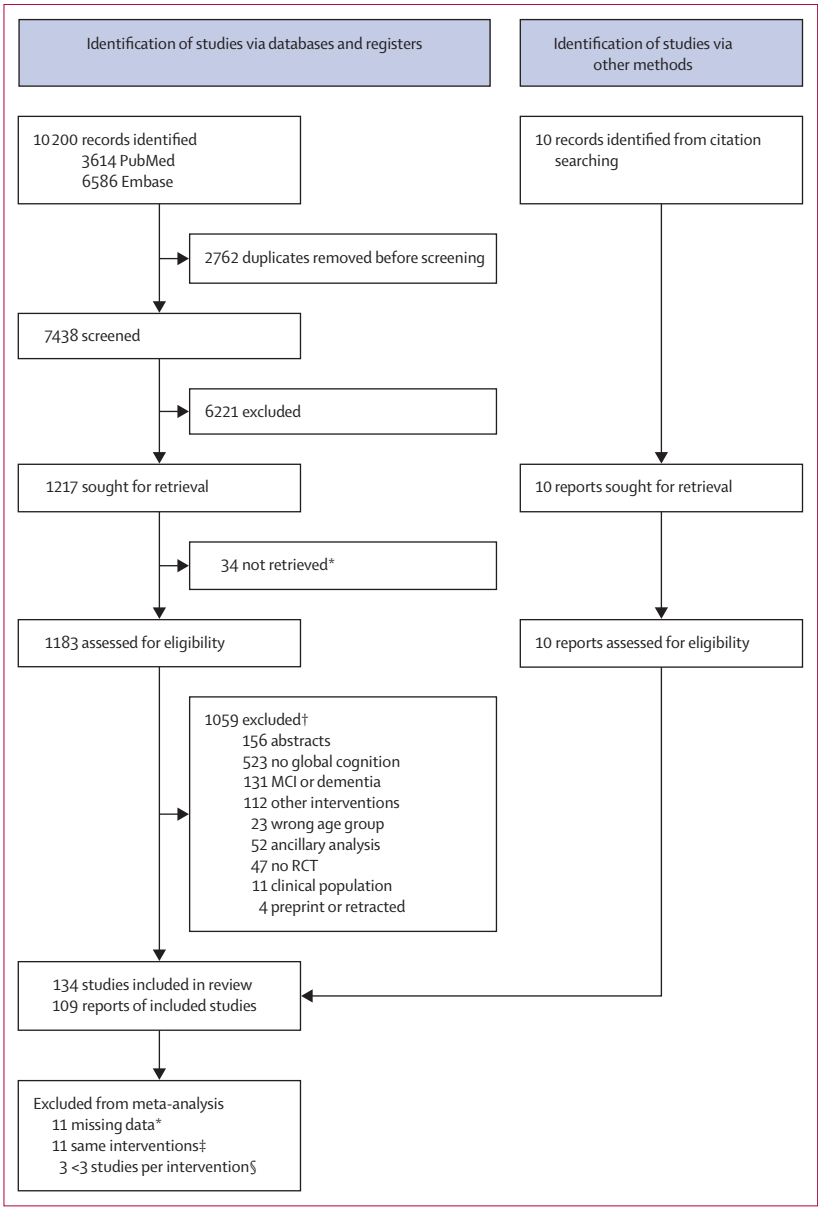

Figure 1: **PRISMA flow diagram of the study selection process**
MCI=mild cognitive impairment. RCT=randomised controlled trial. *An email was sent to the corresponding author, but no response was received. †Some studies met several exclusion criteria; however, the reason for exclusion shown here reflects the rationale provided by the reviewer. ‡Some RCTs compared different modalities of physical exercise or cognitive training and were therefore not included in the network meta-analysis. §Interventions with fewer than three RCTs were excluded to preserve the consistency of the network meta-analysis (two studies of cognitive training plus health education and one study of diet, physical exercise, and cognitive training).

Results

Of the 10 200 citations identified, 1183 full texts were screened for eligibility, of which 109 RCTs were included (23 010 participants, median age 70·1 years [IQR 68·7–73·8], 14 957 [65%] female and 8053 [35%] male) comprising 137 pairwise comparisons (figure 1). Median study duration was 13 weeks (IQR 10–39). Ten studies were done in participants with subjective cognitive decline, and 30 studies were done specifically for participants with some dementia risk factors, such as sedentarism, diabetes, or hypertension. References for the included studies are in appendix pp 16–27 and their characteristics are in appendix pp 28–41.

