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REVIEW ARTICLE

A systematic review and network meta-analysis of interventions for subjective cognitive decline

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Abstract

Background: Subjective cognitive decline (SCD) is considered a risk factor for Alzheimer's disease (AD), highlighting the need for identifying and ranking effective interventions. This was addressed in a systematic review and network meta-analysis (NMA) of pharmacological and non-pharmacological interventions for SCD.

Methods: MEDLINE, Web of Science Core Collection, CENTRAL, and PsycINFO were searched for randomized controlled trials (RCTs) investigating effects on memory, global cognition, and quality of life. Random-effect model NMAs were conducted. The Cochrane Risk-of-Bias-2 tool assessed methodological quality. Prospero-Registration: CRD42020180457.

Results: The systematic review included 56 RCTs. Education programs were most effective for improving memory, second most effective for improving global cognition. Quality of life and adverse events could not be included due to insufficient data. Overall methodological quality of studies was low.

Conclusion: Education programs were most effective for improving memory and cognition, warranting further research into effective elements of this intervention. There is urgent need to address identified methodological shortcomings in SCD intervention research.

KEYWORDS
network meta-analysis, non-pharmacological interventions, pharmacological interventions, subjective cognitive decline, systematic review

1 | INTRODUCTION

Subjective cognitive decline (SCD) is defined as perceived cognitive decline in the absence of objective cognitive impairment.[1] Recently, substantial interest in SCD has emerged, reflecting its recognition as a potential early manifestation of Alzheimer's disease (AD).[2] SCD is associated with a 4.5-fold risk increase for subsequent diagnosis of mild cognitive impairment (MCI) due to AD, and a 6.5-fold increased risk for AD.[3] Individuals with SCD are also more likely to present with AD biomarkers (i.e., increased amyloid burden, neurodegeneration). Thus, identifying effective interventions that allow counteracting or slowing of disease progression at an early stage is of utmost importance.

Several pharmacological and non-pharmacological interventions are currently under investigation that aim to improve cognitive

functioning and psychological well-being in people with SCD.[4] A recent systematic review and meta-analysis that investigated the effectiveness of psychological, cognitive, lifestyle, or pharmacological interventions for SCD concluded that psychological group interventions can improve psychological well-being and that cognitive training interventions resulted in small, but statistically significant, improvement of cognitive performance.[5]

However, while conventional meta-analytical approaches can provide valuable information about the overall effectiveness of a particular treatment across included studies, comparisons of more than two interventions are not possible. This can be achieved by a network meta-analysis (NMA), which allows direct comparisons between all different interventions in the same model by considering direct (within studies) and indirect (between studies sharing a comparable intervention) evidence simultaneously.[6] It also allows establishing efficacy rankings of different interventions for specific outcomes, which is highly relevant for clinical decisions. However, this approach has not yet been used to characterize and rank the effectiveness of pharmacological and non-pharmacological treatments for SCD.

The aim of the present study was to (1) identify and describe all investigated interventions for individuals with SCD in a systematic review; (2) rate the overall research quality of these studies with a risk of bias judgment; (3) evaluate and compare the effectiveness of all investigated interventions on memory, global cognition, quality of life, and adverse events using network meta-analyses; and (4) generate clinically meaningful recommendation rankings for treatment decisions for SCD.

RESEARCH IN CONTEXT

1. **Systematic Review**: MEDLINE, Web of Science Core Collection, CENTRAL, and PsycINFO were searched for randomized controlled trials (RCTs) investigating effects of pharmacological and non-pharmacological interventions in subjective cognitive decline (SCD). Our search yielded 9298 search results and identified $n = 56$ eligible studies.
2. **Interpretation**: Our results confirm that interventions that improved cognition and memory in other populations, like physical activity interventions and cognitive training, were also effective in SCD. Surprisingly, the overall most effective intervention type was education programs. We also identified a lack on studies that investigated quality of life and adverse events, even though such participant-related outcomes are of utmost importance.
3. **Future directions**: SCD may provide a unique window for early interventions aimed at preventing cognitive decline before pathological impairment may manifest. Based on our results, future research on education programs as part of preventive care in SCD should be conducted, investigating participant-related outcomes with the use of proper statistical and reporting methods.

Highlights

- We conducted the first network meta-analysis investigating effectiveness of interventions for subjective cognitive decline (SCD).
- Overall, education programs were identified as most effective for improving memory and global cognition.
- Several methodological shortcomings in current SCD intervention research were identified that need to be addressed in future research.

2 | METHODS

The present systematic review and NMA was pre-registered and the review protocol can be accessed at www.crd.york.ac.uk/PROSPERO/ (ID: CRD42020180457). Reporting follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.[7] The "PRISMA for Abstracts Checklist" and the "PRISMA checklist for systematic reviews" are depicted in Tables S1 and S2 in supporting information. Confirming consent of subjects was not necessary.

2.1 | Systematic review

Systematic reviews of randomized controlled trials (RCTs) are generally considered the highest level of evidence for the relative effectiveness of interventions.[8] The following paragraphs detail the methods of the systematic review.

2.1.1 | Search and study selection

We conducted a systematic search in MEDLINE Ovid, Web of Science Core Collection, CENTRAL, and PsycINFO up to April 15, 2020. Reference lists of relevant reviews were searched for additional publications. Full-text publications were requested from the authors within a 2-week time frame, if not otherwise accessible. Tables S3-S6 in the supporting information provide additional information on the systematic review and search strings.

Titles and abstracts were screened according to predefined eligibility criteria by three individual review authors (MR, XH, SR) using the Covidence software (Veritas Health Innovation). Subsequently, full-text articles of studies meeting inclusion criteria were reviewed for inclusion in the systematic review. If no consensus could be reached between reviewers, cases were discussed until consensus was reached.

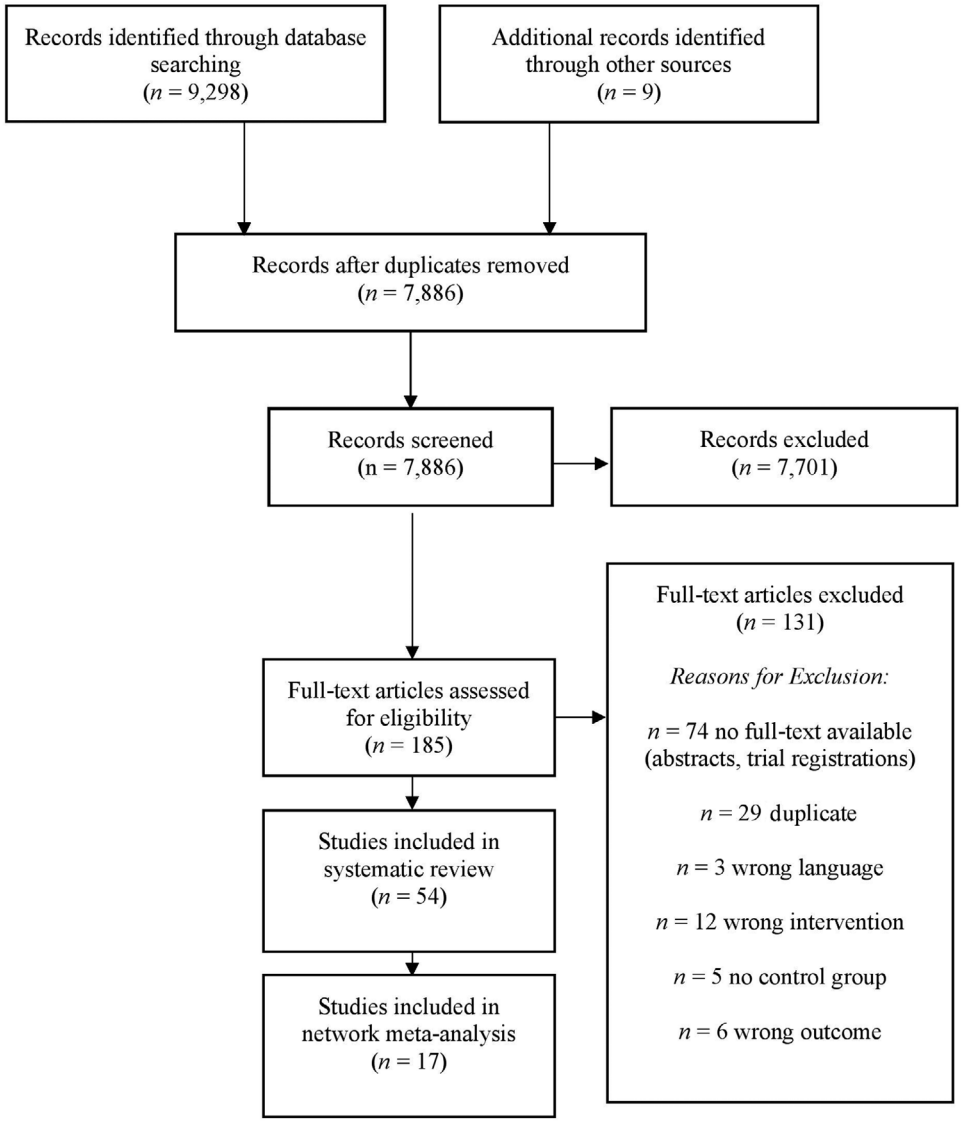


FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram of the study selection process

