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The Role of Physical Exercise in Cognitive Preservation: A Systematic Review

Abstract: *Dementia, or major neurocognitive disorder, is one of the most common causes of disability and dependency in older adults with far-reaching social, physical, and economic impacts. In the absence of adequate treatment, much research has been directed towards prevention. Physical exercise has been shown to increase cerebral blood flow, amplify production of neurotrophic factors, and enhance brain volume. Whether these changes on a structural and cellular level result in cognitive preservation is less clear. This systematic review synthesizes findings from seventeen randomized controlled trials that examine the effects of physical activity on global cognition, memory, and executive function in older adults. Cognitive benefits of exercise are strongest for those who are cognitively intact or with mild cognitive impairment. In studies with long-term follow up, cognitive gains tended to decay after cessation of physical intervention suggesting that sustained physical exercise may be required to preserve cognitive function in older adults prior to onset of dementia.*

Keywords: exercise; activity; dementia; cognition; preservation

Introduction

Major neurocognitive disorder, or dementia, is characterized by progressive deterioration of cognitive function beyond what is considered a normal part of the aging process. In addition to memory, dementia can irreversibly impact behavior, language, learning ability, and comprehension and it remains 1 of the biggest threats to independence and identity. There are several different types of dementia, with Alzheimer's disease (AD) accounting for greater than 60% of cases.[1] As the world's population continues to age, the prevalence of dementia is expected to grow. The World Health Organization predicts that nearly 82 million people worldwide will be living with dementia by 2030.[2] This number does not include people living with mild cognitive impairment (MCI), which is characterized by cognitive deficits that do not yet interfere with daily functioning or independence.[3] Those with MCI are 6.7 times more likely to progress to Alzheimer's disease than those without cognitive impairment.[4]

> "Physical fitness and cognitive gains were associated with increases in regional brain volume or blood flow in some studies."

As there is currently no cure or reversal agent for dementia, there is increased interest in strategies to prevent cognitive decline and halt disease progression. Physical exercise, particularly

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multicomponent aerobic exercise and strength training, is one of the most heavily researched and promoted lifestyle interventions to improve general health and longevity. Regular physical exercise for healthy adults is defined in the Physical Activity Guidelines issued by the U.S. Department of Health and Human Services as 150 minutes of moderate-intensity aerobic exercise in addition to at least 2 days of strength training per week.[2] Regular physical exercise has been shown to lower risk of heart disease, stroke, hypertension, and type II diabetes mellitus, all of which are modifiable risk factors for dementia.

There are several different mechanisms by which aerobic and strength training exercise may influence brain health. In this review, we define the term "physical exercise" and "exercise" to include both aerobic and strength training exercise regimens overall, unless specified otherwise. By increasing cardiac output, physical exercise raises cerebral blood flow which, if repeated on a regular basis, can positively impact neural function, and reduce oxidative stress.[5] Physical Exercise also increases production of several trophic factors, including brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), and insulin-like growth factor (IGF-1), leading to amplified neuroplasticity and angiogenesis. In addition, cellular senescence, or cell cycle arrest, is a key process that results in vascular endothelial dysfunction and contributes to many age-related diseases.[6] As compared to a sedentary lifestyle, habitual aerobic exercise prevents endothelial cell senescence, reduces oxidative and inflammatory responses, and protects the vascular endothelium, all of which contribute to healthy aging.[6] Self-reported aerobic exercise has specifically been shown to reverse the impact of *APOE* status on amyloid deposition in middle age to older adults.[7]

In addition to molecular and biochemical enhancements, aerobic exercise can impact brain structure. In a randomized controlled trial by Colcombe et al, brain volumes were compared between healthy elderly volunteers who participated in either a 6-month aerobic exercise regimen or stretching program. MRI imaging pre- and post-intervention showed significantly increased brain volume in both pre-frontal and temporal cortices in the aerobic exercise group. Both areas mediate higher order cognitive functions and are affected in age-related cognitive decline.[1] The intervention group experienced average reductions in risk of brain volume loss of 42.1%, 33.7%, 27.2%, and 27.3% in the anterior cingulate cortex, right superior temporal gyrus, right middle frontal gyrus, and anterior white matter tracts of the corpus callosum as compared to non-aerobic controls. In another randomized controlled trial, Erickson found a 2% increase ($P < .001$) in bilateral anterior hippocampal volume of cognitively intact adults (mean age 67.6) who participated in 1-year of moderate-intensity exercise. This is compared to a 1.4% decline in hippocampal volume in the stretching control group (mean age 65.5) over the same period of time.[8] Although passive stretching does not improve brain health, stretching exercises that incorporate dynamic and postural movements with meditative practices (i.e.,. Tai chi and yoga) have also been shown to positively impact brain structure.[9-12] Whether these changes on a cellular and structural level have a clinically meaningful effect on cognition is less clear. The primary objective of this review is to synthesize current data that examines the benefits of physical activity on brain health and prevention of cognitive decline.