12 interventions were included, comprising four lifestyle single-domain interventions—diet (n=7), physical exercise (n=52), cognitive training (n=29), and social activity (n=6)—and five groups of multidomain interventions: diet, physical exercise, cognitive training, and health education (n=9); diet, physical exercise, and health education (n=3); physical exercise, cognitive training, and health education (n=3); physical exercise and cognitive training (n=16); and diet and physical exercise (n=3). Three control interventions were also included: no intervention (n=49); an active control (n=20); and health education (n=33). Active control interventions generally involved minimal engagement tasks, such as stretching or low-intensity exercises in physical exercise trials, and puzzles, or Tetris in cognitive training trials. Most of the trials had two groups (n=100), whereas just six trials had three groups and three trials had four groups. The network plot is presented in figure 2 and the number of direct comparisons among interventions is presented in the appendix (p 42).

The random-effects network meta-analysis showed that physical exercise and cognitive training combined (p=0·0011); cognitive training alone (p=0·00092); diet, physical exercise, cognitive training, and health education combined (p=0·028); and physical exercise alone (p=0·0014) significantly improved global cognition compared with health education (figure 3). The comparison with no intervention also revealed that physical exercise and cognitive training combined (p<0·0001); cognitive training alone (p<0·0001); diet, physical exercise, cognitive training, and health education combined (p=0·0012); and physical exercise alone (p<0·0001) significantly improved global cognition. Other interventions showed no statistically significant differences in comparison with health education or no intervention. When compared with active control, only physical exercise and cognitive training combined (p=0·038) and cognitive training alone (p=0·044) revealed significant improvement of global cognition (figure 3). All the direct and indirect effect estimates between interventions are presented in the league table (figure 4) and P scores for common and random-effects models are provided in the appendix (p 43).

Subgroup analyses by age group and intervention duration revealed some variability in the efficacy of interventions on global cognition (appendix pp 44–45). In participants younger than 70 years (57 studies), cognitive training alone (SMD 0·42 [95% CI 0·29–0·56]; p<0·0001) and physical exercise and cognitive training combined (0·36 [0·14–0·57]; p=0·0011) showed the largest effects compared with no intervention, which is consistent with the main network meta-analysis findings. However, in participants aged 70 years and older (50 studies), the largest effect versus no intervention was observed for physical exercise, cognitive training, and health education combined (0·56 [–0·05 to 1·16]; p=0·072), followed by physical exercise

and cognitive training combined (0·29 [0·03 to 0·55]; p=0·032), suggesting that more complex multidomain approaches may be particularly beneficial in older populations. Regarding intervention duration, diet interventions delivered for less than 3 months (51 studies) showed the largest effect versus no intervention (0·68 [0·17–1·20]; p=0·0094; only one study assessed a diet intervention for <3 months), which was not observed in the main analysis when all studies with diet interventions were included. Diet was followed by multidomain physical exercise and cognitive training (0·33 [0·10–0·55]; p=0·0039). By contrast, for interventions lasting longer than 3 months (58 studies), the largest effects were observed for physical exercise and cognitive training combined (0·32 [0·07–0·56]; p=0·0102) and cognitive training alone (0·24 [0·05–0·42]; p=0·010), aligning more closely with the overall findings of the network meta-analysis.

In the pairwise random-effects meta-analysis comparing direct comparisons, we also observed statistically significant SMDs in global cognition (appendix pp 46–51). The multidomain intervention including diet, physical exercise, cognitive training, and health education was superior to health education alone (SMD 0·16 [0·01–0·31]; p=0·041) and no intervention (SMD 0·19 [0·08–0·29]; p=0·0081). Single-domain interventions also revealed significant improvements when compared with no intervention or health education. For instance, physical exercise significantly improved global cognition compared with no intervention (0·30 [0·17–0·42]; p<0·0001). Similarly, cognitive training demonstrated a significant effect compared with no intervention (SMD 0·28 [0·14–0·42]; p=0·0001) and was also more efficacious than health education (SMD 0·17 [0·01–0·32]; p=0·038). Diet showed a significant positive effect compared with health education (SMD 0·24 [0·00–0·47]; p=0·046).