2.1.2 | Eligibility criteria

Studies were considered eligible if they had analyzed effects of interventions for SCD in RCTs in both female and male individuals of all ages. Both pharmacological and non-pharmacological interventions for SCD were included. We did not limit or pre-specify requirements and/or parameters of intervention types. SCD was defined as (1) self-perceived persistent decline in cognitive capacity relative to previous cognitive status, unrelated to an acute event, and (2) normal performance on standardized cognitive tests used to classify MCI adjusted for age, sex, and education.[9] During the initial search, we also included studies in which SCD was not clearly defined, for example, only labeled as "self-reported memory problems" without further specifications. Subsequently, SCD definitions were inspected and only those that had a current SCD definition were included in our main analysis. To confirm our results, a sensitivity analysis was conducted that also included studies without clear SCD definition (see section 3.7). Studies that had only included patients with MCI or dementia or patients with diagnosis of major psychiatric or medical diseases were excluded. We included studies published in English or German; only $n = 3$ studies in other languages were identified (see Figure 1).

Memory was defined as primary outcome, because it is one of the most vulnerable domains in aging,[10] one of the first domains subjectively affected in people with SCD,[1] and the core deficit in MCI and AD. Secondary outcomes were global cognition, quality of life, and adverse events. Only direct pre–post intervention outcome data were considered because only few studies reported long-term follow-up assessments.

2.1.3 | Data extraction

Three review authors (MR, XH, SR) extracted data using a standardized extraction form. If the authors were unable to reach a consen-

sus, a fourth review author (MM) was contacted for final decision. If required, the authors of specific studies were contacted for additional information.[11]

2.1.4 | Quality assessment

For each included study, risk of bias was assessed using the revised Cochrane risk-of-bias tool for randomized trials (RoB2 tool).[12] The tool implements signaling questions for five domains leading to low/high/medium concern for risk of bias. Two review authors (MR, SR) independently assessed risk of bias for each study. If they were unable to reach a consensus, a third review author (MM) was consulted for a final decision.

2.2 | Network meta-analyses

Network meta-analyses extend the principles of pairwise comparisons of meta-analyses to the evaluation of multiple treatments in a single analysis. This is achieved by combining direct and indirect evidence. Direct evidence refers to evidence obtained from RCTs in a trial comparing interventions A and B, indirect evidence refers to the evidence obtained through one or more common comparators (e.g., two studies sharing a comparable control condition[6]). Network meta-analyses rely on the same assumptions underlying pairwise meta-analysis, that is, the included studies are sufficiently homogenous in terms of the condition being studied, the included participants, and the definition of active and control interventions.[13] Additionally, an important precondition for the NMA is that all investigated interventions are linked via at least one direct comparison to the overall network.

2.2.1 | Main analyses

We performed a NMA using a random-effects model. To evaluate the extent to which treatments were connected, a network plot is provided for primary and secondary outcomes. For each comparison, the estimated treatment effect along with its 95% confidence interval (CI) is provided. We graphically present the results using forest plots, with either control group or placebo group as reference treatment. For studies with multiple treatment groups, we combined arms as long as they could be regarded as subtypes of the same intervention.[11] We used the R package *netmeta 1.0-1*[14] for statistical analyses. To evaluate the presence of statistical heterogeneity and inconsistency within the resulting networks, we used the generalized heterogeneity Q total and the generalized Iš statistic.[15] We interpreted Iš values as follows:[16] 0% to 40% might not be important, 30% to 60% may represent moderate heterogeneity, 50% to 90% may represent substantial heterogeneity, 75% to 100% represents considerable heterogeneity. Appendix A in the supporting information provides additional details of the statistical methods used, including assessment of heterogeneity.

2.2.2 | Sensitivity analysis

Sensitivity analyses were conducted to test the robustness of our results by analyzing studies with low and medium risk of bias only (primary analyses; i.e., that only included studies with proper SCD definition). A sensitivity analysis is a repeat of the primary analysis, substituting alternative decisions or ranges of values for decisions that were arbitrary or unclear.[17] We judged studies as high risk if two risk of bias domains are judged as high risk. Additional sensitivity analyses were conducted including all studies, regardless of their SCD definition. Results of these analyses are reported in supporting information.

3 | RESULTS

3.1 | Results of the search

Our initial search yielded $n = 9298$ studies. $N = 9$ studies were identified through other sources. After removal of duplicates, $n = 7889$ were screened. After abstract review, $n = 185$ full-text articles were assessed for eligibility; $n = 54$ studies on different interventions with participants with SCD were included. $N = 17$ studies could be included in the network meta-analyses. For an overview of the study selection process, see the PRISMA flow diagram in Figure 1. References of the included study are listed in supporting information.

3.2 | Systematic review: characteristics of the included studies

A total of 4692 participants with SCD from $n = 54$ different studies were included in the systematic review, investigating all possible SCD interventions. Studies included interventions using educational programs, memory techniques, cognitive training, meditation, physical exercise, nutritional supplements, pharmaceutical interventions, and non-invasive brain stimulation. An in-depth overview can be found in Table 1 and Appendix B in the supporting information.

3.3 | NMA: primary outcome: memory

A total of $N = 21$ studies provided data on memory outcomes; however, only $n = 11$ studies used a sufficient SCD definition and were therefore included in the analyses,[18–28] leading to 17 pairwise comparisons and 6 different treatments in the NMA (see Figure 2 for the network graph on memory). Several interventions could not be included (e.g., all pharmacological studies, repetitive transcranial brain stimulation, and stretching) because they did not use and/or report current criteria for SCD. Two studies that assessed effects of matured hop bitter acids (MHBA) and whey peptide treatment provided sufficient data, but could not be integrated in the network as they were not linked to the network.[29,30] As the NMA in Figure 3 shows, education

TABLE 1 Study and sample characteristics

Study	Participants									Outcomes					
	n[1]	Age (M, SD)	Sex female (in %)	Education (in years)	SCD definition	I 1	12	13	I4	Global cognition	Memory	QoL	Adverse events	Others	FU
Andrewes et al., 1996	40; 20; 20	n.a.; age range for recruitment 60–70	50.00	n.a.	Subjective memory complaints; MDRS >123	Techniques for face-name and prospective memory	First letter mnemonic, method of loci, narrative story method				x				4m
Ban et al., 2018	75; 30; 30; 15	53.66 (5.44); 54.5 (4.9); 52.3 (5.6); 54.7 (5.9)	86.70; 86.70 86.70 86.70	14.62; 14,3; 15.2; 14.2	Subjective cognitive complaints with no clinical impairments; MMSE >24 or CDR <0.5	Nutritional supplement Tremella fuciformis 600mg/d, 8 weeks	Nutritional supplement Tremella fuciformis 1200 mg/d for 8 weeks	Placebo capsule			x			X	
Barnes et al., 2013	126; 32; 31; 31; 32; Total dropout: 26	73,42 (6.00); 74.8 (6.3); 71.1 (5.5); 73.8 (5.7); 73.9 (6.1)	62.70; 62.50; 67.70; 58.10; 62.50	16.35; 16.7; 15.6; 16.8; 16.3	Subjective cognitive complaint; exclusion: dementia (self-report, physician diagnosis or TICS-M <17)	mental activity, 60 min/d, 3 days/wk for 12 weeks (6 weeks visual tasks, 6 weeks auditory tasks) + exercise, 60 min/d, 3 days/wk for 12 weeks (10 min warm-up, 30 min aerobic, 5 min cool-down, 10 min strength training, 5 minutes stretching)	mental activity control (educational lectures + MC questions) + exercise, 60 min/d, 3 days/wk for 12 weeks (10 warm-up, 30 aerobic, 5 cool-down, 10 strength training, 5 minutes stretching)	mental activity, 60 min/d, 3 days/week for 12 weeks (6 weeks visual tasks, 6 weeks auditory tasks) + exercise control (10 min warm-up, 30 min stretching and toning, 10 minutes strength, 10 minutes relaxation)	mental activity control (educational lectures + MC questions) + exercise control (10 min warm-up, 30 min stretching and toning, 10 min strength, 10 min relaxation)	X	x		X	X	

(Continues)

TABLE 1 (Continued)