The global inconsistency test (Q=39·37, df=29, p=0·093) did not show statistically significant inconsistency between designs within the network. This finding suggests that the direct and indirect evidence are generally in agreement. The estimated within-design heterogeneity was τ=0·124 with a variance of τ^2=0·015. The node-splitting analysis revealed no significant local inconsistencies in most treatment comparisons (p>0·05), indicating good agreement between direct and indirect evidence across the network. However, a statistically significant inconsistency was identified in the comparison between social activity and health education (p=0·029). The detailed table for the node-splitting analysis and the net heat plot can be found in the appendix (pp 52–57). Moreover, the transitivity assumption was mostly observed regarding the age and sample sizes of the different intervention groups, even though we observed several significant differences in the sex distribution among interventions (appendix pp 58–59).

Overall, only eight studies were rated as low risk of bias, whereas 57 studies were classified as having some concerns and 44 as having high risk of bias. Results for each domain of the risk-of-bias assessment are presented separately by intervention type in the appendix (pp 60–65). The results of the network meta-analysis remained consistent after excluding studies with a high risk of bias in the first and second domains (appendix p 66).

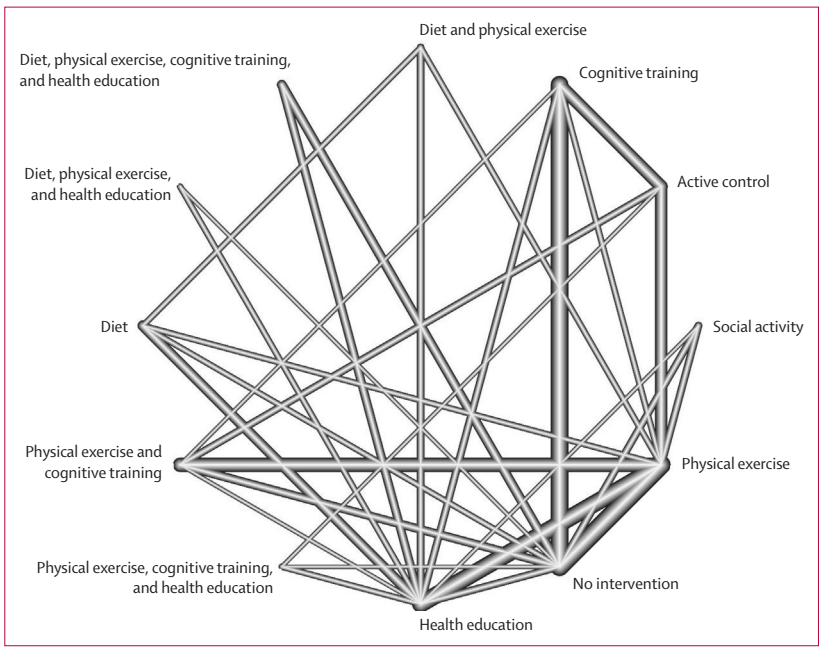

Figure 2: **Studies and their direct comparisons**
The thickness of the connecting lines reflects the number of studies contributing to each direct comparison in the network plot.

The funnel plots for the comparisons against no intervention and active control displayed a symmetrical distribution of effect estimates and no statistically significant evidence of asymmetry according to Egger's test (p=0·556 and p=0·563, respectively). By contrast, the funnel plot comparing interventions to health education showed a less balanced distribution, with Egger's test statistically significant (p=0·011), suggesting the presence of small-study effects or possible publication bias. Specifically, smaller trials appeared more likely to report larger effect sizes, leading to an asymmetrical funnel shape (appendix p 67).