Study	Participants					Outcomes									
	n[1]	Age (M, SD)	Sex female (in %)	Education (in years)	SCD definition	I 1	12	13	I4	Global cognition	Memory	QoL	Adverse events	Others	FU
Beck et al., 2016	61; 31; 30	77.3 (4.47); 57.5 (4.6); 57.1 (4.4)	48.39; 60.00	n.a.	Normal laboratory parameters, PRMQ (one item answered with "rather often", "very often", or five with "sometimes")	240 mg EGB 761 ® (Ginkgo) daily in the morning, 56±4 days	Placebo				x				
Ben-Itzhak et al., 2008	26	73.8 (1.2)	65.38	13.2	Subjective memory complaint; MMSE > 23; exclusion: dementia diagnosis	Single dose 20 mg methylphenida	Cross-over placebo				x			X	
Boa Sorte Silva, Gill, Owen et al., 2018[7]	127; 63; 64	67.45 (7.32); 67.6 (7.5); 67.4 (7.2)	70.86; 69.80; 71.90	13.55; 13.3; 13.8	Subjective cognitive complaint; IADL 8/8; MMSE > 24; exclusion: dementia, MDD	Multiple modality & mind-motor training (M4) exercise 60 min/d, 3 d a week for 24 weeks	Multiple modality training (M2) exercise 60 min/d, 3 d a week for 24 weeks			x	x			X	7m
Boa Sorte Silva, Gill, Gregory et al., 2018[7]	109;57;	67.4 (7.2); 67.6 (7.5)	71.9; 69.8	13.8 (3); 13.3 (2.7)	Subjective cognitive complaint; IADL 8/8; MMSE > 24; exclusion: dementia, MDD	Multiple modality & mind-motor training (M4) exercise 60 min/d, 3 d a week for 24 weeks	Multiple modality training (M2) exercise 60 min/d, 3 d a week for 24 weeks			x				X	

(Continues)

TABLE 1 (Continued)

Study	Participants									Outcomes						
	n[1]	Age (M, SD)	Sex female (in %)	Education (in years)	SCD definition	I 1	12	13	I4	Global cognition	Memory	QoL	Adverse events	Others	FU
Brautigam et al., 1998	241; 77; 82; 82 Drop-out: 44; 15; 14; 15	68.95 (7.77); 69.45 (7.18); 68.60 (8.28); 68.83 (7.86)	59.34; 59.74; 60.98; 57.32	n.a.	Subjective cognitive complaints; MMSE > 19; BDI < 20; Exclusion: memory loss of known origin	Ginkgo extract, 1.9 ml 3 times a day for 24 weeks	Ginkgo extract, 1.9 ml (1:1 diluted with placebo) 3 times a day for 24 weeks	Placebo			x		x	X	
Chan et al., 2017	48; 26; 22	68.96 (5.86); 69.50 (6.89); 68.34 (4.42)	75.00; 80.77 68.18	9.21; 8.69; 9.82	CMSS > 2; CGDS-SF < 8; BAI < 16; CDRS > 111	Memory Intervention (Troyer et al., 2008), 90 min/session, once a week for 10 weeks	Dejian Mind-Body Intervention, 90 min/session once a week for 10 weeks				x			X	18m (Chan et al., 2018)
Chan et al., 2018 [follow up to Chan et al. (2017)]	29; 18; 11	68.79 (6.15); 68.6 (6.8); 69.1 (5.2)	75.86: 77.78; 72.73	9.08; 8.70; 9.70	Chinese memory symptoms scale > 2; CGDS-SF < 8; BAI < 16; CDRS > 111	Memory Intervention (Troyer et al., 2008), 90 min/session, once a week for 10 weeks	Dejian Mind-Body Intervention, 90 min/session once a week for 10 weeks				x				
Cheng et al., 2018	93; 47; 46	73.90 (7.40)	81,00	6.20 (4.70)	Memory Inventory for the Chinese > 2	Integrated Attention Training Program (IATP)	Health-related education program			x	x			X	6m
Çinar & Şahiner, 2020	120; 30; 30; 30; 30	69.99 (9.48); 68.3 (10.94); 66.5 (9.79); 70.85 (7.78); 74.3 (7.56)	55.83; 66.67; 56.67; 46.67; 53.33	11.08; 11.57; 13.27; 11.63; 7.83	SCI: subjective cognitive decline without objective manifestation; AD: definded by NINCDS-ADRDA criteria	SCI control group	SCI/BEYNEX: 15-20 min physical and cognitive exercise daily. Used for at least 1200 min.	AD control group: Rivastigmin patch	AD/BEYNEX: 15-20 minute physical and cognitive exercise daily. Used for at least 1200 min.+ Rivastigmine patch	x	x			X	

(Continues)

TABLE 1 (Continued)

Study	Participants					Intervention				Outcomes					
	n[1]	Age (M, SD)	Sex female (in %)	Education (in years)	SCD definition	I 1	12	13	I4	Global cognition	Memory	QoL	Adverse events	Others	FU
Cohen-Mansfield et al., 2015	44; 15; 15; 14	73.49 (5.18); 72.80 (3.78); 74.44 (5.78); 73.21 (5.97)	72.7; 60.0; 86.7; 71.4	14.82; 14.25; 14.50; 16.00;	Subjective memory decline; MMSE >23	ACTIVE (cognitive training) for 10 weeks	Health promotion for 10 weeks	Participant-centered intervention for 10 weeks		x		x			
Epperson et al., 2011	16 baseline; 12 completed both arms	54.0 (2.8)	100	16.4	Subjective cognitive decline; MMSE > 26	Atomoxetin 80 mg/d, 6 weeks	Placebo controlled cross-over design				x			X	
Frankenmolen et al., 2018	60; 31; 29	67.07 (7.54); 66.2 (7.3); 68.0 (7.8)	48.43; 32.00; 66.00	ISCED: 4.6; 4.5; 4.7	Subjective cognitive decline without objective manifestation; IADL	Adapted version of the memory strategy training (MST) protocol of Koning-Haanstra et al. (1990): seven group sessions a 90 minutes, homework during the week between sessions	COGPACK attention and memory tasks.				x	x		X	6m
Fukuda et al., 2020	57; 27; 30	55.0 (5.3); 54.6 (5.4); 55.4 (5.3)	52.6; 51.9; 53.3	14.6; 14.5; 14.7	EMC: 3 revised questions	Matured hop bitter acids (12 weeks, 35 mg/d)	Placebo				x				

(Continues)

TABLE 1 (Continued)

Study	Participants									Outcomes					
	n[1]	Age (M, SD)	Sex female (in %)	Education (in years)	SCD definition	I 1	12	13	I4	Global cognition	Memory	QoL	Adverse events	Others	FU
Heath et al., 2017	63; 32; 31	67.0 (7.5); 65.7 (6.6); 68.3 (8.1)	74; 74; 75	14.2 (2.8); 14.0 (2.7); 14.2 (2.8)	MoCA; IADL >6; MMSE >24	Multiple modality & mind-motor training (M4) exercise 60 min/d, 3 d a week for 24 weeks	Multiple modality training (M2) exercise 60 min/d, 3 d a week for 24 weeks			x					
Hong et al., 2020	56; 23; 15; 18	65.88 (5.15); 66.22 (5.73); 65.40 (4.82); 65.83 (4.89)	76.78; 73.9; 93,3; 66,7	11.37 (3.66); 10.43 (3.72); 11.20 (3.97); 12.72 (3.05)	Guideline by Jessen et al. (2014)	Multi-domain cognitive training in small groups, twice a week with 90 minutes per session	Education Program, weekly phone calls as a reminder				x				
Hoogenhout et al., 2012	50; 24; 26	66.05 (4.32); 66.00 (4.23); 66.10 (4.48)	100; 100; 100	Eight-point scale: 4.07 (1.94); 4.14 (2.03); 4.00 (1.90)	Self-reported subjective cognitive decline; MMSE >24	Educational group intervention including eight 1.5-hour sessions over 4 weeks and homework	Waiting list				x	x			1 w
Hooper et al., 2017	183; 98; 85	75.94 (4.55); 75.9 (4.7); 76.0 (4.4)	65.59; 69.4; 61.2	No. of persons reaching university level: 38; 24; 14	No dementia: limitation in one or more IADL, or gait speed slower 0.8 m/s	n-3-PUFA (800 mg DHA, 225 mg EPA) supplementation, daily for three years	Placebo			x					

(Continues)

TABLE 1 (Continued)

Study	Participants									Outcomes					
	n[1]	Age (M, SD)	Sex female (in %)	Education (in years)	SCD definition	I 1	12	13	I4	Global cognition	Memory	QoL	Adverse events	Others	FU
Hsieh et al., 2019	24; 7; 17	68.3 (6.4); 66.0 (4.23); 67.5 (7.3)	79.2; 71.2; 82.4	11.2; 10.6; 11.6	CDR = 0; AD8 < 2; 4 CERAD questions	Physical fitness training, hand-eye coordination, meditation, 1 hour for each modality, twice a week for 16 weeks	Same intervention, different population (non-SMC)			x	x				
Innes et al., 2018[2,3]	53; 25; 28	60.47 (1.17); 60.71 (1.38); 60.2 (1.63)	86.79; 92.00 96.43	≥ 12 years: 81.13%; 88.00%; 75.00%	Guideline by Abdulrab and Heun (2008), Jessen et al. (2010), Jessen et al. (2014), & Reisberg et al. (2008)	Kirtan Kriya Meditation, 12 min/d, 12 weeks	Music listening					x			3 m
Innes et al., 2016[2,3]	60 (drop-out: 7); 30; 30	60.58 (1.01); 60.93 (1.56); 60.23 (1.32)	86.79; 90.00; 96.67	15.43; 16.17; 14.7	Guideline by Abdulrab and Heun (2008), Jessen et al. (2010), Jessen et al. (2014), & Reisberg et al. (2008)	Kirtan Kriya Meditation, 12 min/d, 12 weeks	Music listening					x			3 m
Jeon et al., 2016	75; 30; 30; 15	53.76 (5.72); 53.4 (6.4); 54.2 (5.4); 53.6 (5.2)	76.02; 76.7; 76.7; 73.3	14.7; 14.5; 15.0; 14.7	GDS ≥2; exclusion: MCI or AD	Ganglioside 660 μg/d for 8 weeks	Ganglioside 330μg/d for 8 weeks	Placebo					x		
Kita et al., 2018	98; 48; 50	52.04 (4.76); 52.3 (4.3); 51.8 (5.2)	85.16; 87.4; 83.0;	14.3; 14.5; 14.1	HDS-R ≤20	Whey peptide 1 g/d for 12 weeks	Placebo			x			x		
Kwok et al., 2013	223; 111; 112	75.40 (5.81); 75.42 (5.82); 75.38 (5.83)	85.2; 87.4; 83.0	Secondary educa-tion; 21.1%; 18.9%; 23,2%	CMSS ≥3; Chinese MMSE ≥ 20	1.5 h cognitive training once a week for 12 weeks	Health-related educational lectures				x				9 m

(Continues)

TABLE 1 (Continued)

Study	Participants									Outcomes					
	n[1]	Age (M, SD)	Sex female (in %)	Education (in years)	SCD definition	I 1	12	13	I4	Global cognition	Memory	QoL	Adverse events	Others	FU
Kwon et al., 2015	75; 30; 30; 15	40.16 (11.76); 42.5 (11.2); 37.6 (11.7); 40.6 (12.7)	52.5; 56.7; 60.0; 26.7	100% high school or higher	GDS = 2; ≥1 symptoms of subjective memory impairment; CDR < 0,5; MMSE ≥25	Herbal mixture 1200 mg/d for 8 weeks	Herbal mixture 600 mg/d for 8 weeks	Placebo			x		x		
Latorre Postigo et al., 2010	45; 15; 15; 15	66.9 (3.14); 67.8 (2.85); 65.73 (3.36); 67.4 (2.99)	64.44; 73.3; 66.7; 53.3	Percentag of persons with secondary education: 8.9; 13.3; 6.7; 6.7	MEC >27; GDS <19; "yes" to ≥2 questions by Montejo et al. (1999)	Group memory training 10 times twice a week for 90 min	Wait list (control)	Health education (placebo)			x				6 m
Lautenschlager et al., 2008	170; 85; 85	68.65 (8.58); 68.6 (8.7); 68.7 (8.5)	50.6; 49.4; 51.8	12.35; 12.1; 12.6	MMSE ≥24; CDR < 1; able to walk for 6 minutes; no dementia diagnosis; "yes" to "Do you feel like your memory is getting worse?"	Physical activity + behavioural intervention	Education and usual care			x	x	x	x	x	6, 12 & 18 m
Macpherson et al., 2012	56; 28; 28	71.1 (4.59); 71.9 (4.81); 70.3 (4.3)	100; 100; 100	12.0; 11.9; 12.0	MMSE ≥ 24; screening by Jorm et al. (1997); "yes" to "Do you feel like your memory is getting worse?"	Multivitamin supplementation (Swisse Women's Ultivite 50+ TM) once daily for 16 weeks	Placebo				x				

(Continues)

TABLE 1 (Continued)

Study	Participants									Outcomes					
	n[1]	Age (M, SD)	Sex female (in %)	Education (in years)	SCD definition	I 1	12	13	I4	Global cognition	Memory	QoL	Adverse events	Others	FU
Manenti et al., 2017	22; 11; 11	74.5 (5.9); 75.9 (7.1); 73.1 (4.7)	63.64; 63.64; 63.64	9.9; 9.6; 10.3	MMSE ≥ 27; normal[4] objective memory and cognitive performance; EMQ score > 1 SD above mean score of health older adults	Anodal transcranial current stimulation left lateral prefrontal cortex; 15 minutes; 1.5 mA	Sham stimulation				x				30 d
McEwen et al., 2018	55; 26; 29	66.16 (4.2); 67.0 (5.1); 65.4 (3.0)	65.5; 73.1	n.a.	MoCA ≥ 23; MEM-Q-24	Memory training + exercise (simultaneously)	Memory training + excercise (sequentially)				x	x			
McNamara et al., 2018	76; 17; 19; 20; 20	67.96 (4.65); 69.0 (5.2); 68.0 (3.9); 68 (4.7); 67 (4.9)	53.9; 41.2; 57.9; 65.0; 50.0	15.3; 15.6; 15.0; 16.1; 14.7	CDR = 0; MoCA > 25 or normative CVLT	Fish oil (1.6 mg EPA, 0.8 mg DHA) daily for 24 weeks	25 g blue berry powder daily for 24 weeks	Fish oil + blue berry powder daily for 24 weeks	Placebo		x		x		6 m
Middleton et al., 2018	126; 32; 31; 31; 32	73.4 (6.0); 74.8 (6.1); 73.8 (5.7); 71.1 (5.5); 73.9 (6.3)	65.0; 62.5; 58.1; 67.7; 62.5	16.4 (2.4); 16.7 (2.2); 16.8 (2.3); 15.6 (2.8); 16.3 (2.1)	Self-reported subjective cognitive decline;	Aerobic exercise 60 min a day, 3 days a week for 12 weeks + computer-based cognitive training 30 min a day, 3 times a week for 12 weeks	Computer-based cognitive training 30 min a day, 3 times a week for 12 weeks + stretching/toning	Aerobic exercise 60 min a day, 3 days a week for 12 weeks + educational DVDs	Stretching/tor + educational DVDs			x			

(Continues)

TABLE 1 (Continued)

Study	Participants									Outcomes					
	n[1]	Age (M, SD)	Sex female (in %)	Education (in years)	SCD definition	I 1	12	13	I4	Global cognition	Memory	QoL	Adverse events	Others	FU
Oh et al., 2018	53; 18; 19; 16	59.3 (5.0); 59.28 (5.1); 58.78 (5.0); 59.94 (5.2)	52.8; 50.0; 52.6; 56.3	13.94; 14.22; 14.16; 13.38	Subjective cognitive decline measured by the subjective memory complaints questionnaire	Smartphone-based brain Anti-aging and memory Reinforce-ment Training (SMART), 15-20 min/d, 5 d/week for 8 weeks	Fit Brains ® (other cognitive training app), 15-20 min/d, 5 d/week for 8 weeks	Wait-list			x				
Pereira-Morales et al., 2018	40; 17; 12; 11	64.5 (4.8); 69.3 (4.8); 65.6 (7.2)	90.00; 13.30 09.09 10.00	10.5 (4.1); 13.2 (3.1); 13.3 (3.2)	Subjective cognitive decline measured by the subjective memory complaints questionnaire	Integrated Psychostim-ulation Program, 8w, 90 minutes/day, 4 days/week	Computerized Cognitive Training, w, 90 minutes/day, 4 days/week	Control Group		x	x			x	
Pike et al., 2018	150; SCD: 53	73.8 (8.3)	56.00	14.5 (4.2)	Level of SMD was determined using the self-report Memory Assessment Clinics Ques-tionnaire.	Semantic Association	Spaced Retrival	Control group		x	x			x	
Schwarz et al., 2018[5]	28; 14; 14	69.0 (6.0); 70.0 (5.0)	64.28; 64.28 64.28	15.0 (2.0); 16.0 (4.0)	Subjective cognitive decline	Placebo Group	Spermidine Group						x	x	
Scogin et al., 1985	47; 20; 27	n.a.	n.a.	n.a.	Memory complaints were assessed by the Metamemory Question-naire	Memory Training	Control Group				x			x	

(Continues)

TABLE 1 (Continued)