Discussion

This network meta-analysis included 109 RCTs and evaluated the effects of four single-domain and five multidomain lifestyle interventions compared with health education, active control, or no intervention. Our findings indicate that both single-domain interventions, particularly cognitive training and physical exercise, and selected multidomain approaches, such as the combination of physical exercise and cognitive training and diet, physical exercise, cognitive training, and health education, demonstrate significant cognitive benefits compared with no intervention or health education. Notably, physical exercise and cognitive training were consistently among the most efficacious interventions, demonstrating the largest effect sizes among all interventions when compared with the three controls, and irrespective of the age of the participant and the duration of the intervention. Among multidomain strategies,

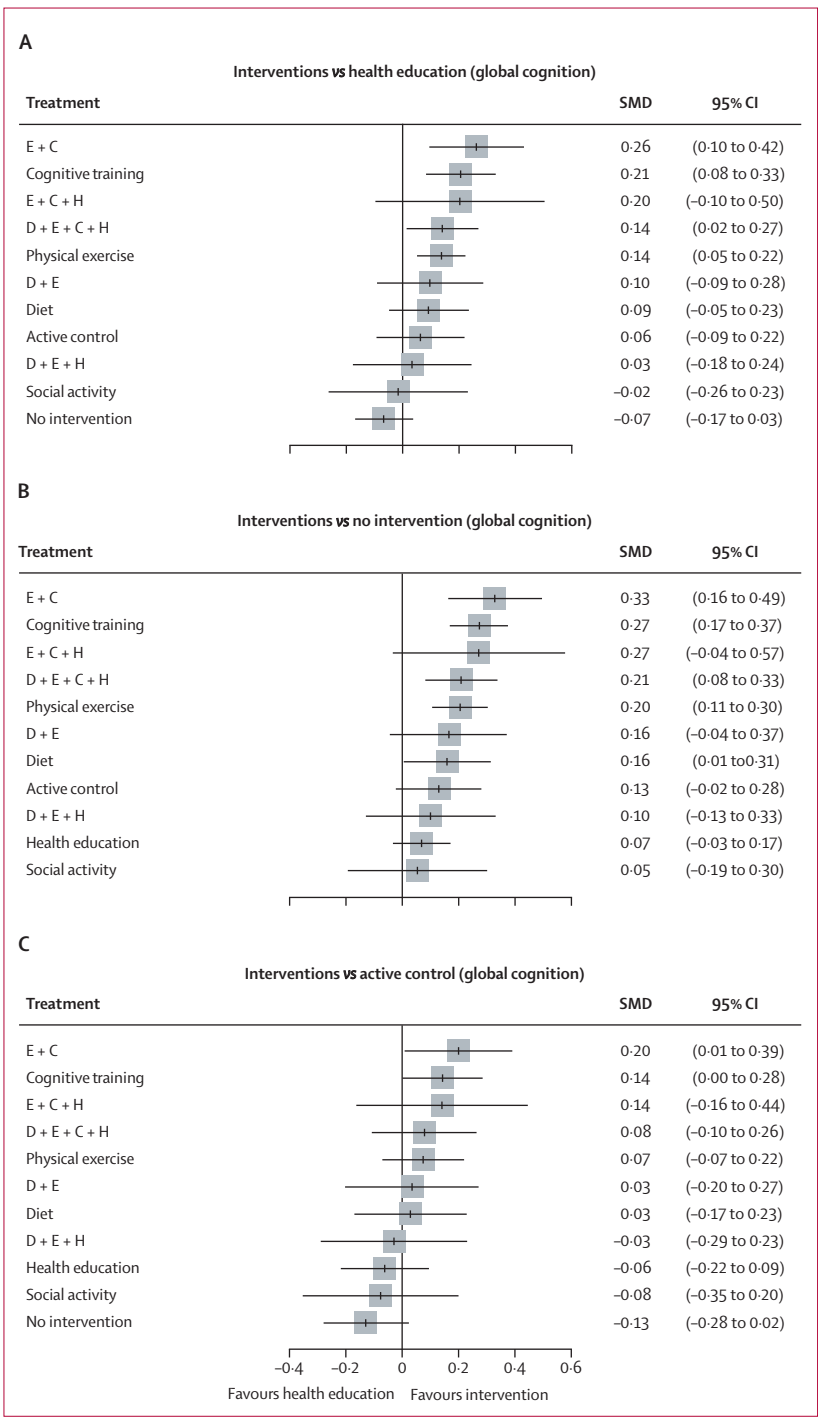

Figure 3: **Effect estimates for all interventions included in the network meta-analysis**
Treatment effects (95% CIs) compared with health education (A), no intervention (B), and active control (C). E + C: Physical exercise and cognitive training; E + C + H: Physical exercise, cognitive training, and health education; D + E + C + H: Diet, physical exercise, cognitive training, and health education; D + E: Diet and physical exercise; D + E + H: Diet, physical exercise, and health education. C=cognitive training. D=diet. E=physical exercise. H=health education. SMD=standardised mean difference.