Study	Participants									Outcomes					
	n[1]	Age (M, SD)	Sex female (in %)	Education (in years)	SCD definition	I 1	12	13	I4	Global cognition	Memory	QoL	Adverse events	Others	FU
Small et al., 2006	17; 8; 9	54.0 (12.0); 53.0 (10.0)	63.0; 67.0	18.0 (3.0); 17.0 (4.0)	All subjects had mild age-related memory complaints measured by Memory Functioning Question-naire (MFQ)	Health Lifestyle Program	Control Group				x				
Smart et al., 2016	38; SCD: 15	69.60 (3.58)	72.72	16.40 (2.69)	"Are you concerned or worried that you are experiencing significant decline in your thinking abilities, more than just normal aging?" In response to the question, "Have you ever been diagnosed with a psychological condition, such as depression or anxiety?" (yes/no),	Mindfulness Training	Psychoeducat			x				x	
Solé-Padullés et al., 2006	39; 20; 19	66.95 (9.43); 68.68 (7.78)	66.66; 53.84	n.a.	Memory complaints	rTMS	Control Group				x				

(Continues)

TABLE 1 (Continued)

Study	Participants									Outcomes					
	n[1]	Age (M, SD)	Sex female (in %)	Education (in years)	SCD definition	I 1	12	13	I4	Global cognition	Memory	QoL	Adverse events	Others	FU
Stoynova et al., 2019	26	68.96 (6.02)	53.84	n.a.	Memory complaints	Transcranial direct current stimulation; pre-session, 12 training sessions (three per week for 4 weeks), a post-session 4 days	Control Group				x				3m
Tabue-Teguo et al., 2018	1464, non-frail: 799	74.41 (4.00)	63.70	n.a.	Reporting subjective memory complaints, but free from clinical dementia.	Cognitive Training with polyunsatu-rated fatty acids	Polyunsaturat fatty acids	Cognitive Training	Placebo	x	x				
Tsai et al., 2008	25; 14; 11	69.44; 68.71; 70.36	n.a.	n.a.	Self-reported memory complaints	Cognitive Training	Cognitive Stimulation			x	x				
Valentijn et al., 2005	149; 39; 40; 38	68.56 (7.43); 69.32 (7.77); 68.07 (6.58); 68.30 (8.03)	70.0; 63.0; 63.0	3.81 (2.00); 3.83 (1.96); 3.74 (1.84); 3.86 (2.24)[6]	Self-reported subjective memory complaints	Memory Training (individual)	Memory Training (collective)	Control Group			x			x	4m
van Hooren et al., 2007	69; 37; 30	62.76 (5.62); 62.35 (5.39); 63.27 (5.95)	82.00; 83.00	3.66 (1.86); 3.57 (1.76); 3.77 (2.01)[6]	Self-reported memory complaints	Goal Management Training, 6w	Control Group			x				x	

(Continues)

TABLE 1 (Continued)

Study	Participants									Outcomes					
	n[1]	Age (M, SD)	Sex female (in %)	Education (in years)	SCD definition	I 1	12	13	I4	Global cognition	Memory	QoL	Adverse events	Others	FU
Wahjoepramono et al., 2016	44; 22; cross over	n.a.	Only male participants	n.a.	Self-reported memory complaints	Testosterone Treatment, 24 weeks	Placebo Group			x	x			x	
Watson et al., 2019	41; 25; 16	60.88 (5.79); 59.56 (5.69)	56.00; 69.00	n.a.	Self-reported memory complaints	Liraglutide treatment, 12 weeks	Placebo Group				x			x	
Wirth et al., 2018[5]	28; 14; 14	69.90 (5.33); 70.4 (5.2); 69.4 (5.6)	64.28; 64.28; 64.28;	15.65 (2.85); 16.0 (3.70); 15.3 (1.70)	Presence of subjective cognitive complaints for at least 6 months and self-reported associated concerns (worries)	Spermidine Treatment	Placebo Group				x				
Youn et al., 2019	201; 112; 89	69.57 (4.89); 69.93 (5.10); 69.11 (4.60)	57.14; 67.42	10.10 (3.72); 10.01 (3.89); 10.09 (3.52)	The diagnosis of SMC took place through a questionnaire validated for the Korean population consisting of 14 items with dichotomous "yes" or "no" answers and a cut-off value of >5	Multi-strategic memory training of 10 weekly 90-minutes sessions,	Control Group			x	x			x	

(Continues)

TABLE 1 (Continued)

Study	Participants									Outcomes					
	n[1]	Age (M, SD)	Sex female (in %)	Education (in years)	SCD definition	I 1	12	13	I4	Global cognition	Memory	QoL	Adverse events	Others	FU
Youn et al., 2011	32; 16; 16	68.88 (4.00); 68.75 (4.60); 69.00 (3.45)	62.50; 56.25	9.88 (2.82); 10.19 (3.19); 09.56 (2.45)	Subjective memory complaints	Multi-strategic memory training of 10 weekly 90-min sessions	Control Group			x	x			x	
Zhu et al., 2016	98; 47; 51	66.57 (10.51); 69.68 (9.52); 64.03 (10.73)	68.40; 70.20 66.70	n.a.	Subjective hypomne-sis/forgetfulne loss (SML) and subjective atten-tion/concentra deficits (SAD), were screened using a self-administered 5-point scale (1 = no symptoms or occasional slight symptoms complaints; 2 = slight/mild symptom complaints; 3 = moderate severe symptom complaints; 4 = severe symptom complaints; 5 = very severe symptom complaints)	BrainPower Advanced Capsule Treatment	Placebo Group				x			x	

(Continues)

TABLE 1 (Continued)

Study	Participants									Outcomes					
	n[1]	Age (M, SD)	Sex female (in %)	Education (in years)	SCD definition	I 1	12	13	I4	Global cognition	Memory	QoL	Adverse events	Others	FU
Zuniga et al., 2016	179	n.a.	n.a.	n.a.	Self-perceived memory complaints	Walking Group, 12m	Flexiblity, Toning, and Balance				x	x		x	

Abbreviations: AD, Alzheimer's disease; AD8, Ascertainment of Dementia 8; ADRDA, Alzheimer's Disease and Related Disorders Association; BAI, Beck's Anxiety Inventory; BDI, Beck's Depression Inventory; CDR, Clinical Dementia Rating; CDRS, Chinese Dementia Rating Scale; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; CGDS-SF, short form Chinese Geriatric Depression Scale; CMSS, Chinese Memory Symptoms Scale; CVLT, California Verbal Learning Test; d, days; DHA, docosahexaenoic acid; EMC, Everyday Memory Checklist; EMQ, Everyday Memory Questionnaire; EPA, eicosapentaenoic acid; GDS, Global Deterioration Scale; HDS-R, Hierarchic Dementia Scale Revised; I, intervention; IADL, Instrumental Activities of Daily Living; m, month; MDD, major depressive disorder; MDRS, Mattis Dementia Rating Scale; MCI, mild cognitive impairment; MEC, Mini-Examen Cognoscitivo (Spanish version of the Mini-Mental State Examination); MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; PRMQ, prospective and retrospective memory questionnaire; QoL, quality of life; rTMS, repetitive transcranial magnetic stimulation; SCD, subjective cognitive decline; SMD, standardized mean difference; TICS-M, modified Telephone Interview for Cognitive Status; w, week

[1] n total in study, n for I1, n for I2 and so on.

[2] Inclusion criteria contained MCI, but the results only report subjects with SCD.

[3] Probably the same sample.

[4] Based on the information provided it remained unclear which test was used (Memory Function Questionnaire or Subjective Memory Questionnaire)

[5] Probably the same sample as Schwarz et al.

[6] Education was measured with a scale rather than in years of education.

[7] Probably the same sample

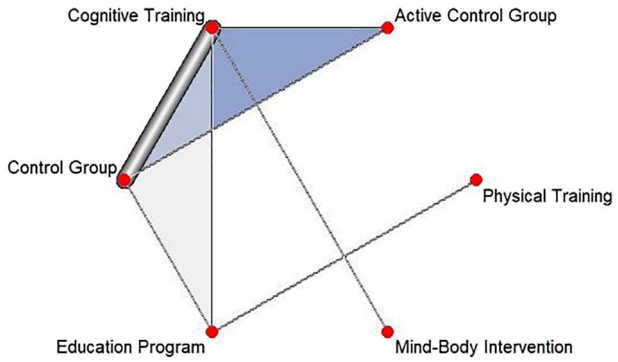


FIGURE 2 Network of analyzed comparisons for the outcome memory. Each circle corresponds to a regimen included in the analysis. Each line represents direct comparisons between these regimens, with the thickness of the line corresponding to the number of available direct within-trial comparisons. Regimens are described in the supporting information. Blue shaded regions correspond to studies with multiple comparisons

programs (standardized mean difference [SMD]: 2.64, 95% CI: 1.17 to 4.10), physical training (SMD: 2.71, 95% CI: 0.03 to 5.38), and cognitive training (SMD: 1.24, 95% CI: 0.27 to 2.21) were significantly superior to the control group. P-score ranking displays education programs as the optimal treatment regarding improvement of memory, followed by physical training and cognitive training. The P-scores measure the degree of certainty that one treatment is better than another treatment, averaged over all competing treatments.[31,32]

Regarding heterogeneity, Iš was 51% in the analysis, with 95% CI ranging from 0% to 82%, indicating a moderate heterogeneity,[16] Tauš was 0.70, 95% CI from 0.0 to 37.56. Figure S1 in the supporting information shows the assessment of inconsistencies between direct and indirect comparisons.

To assess publication bias, a comparison-adjusted funnel plot was conducted,[33] demonstrating no asymmetry in the present data (Egger's test $P = .31$; see also funnel plot, Figure 4).

3.4 | Secondary outcome: global cognition

We included $n = 5$ studies in the analysis,[19,21,23,28,34] with seven pairwise comparisons of $n = 4$ treatments (cognitive training, education program, physical training, control group). The network graph is depicted in Figure S2 in the supporting information. As the NMA in Figure 5 shows, cognitive training (SMD: 1.32, 95% CI: −4.11 to 6.76) was superior to the control group, even though not significantly. P-score ranking displays cognitive training as the optimal treatment regarding improvement in global cognition, followed by the control group. Education programs (SMD: −10.85, 95% CI: −18.42 to −3.28) and physical trainings (SMD: −12.14, 95% CI: −23.79 to −0.49) perform worse than the control group.

Heterogeneity was considerable with Iš = 77% (95% CI: 25% to 93%) and Tauš = 52.87 (95% CI: 0.00 to 455.39). Figure S3 in the supporting information shows the assessment of inconsistencies between direct and indirect comparisons.

3.5 | Secondary outcomes: quality of life and adverse events

No overall statement was possible for both outcomes due to the fact that the data were too heterogeneous and measurements took place at different assessment time points.

3.6 | Risk of bias in included studies

Risk of bias assessment of the included studies is illustrated in Table 2. The overall risk of bias in the included studies is rated as low risk in $n = 2$ studies and high risk in $n = 12$ studies, leaving $n = 42$ studies with a medium overall risk of bias. Most studies showed a medium or high risk of bias in the domain "Risk of bias in selection of the reported results," as they did not include a preregistration or clinical trial registration number.

3.7 | Sensitivity analyses

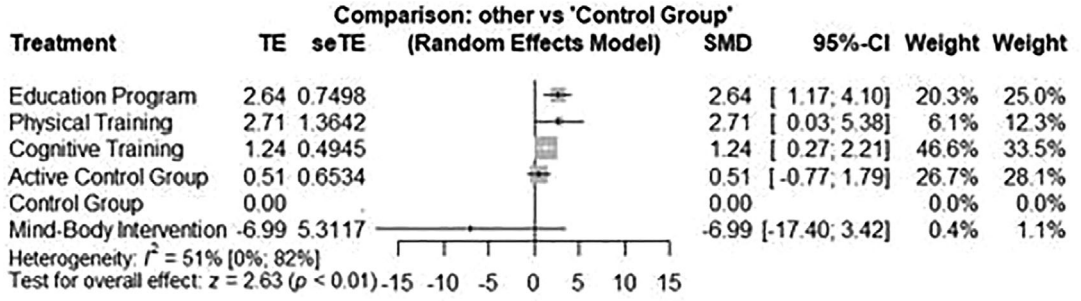
Sensitivity analyses including all studies with sufficient data regardless of whether the study provided an adequate SCD definition were conducted for all outcomes (Figures S4-S9 in the supporting information). This analysis also included pharmacological and other interventions that could not be included in the primary analysis.

Regarding memory, $n = 21$ studies were included with 41 pairwise comparisons of $n = 15$ treatments. Education programs were still rated as the most effective treatment program (SMD: 2.57, 95% CI: 1.50 to 3.65), followed by testosterone treatment (SMD: 2.45, 95% CI: −0.33 to 5.24; even though results of this study have to be interpreted carefully as only male participants were included and the study had a crossover design) and repetitive transcranial magnetic stimulation (SMD: 2.23, 95% CI: −0.26 to 4.72). Liraglutide treatment (a medication that was originally used to treat diabetes and obesity; SMD: −1.22, 95% CI: −4.18 to 1.75) and mind–body interventions (SMD: −6.71, 95% CI: −17.06 to 3.65) were less effective than the control group.

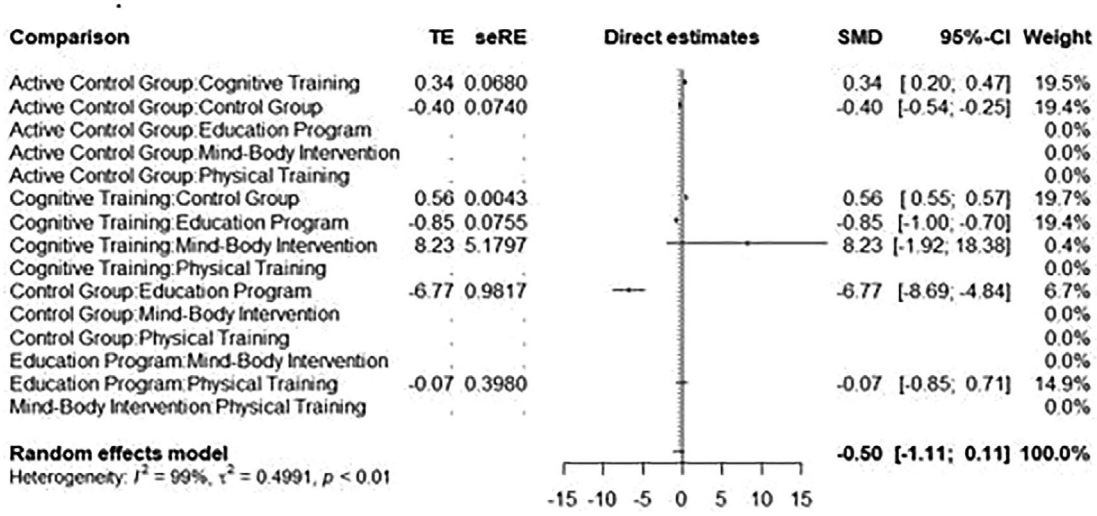
The ranking of treatments for global cognition was largely consistent with the main analyses. Cognitive stimulation (SMD: 2.31, 95% CI: −0.89 to 5.52), testosterone treatment (SMD: 1.30, 95% CI : −2.10 to 4.70), and cognitive training plus polyunsaturated fatty acid treatment (SMD: 1.29, 95% CI : −1.74 to 4.33) were the most effective; education programs (SMD: −3.63, 95% CI : −5.98 to −1.28) and physical training (SMD: −4.29, 95% CI: −8.3 to −1.49) were less effective than the control group.

In the network analysis investigating quality of life, $n = 5$ studies were included, including $n = 5$ treatments (cognitive training, education program, physical training, active control group, control group) in seven pairwise comparisons. The active control group was ranked as most

(A) Network Analysis of the outcome memory.



(B) Direct Comparisons of the treatments for memory.



(C) Indirect Comparisons of the treatments for memory.

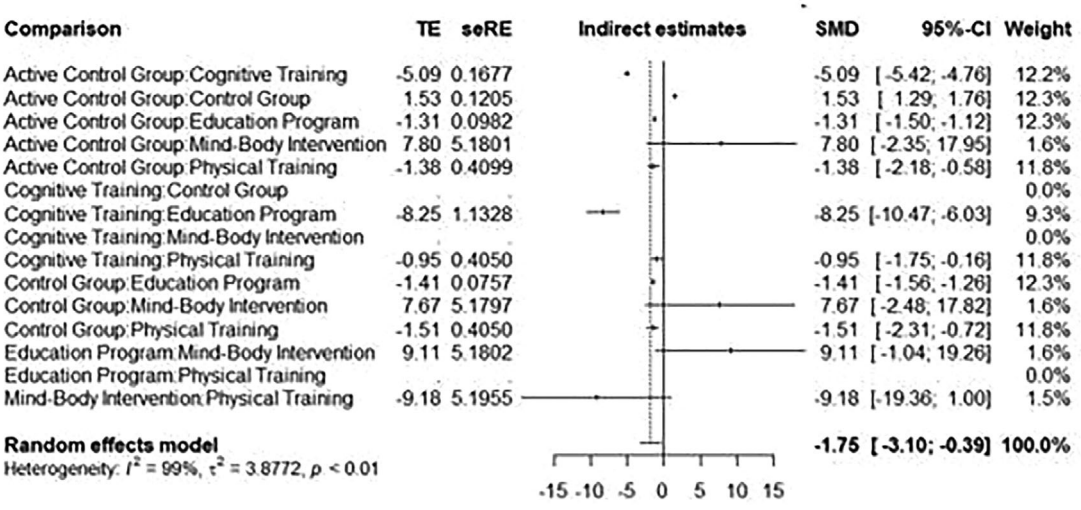


FIGURE 3 Network meta-analysis for the outcome memory. A, Network analysis of the pooled data of five treatments compared to each other and the control group reporting memory. Treatments were ranked through P-scores. The education program (standardized mean difference [SMD]: 2.64, 95% confidence interval [CI]: 1.17 to 4.10), physical training (SMD: 2.71, 95% CI : 0.03 to 5.38), and cognitive training (SMD: 1.24, 95% CI : 0.27 to 2.21) were significantly superior to the control group. B, Meta-analysis of direct comparisons for memory. C, Meta-analysis of indirect comparisons for memory. seRE, standard error of regression estimate; seTE, standard error of treatment estimate; TE, estimate of treatment effect