more comprehensive protocols that included diet, exercise, cognitive training, and health education also showed beneficial effects; however, despite adding further interventions beyond physical exercise and cognitive training, they did not offer more efficacy. Subgroup analyses further suggested that younger participants (age <70 years) tended to derive greater cognitive benefits from standalone cognitive training, physical exercise, and health education in comparison with older participants. Moreover, most interventions consistently showed significant results when lasting longer than 3 months, apart from cognitive training, which demonstrated similar efficacy regardless of its duration. On the other hand, multidomain approaches involving more than three interventions, such as diet, physical exercise, cognitive training, and health education, seemed to be more efficacious when implemented for longer than 3 months. Taken together, these findings highlight the potential of both targeted single-domain and carefully designed multidomain interventions to support cognitive health in older adults who are cognitively unimpaired, while also underscoring the importance of considering factors such as age, intervention duration, and adherence when designing future prevention programmes.

These findings align with evidence from landmark multidomain prevention trials, such as the FINGER trial, which demonstrated that a structured multidomain intervention, combining diet, physical exercise, cognitive training, and vascular risk management, could effectively slow cognitive decline in older adults at risk of dementia.[13] Similarly, other trials showed modest cognitive benefits from multidomain interventions, such as MAPT, or no effects, as with Agewell.de.[14,15] Therefore, although modest by conventional standards, our effect sizes are similar to those reported in landmark trials and might still reflect meaningful benefits at the population level, particularly in light of the current absence of effective alternatives for dementia prevention in asymptomatic individuals. However, these trials share important methodological differences, mainly in intervention delivery,[16] and they did not directly compare different combinations of interventions or contrast single-domain and multidomain interventions within the same analytical framework. Hence, this network meta-analysis directly addresses this gap by generating a comparative hierarchy of interventions, leveraging both direct and indirect evidence across a broad set of interventions and control conditions. Importantly, our results suggest that certain targeted interventions, such as cognitive training and physical exercise, offer substantial cognitive benefits even when delivered as standalone interventions, whereas selected multidomain combinations, especially those combining physical exercise with cognitive training, showed similar or superior benefits to either interventions alone.[30] These findings highlight that more is not always better—adding additional interventions does not necessarily enhance efficacy and might introduce adherence challenges, particularly in multidomain protocols with more than three interventions.

The observation that multidomain interventions do not consistently outperform simpler and more targeted interventions could reflect the complex interplay between intervention intensity, adherence, and effectiveness.[13,14,16]