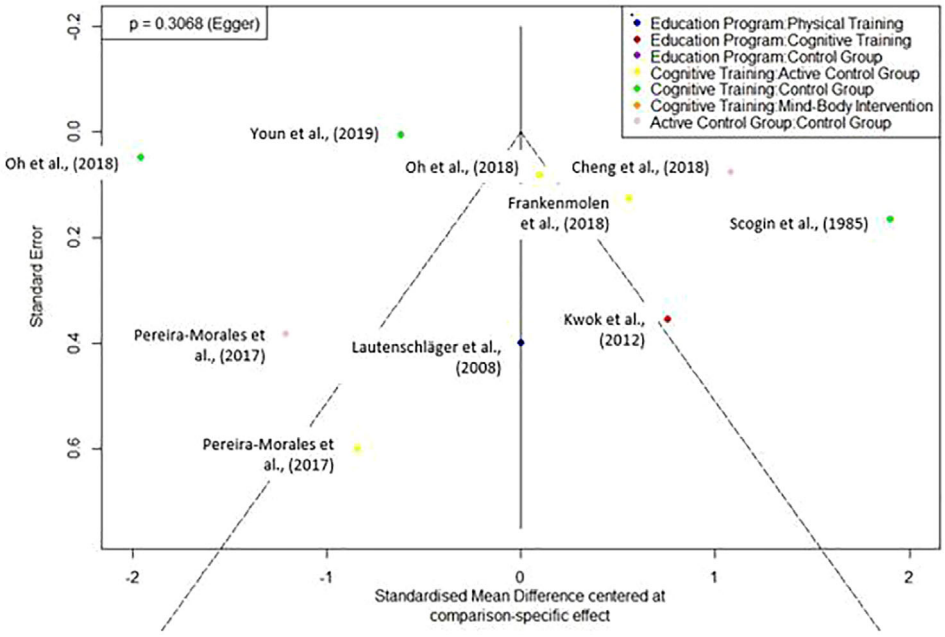


FIGURE 4 Funnel plot for studies comparing interventions on memory. A comparison-adjusted funnel plot for the different treatment comparisons for the outcome memory. Egger's regression test for funnel plot asymmetry was not significant ($P = 0.31$)

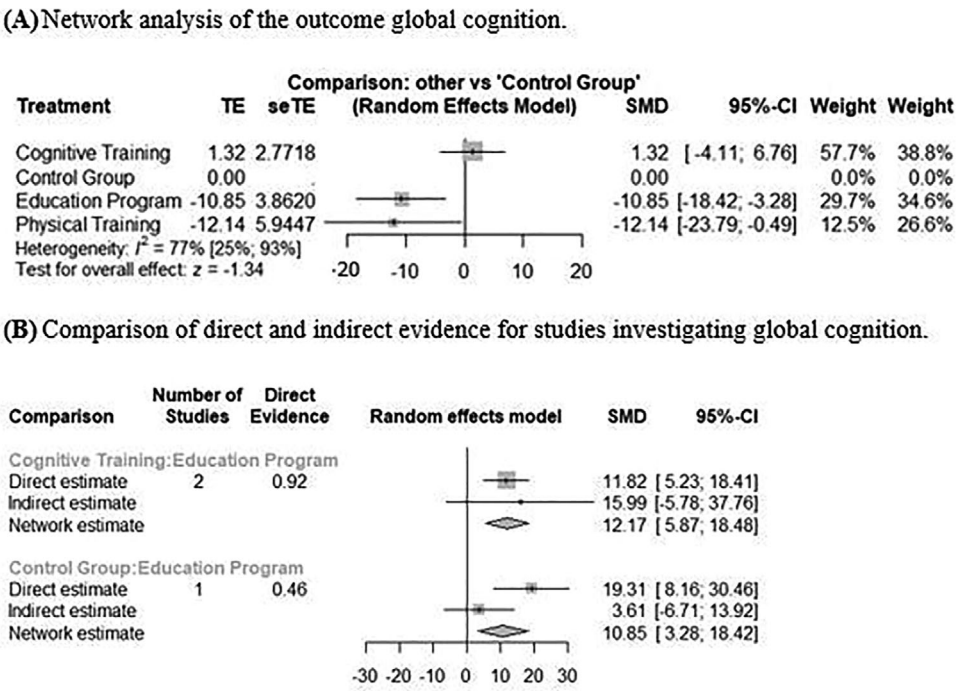


FIGURE 5 Network analyses of the secondary outcome global cognition. A, Network analysis of the pooled data of four treatments compared to each other and the control group reporting global cognition. Treatments were ranked through P-scores. B, Meta-analysis of direct and indirect comparisons for global cognition. CI, confidence interval; seTE, standard error of treatment assessment; SMD, standardized mean difference; TE, estimate of treatment effect

successful in improving quality of life in participants with SCD (SMD: 3.62, 95% CI : −2.72 to 9.96), followed by cognitive training (SMD: 2.01, 95% CI : −1.93 to 5.95) and physical training (SMD: 0.76, 95% CI: −5.08 to 6.60). Education programs were ranked as less effective than the control group (SMD: 0.00, 95% CI: −3.31 to 3.32).

We performed an additional sensitivity analysis including only studies with low and medium risk of bias and an adequate SCD definition. Only $n = 2$ studies had to be excluded from the analyses due to low-rated study quality;[23,34] results are displayed in Figure S10A-C in the supporting information.

TABLE 2 Risk of bias assessment for included studies

	Domain 1: RoB arising from the randomization process	Domain 2: RoB due to deviations from the intended interventions	Domain 3: Missing outcome data	Domain 4: RoB in measurement of the outcome	Domain 5: RoB in selection of the reported results	Overall RoB
Andrewes et al. (1996)	Some concerns	High	Low	Low	Some concerns	High
Ban et al. (2018)	Some concerns	Low	Low	Low	Some concerns	High
Barnes et al. (2013)	Low	Low	Low	Low	Some concerns	Some concerns
Beck et al., (2016)	Low	Low	Low	Low	Some concerns	Some concerns
Ben-Itzah et al., (2008)	Some concerns	Low	Low	Low	Some concerns	Some concerns
Boa Sorte Silva, Gill, Owen et al., (2018)	Low	Low	Low	Low	Some concerns	Some concerns
Boa Sorte Silva, Gill, Gregory et al., (2018)	Low	Low	Low	Low	Some concerns	Some concerns
Brautigam et al. (1998)	Some concerns	Low	Low	Low	Some concerns	Some concerns
Chan et al., (2017)	Some concerns	Low	Low	Low	Some concerns	Some concerns
Cheng et al. (2018)	Low	Low	High	Low	Some concerns	High
Cinar & Sahiner, (2020)	Some concerns	Low	High	Low	Some concerns	High
Cohen-Mansfield et al., (2015)	Some concerns	Low	Low	Low	Some concerns	Some concerns
Epperson et al., (2011)	Low	Low	Low	Low	Some concerns	Some concerns
Frankenmolen et al., (2018)	Low	Low	Low	Low	Some concerns	Some concerns
Fukoda et al., (2020)	Low	Low	Low	Low	Some concerns	Some concerns
Heath et al., (2016)	Some concerns	Low	Low	Low	Some concerns	Some concerns
Hong et al., (2020)	Some concerns	Low	Low	Low	Low	Some concerns
Hoogenhout et al., (2012)	Low	Low	Low	Low	Some concerns	Some concerns
Hooper et al., (2017)	Low	Low	Low	Low	Some concerns	High
Hsieh et al., (2019)	Some concerns	Low	Low	Low	Some concerns	Some concerns
Innes et al., (2018)	Low	Low	Low	Low	Some concerns	Some concerns
Innes et al., (2016)	Low	Low	Low	Low	Some concerns	Some concerns
Jeon et al., (2016)	Low	Low	Low	Low	Some concerns	Some concerns
Kita et al., (2018)	Low	Low	Low	Low	Low	Low
Kwok et al., (2012)	Some concerns	Low	Low	Low	Some concerns	Some concerns
Kwon et al., (2015)	Low	Low	Low	Low	Some concerns	Some concerns
Latorre Postigo et al., (2013)	Low	Low	Low	Low	Some concerns	Some concerns
Lautenschlager et al., (2008)	Low	High	Low	Low	Some concerns	High
Macpherson et al., (2012)	Low	Low	Low	Low	Some concerns	Some concerns
Manenti et al., (2017)	Some concerns	High	Low	Low	Some concerns	High
McEwen et al., (2018)	High	Low	Low	Low	Some concerns	High
McNamara et al., (2018)	Low	High	Low	Low	High	High
Middleton et al., (2018)	Low	Low	Low	Low	Some concerns	Some concerns
Oh et al., (2018)	Low	Low	Low	Low	Some concerns	Some concerns
Pereira-Morales et al., (2018)	Low	Low	Low	Low	Some concerns	Some concerns
Pike et al., (2018)	Some concerns	Low	Low	Low	Some concerns	Some concerns
Schwarz et al., (2018)	Low	Low	Low	Low	Some concerns	Some concerns
Scogin et al., (1985)	Low	Low	Low	Low	Some concerns	Some concerns
Small et al., (2006)	Low	Low	Low	Low	Some concerns	Some concerns
Smart et al., (2016)	Low	Low	Low	Low	Some concerns	Some concerns

(Continues)

TABLE 2 (Continued)

	Domain 1: RoB arising from the randomization process	Domain 2: RoB due to deviations from the intended interventions	Domain 3: Missing outcome data	Domain 4: RoB in measurement of the outcome	Domain 5: RoB in selection of the reported results	Overall RoB
Solé-Padullés et al., (2006)						
Stoynova et al., (2019)						
Tabue-Teguo et al., (2018)						
Tsai et al., (2008)						
Valentijn et al., (2005)						
Van Hooren et al., (2007)						
Wahjoepramono et al., (2016)						
Watson et al., (2019)						
Wirth et al., (2018)						
Youn et al., (2011)						
Youn et al., (2019)						
Zhu et al., (2016)						
Zuniga et al., (2016)						

Note. Red color indicates a high risk of bias, yellow color indicates a medium risk of bias, green color indicates a low risk of bias, assessed with the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2).
Abbreviations: RoB, Risk of Bias.

4 | DISCUSSION

To the best of our knowledge, this is the first NMA that investigated the effectiveness of pharmacological and non-pharmacological interventions for SCD while using the most recent reporting standards in the field. We identified 56 eligible studies that had included 4692 participants. A total of 16 different interventions were investigated in these studies. $N = 17$ studies that had used proper SCD criteria were included in the network meta-analyses. Overall risk of bias in these studies was medium to high, indicating overall low quality of evidence in this field. With regard to our primary outcome measure, education programs, physical interventions and cognitive trainings were the most effective interventions for improving memory performance in SCD. Cognitive training was most effective in improving global cognition, followed by education programs. Due to a high heterogeneity in the included studies and a lack of sufficient data, effects on quality of life and adverse events could not be assessed. Results of the sensitivity analyses that included all studies regardless of their SCD definition were largely consistent with the primary analysis and revealed additional information on the potential effectiveness of pharmacological and other interventions that could not be included in the main analysis due to a lack of proper SCD definition. Specifically, education programs were still ranked as most effective for improving memory in SCD, followed by testosterone treatment and repetitive transcranial magnetic stimulation. Liraglutide treatment and mind–body interventions were less effective than passive control groups.

Regarding our primary outcome (memory), education programs were identified as the most effective intervention for people with SCD in both our main and sensitivity analyses. Importantly, these programs provided the participants with information about different healthy lifestyle strategies associated with lowering the risk of dementia (e.g., dietary modification, relaxation techniques), but also mnemonic strategies.[19,21–23,27] The current study was not designed to identify the specific active components underlying the superior effectiveness of these education programs. Tentatively, however, it is conceivable that making available several potential interventions to the participants and providing additional information and guidelines may have increased self-efficacy and motivation to address the self-perceived cognitive impairment.[27]

Physical interventions were ranked as the second most effective treatment to improve memory performance in SCD. This finding is in line with evidence from epidemiological, cross-sectional, and neuroimaging studies showing that moderate-intensity physical exercise can be beneficial to cognitive health, including memory, even though evidence from RCTs is still mixed.[35] Exercise-induced molecular cascades, which affect neural plasticity, may play an import role in explaining the effects of physical interventions on cognition and especially memory by promoting brain vascularization, hippocampal neurogenesis, and other neuro-functional changes.[36,37] These beneficial physiological effects on brain function are likely responsible for the observed improvement of memory function in SCD, which are in line with those reported previously in other populations.

Cognitive training was ranked as the third most effective intervention for improving memory functions in SCD and also most effective for improving global cognition. The latter result is largely consistent with previous meta-analytic studies on non-pharmacological

interventions for SCD. For example, Smart et al.[4] demonstrated that such interventions improved cognitive outcomes with a small effect size and those were more pronounced compared to other intervention types. However, because cognitive training usually targets specific cognitive domains and transfer effects are often limited to closely related tasks,[38,39] effects are likely stronger for measures of global cognition compared to memory.

Of all the reviewed studies that were initially considered eligible in the systematic review, the majority (37 of 54) had to be excluded from the NMA due to the lack a proper SCD definition, a problem that earlier reviews had also discussed,[4] resulting in a total of $n = 17$ studies that were included in the present NMA.

Definitions in these studies ranged from asking a single question (e.g., "Do you have the feeling that your memory gets worse?") to only assuming that participants have SCD (e.g., advertising a study for adults with SCD but never asking if they feel that their memory gets worse). It is important to acknowledge that many of the included studies were published before SCD was formally defined in the literature[9] and until today, variations of these criteria have been used.[40] Clear definitions and diagnostic criteria are of utmost importance to ensure comparability among studies. In the present review and NMA, we therefore decided to only include studies that adhered to the currently most widely used definition of SCD. Nonetheless, it is important to note that the results of the sensitivity analysis that included all studies were largely consistent with those reported in the main analysis. Heterogeneity assessment for our primary outcome memory shows moderate heterogeneity, which is expected when comparing different interventions in a NMA. The outcome global cognition, however, showed substantial heterogeneity (Iš = 77%). Yet, results of our sensitivity analyses that included only studies with low or medium risk of bias decreased this heterogeneity, without affecting the effectiveness rankings of the interventions. For further details on the sensitivity analyses and results, please see Appendix A and Figure S10 in the supporting information.

Unsurprisingly, interventions that have been shown to be effective for improving memory and cognition in MCI and AD (e.g., cognitive or physical training) are also effective for individuals with SCD. However, our results also demonstrate for the first time that education programs, which are often used as a control rather than experimental group, are overall most effective in individuals with SCD. Therefore, future research into these programs is warranted to identify the key elements by which these programs improve memory and cognitive functions in this particular population.

The present systematic review and NMA also identified several important shortcomings in this field: Data on patient-related outcomes like quality of life, depression, anxiety, and adverse events were often not assessed and/or reported. This is rather surprising because these outcomes are highly relevant in a population that has no objective cognitive impairment but suffers from insecurity and the fear of cognitive decline. Future research should include these participant-related outcomes to assess if specific interventions are suited to improve quality of life and psychological well-being in individuals with SCD. Moreover, overall risk of bias judgment of the investigated studies was rather poor and most of the studies were rated as moderate and high risk of bias. In most instances, this was because studies were not pre-registered and/or pre-registration was not clearly stated in the paper. To increase transparency and to reduce the possibility of publication bias, pre-registration of studies is strongly encouraged for future studies.

This is the first systematic review and NMA investigating all possible pharmacological and non-pharmacological interventions for SCD. Identifying suitable intervention options is of utmost importance because these interventions may not only improve participants' memory and global cognition, but also help in improving quality of life and overall well-being. It is highlighted that more research on the effective elements of education programs, which were ranked as most effective for improving memory in our NMA, is required. Our analysis also identifies a number of limitations in current SCD intervention research that need to be addressed in the future, including use of proper SCD definitions, improvement of trial quality, and inclusion of patient-related outcomes.

5 | CONCLUSIONS

SCD may provide a unique window for early interventions aimed at preventing cognitive decline before pathological impairment may manifest or even to prevent progression to dementia. The current review and NMA shows that education programs, physical interventions, and cognitive training were most effective for improving memory in participants with SCD and that cognitive training was most effective in improving global cognition. We also identified a lack of studies that investigated quality of life and adverse events, even though such participant-related outcomes are of utmost importance in individuals with subjectively perceived cognitive impairment. These outcomes need to receive more attention in future research. Frequently, current research did not use proper SCD definitions and several shortcomings were identified, including lack of study pre-registration and low methodological transparency.

In sum, our findings suggest that education programs as part of preventive care in SCD have potential to empower individuals to take proactive steps in support of their own cognitive and emotional well-being, which in turn may decrease future burdens on healthcare systems. Important shortcomings in SCD intervention research were identified that need to be addressed in future studies.

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CONFLICTS OF INTEREST

Agnes Flöel is co-author of one of the reviewed studies (Wirth et al.); however, she was not involved in data extraction and quality assessment of this particular study to avoid a potential conflict of interest. All other authors do not have any conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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