E + C	0·32 (−0·34 to 0·97)			0·14 (−0·03 to 0·30)			−0·11 (−0·50 to 0·29)			0·63 (0·08 to 1·19)	0·32 (−0·07 to 0·70)
0·06 (−0·12 to 0·23)	Cognitive training			0·08 (−0·30 to 0·46)			0·16 (−0·02 to 0·34)			0·16 (−0·08 to 0·39)	0·28 (0·16 to 0·40)
0·06 (−0·27 to 0·39)	0·00 (−0·31 to 0·31)	E + C + H					0·16 (−0·28 to 0·61)			0·26 (−0·15 to 0·68)	0·29 (−0·37 to 0·96)
0·12 (−0·07 to 0·31)	0·06 (−0·09 to 0·22)	0·06 (−0·26 to 0·38)	D + E + C + H							0·16 (0·00 to 0·33)	0·19 (0·02 to 0·35)
0·12 (−0·02 to 0·27)	0·07 (−0·05 to 0·19)	0·07 (−0·24 to 0·37)	0·00 (−0·13 to 0·14)	Physical exercise	−0·09 (−0·36 to 0·18)	0·05 (−0·22 to 0·32)	0·14 (−0·08 to 0·35)		0·28 (−0·07 to 0·62)	0·10 (0·00 to 0·20)	0·30 (0·16 to 0·44)
0·17 (−0·07 to 0·41)	0·11 (−0·11 to 0·33)	0·11 (−0·25 to 0·46)	0·04 (−0·18 to 0·27)	0·04 (−0·15 to 0·24)	D + E	0·14 (−0·13 to 0·41)				0·09 (−0·12 to 0·30)	
0·17 (−0·03 to 0·37)	0·11 (−0·06 to 0·29)	0·11 (−0·22 to 0·44)	0·05 (−0·13 to 0·23)	0·05 (−0·10 to 0·20)	0·00 (−0·21 to 0·22)	Diet				0·18 (0·01 to 0·35)	0·07 (−0·18 to 0·32)
0·20 (0·01 to 0·39)	0·14 (0·00 to 0·28)	0·14 (−0·16 to 0·44)	0·08 (−0·10 to 0·26)	0·07 (−0·07 to 0·22)	0·03 (−0·20 to 0·27)	0·03 (−0·17 to 0·23)	Active control				
0·23 (−0·03 to 0·49)	0·17 (−0·07 to 0·41)	0·17 (−0·20 to 0·53)	0·11 (−0·13 to 0·35)	0·10 (−0·12 to 0·33)	0·06 (−0·22 to 0·34)	0·06 (−0·19 to 0·31)	0·03 (−0·23 to 0·29)	D + E + H		0·02 (−0·19 to 0·24)	0·21 (−0·53 to 0·95)
0·28 (0·00 to 0·56)	0·22 (−0·04 to 0·48)	0·22 (−0·16 to 0·60)	0·16 (−0·11 to 0·42)	0·15 (−0·09 to 0·39)	0·11 (−0·19 to 0·42)	0·11 (−0·17 to 0·38)	0·08 (−0·20 to 0·35)	0·05 (−0·27 to 0·37)	Social activity	0·44 −0·04 to 0·93)	−0·13 (−0·54 to 0·27)
0·26 (0·10 to 0·42)	0·21 (0·08 to 0·33)	0·20 (−0·10 to 0·50)	0·14 (0·02 to 0·27)	0·14 (0·05 to 0·22)	0·10 (−0·09 to 0·28)	0·09 (−0·05 to 0·23)	0·06 (−0·09 to 0·22)	0·03 (−0·18 to 0·24)	−0·02 (−0·26 to 0·23)	Health education	−0·15 (−0·44 to 0·13)
0·33 (0·16 to 0·49)	0·27 (0·17 to 0·37)	0·27 (−0·04 to 0·57)	0·21 (0·08 to 0·33)	0·20 (0·11 to 0·30)	0·16 (−0·04 to 0·37)	0·16 (0·01 to 0·31)	0·13 (−0·02 to 0·28)	0·10 (−0·13 to 0·33)	0·05 (−0·19 to 0·30)	0·07 (−0·03 to 0·17)	No intervention

Figure 4: **Net league table of the network meta-analysis**

Each cell displays the effect size, presented as the SMD with 95% CI, for the respective treatment comparison. Treatments are ordered on the basis of their ranking, with higher-ranking treatments appearing further to the left. Positive SMD values indicate greater cognitive improvement for the treatment listed in the row (lower-left triangle) or column (upper-right triangle). Results from the network meta-analysis are shown in the lower-left half of the table (blue), and results from direct pairwise meta-analyses are shown in the upper-right half (red). For example, consider the cell in which E + C appears in the column and cognitive training in the row: a positive SMD indicates that E + C led to greater cognitive improvement than cognitive training based on network meta-analysis results (lower-left triangle). Conversely, if E + C is in the row and cognitive training in the column, a positive SMD reflects the advantage of E + C based on direct pairwise comparisons (upper-right triangle). The colour palette indicates the SMD between interventions. Lighter tones represent SMD values lower than 0·2, medium tones correspond to SMD values between 0·2 and 0·4, and darker tone indicates SMD values greater than 0·4. C=cognitive training. D=diet. E=physical exercise. H=health education. SMD=standardised mean difference.

In multidomain protocols, participants must simultaneously modify their behaviour across several domains, such as diet, physical activity, cognitive training, and vascular risk management. Although theoretically appealing, this behavioural burden might reduce long-term adherence, which is often heterogeneous across participants and intervention domains.[31,32] This finding aligns with broader research on lifestyle recommendations, which shows that the number of recommended behaviour changes within an intervention follows a curvilinear relationship with adherence and clinical outcomes, with moderate-complexity interventions yielding the greatest effects.[33] Drawing a parallel to multidomain interventions, it is possible that cognitive training embedded within a complex multidomain intervention could be less intensive, individualised, or tailored compared with standalone cognitive training, potentially reducing its effect size. Furthermore, evidence from the MAPT trial supports this non-linear dose–response relationship, showing that cognitive benefits plateaued after approximately half of the planned training sessions were completed, suggesting that increasing the number of sessions does not necessarily enhance cognitive outcomes.[34] From a biological perspective, several lifestyle interventions share overlapping mechanisms, such as promoting synaptic plasticity, modulating neurotrophic factors, and reducing neuroinflammation.[35–37] This mechanistic overlap might reduce the additive benefit of combining multiple interventions, especially if lifestyle interventions partially share the same biological pathways. As such, although multidomain approaches remain conceptually attractive, their success probably depends on the careful selection and integration of complementary interventions, tailored to individual needs, preferences, and baseline risk factors.[2,6] Future studies are needed to clarify which specific types, intensities, and combinations of lifestyle interventions are most effective in enhancing cognitive outcomes.

This study has several strengths that contribute to the growing body of evidence on dementia risk-reduction strategies for older adults who are cognitively unimpaired. First, the use of global cognition allows for a comprehensive evaluation of overall cognitive functioning across domains and reflects the diversity of measures commonly used in clinical practice and research, including

brief tools like the MMSE and MoCA.[16] Despite their limited sensitivity in cognitively unimpaired populations, these measures enhance ecological validity and real-world relevance, particularly for informing public health and dementia prevention programmes aimed at preserving broad cognitive resilience that supports independent living and quality of life.[6] However, the study also has important limitations. Risk of bias was moderate to high in many included studies, largely because of inadequate allocation concealment, absence of blinding, and incomplete adherence reporting, which highlight several methodological limitations when testing these interventions.[38,39] Moreover, our meta-analysis did not include follow-up data because of its limited availability, making it unclear whether the observed superiority of certain interventions is sustained over time. The results concerning intervention duration and participant age should be interpreted with caution, given that the subgroup analyses were done post-hoc. Publication bias was suggested in comparisons involving health education, with smaller studies showing larger effect sizes.[40] Although smaller trials contributed proportionally less to the overall estimates because of sample-size weighting, and sensitivity analyses produced results consistent with the main findings, this finding highlights the need for cautious interpretation of intervention rankings. These results also underscore the importance of preregistering future studies and ensuring higher methodological quality across trials testing lifestyle interventions. Lastly, the imbalance in sex distributions in some intervention groups might violate the assumption of transitivity and introduce bias into some comparisons (eg, physical exercise and cognitive training *vs* diet, physical exercise, cognitive training, and health education), even though we do not expect that lifestyle interventions have sex-specific effects on cognition.[41]

In summary, our study provides important insights into the implementation of lifestyle strategies for preserving global cognition in older adults who are cognitively unimpaired. However, future research should investigate how lifestyle interventions can be optimally combined and delivered, considering variations in intensity and duration, and tailored according to the characteristics of the target population, such as age, sex, cardiovascular health, and lifestyle preferences. An understanding of these dynamics will be crucial to the implementation of dementia prevention programmes and their real-word applicability.

Contributors

AJM, FR, SC, and GBF conceptualised the study. AJM and FR supervised the study. AJM, OS, GK, RM, GV, GR, UN, and SG-L independently screened abstracts and full-text articles for eligibility, extracted the data from the included studies, and conducted the risk-of-bias assessment. AJM analysed the data and wrote the original draft of the manuscript. All authors confirm that they had complete access to and verified all study data and accept full responsibility for the decision to submit this manuscript for publication.

Declaration of interests

GBF has received consulting fees through his institution from Biogen, Diadem, Roche, Eisai, Eli Lilly, Ac Immune, Novo Nordisk, Schwabe, Bromatech, AtonRâ, World Clinical Trials, and J&J Innovative Medicine. GBF has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events through his institution from Biogen, Roche, Novo Nordisk, GE HealthCare, and Vifor Pharma. All other authors declare no competing interests.

Data sharing

The dataset analysed in this study is available from the corresponding author upon reasonable request.

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