Methods

Search Strategy

A systematic review was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. We identified all literature related to clinical outcomes of aerobic and strength training exercise or physical activity on cognition for individuals with different levels of cognition. We analyzed studies ranging from cognitively intact individuals to those with moderate cognitive impairment and a diagnosis of dementia that were published between January 2000 and March 2023. Two reviewers (P.D. and M.K.) independently conducted global searches in March 2023 using the following databases: PubMed, Google Scholar, and EMBASE. A search using the following MeSH terms of "cognitive impairment" or "Alzheimer's disease" or "dementia" AND specific intervention ("physical activity" or "exercise") was conducted to evaluate the literature base. Inclusion criteria consisted of randomized control studies written in or translated into English that evaluated the impact aerobics or strength training exercise and physical activity has on either cognitively intact participants or those with mild to moderate cognitive impairments. Exclusion criteria involved non–English language studies, studies without a proper control group of usual activity, and those that included confounding variables such as supplemental mental training or nutritional supplements (i.e., omega-3s). Additionally, articles studying those with severe dementia or with interventions less than 12 weeks in duration were excluded. After the literature search and application of inclusion/exclusion criteria, all articles selected for inclusion were cross-referenced to ensure no studies were overlooked during the

initial search. The references of chosen articles were also reviewed for pertinent studies.

Study Selection and Quality Assessment

Studies were included if they were randomized controlled trials (RCT) published after January, 2000, had a sample population that was either cognitively intact, with MCI, or mild to moderate dementia and included at least 1 exercise intervention that lasted 3 months (12 weeks) or longer. Studies with sample populations diagnosed with severe cognitive impairment or with underlying psychiatric conditions were excluded to minimize confounding factors, as these have been reviewed elsewhere.[13] The Cochrane Risk of Bias Tool was used to assess the quality and risks of bias of studies identified in the investigation. The Cochrane Risk of Bias Tool criteria evaluate studies based upon 5 different domains of bias: selection, performance, attrition, reporting and other.[14] This tool has been typically used to evaluate randomized control trials and in each domain the rater (MK) is to evaluate the study for High, Low or Unclear risks of bias.[14]

Results

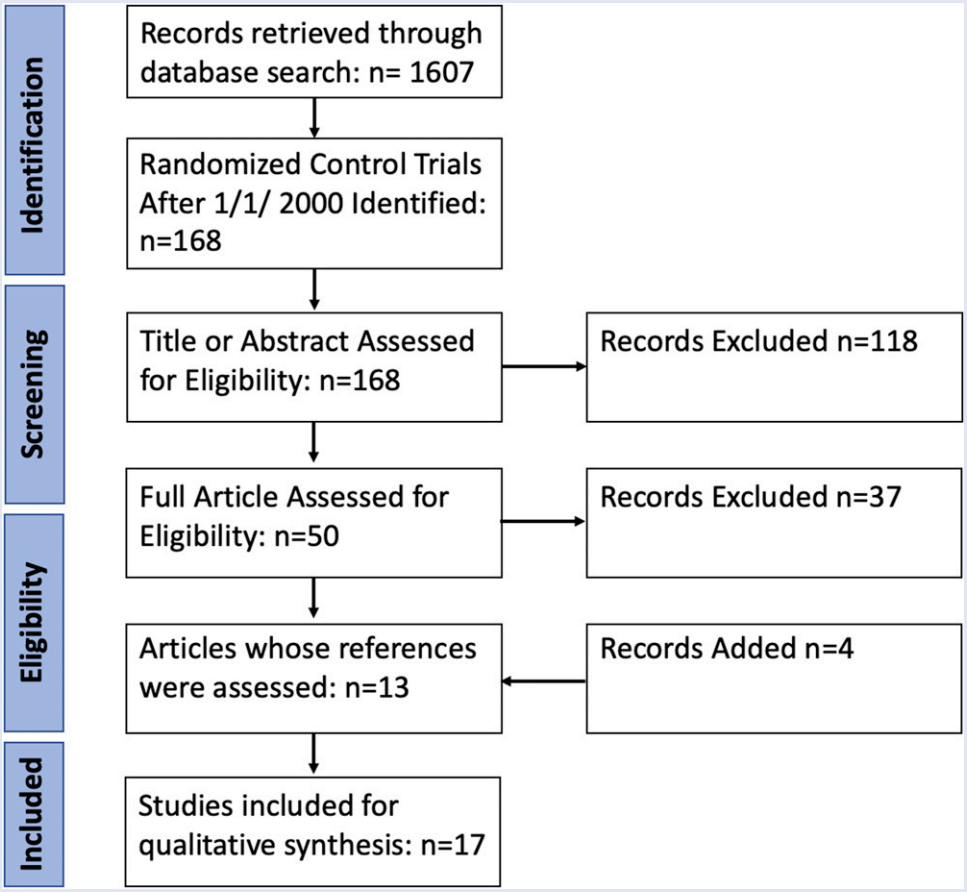
Results of the search process are displayed in Figure 1. A total of 1607 studies were identified from our initial search. 171 of these studies were randomized controlled trials, 168 of which were published after January 2000. After assessing the title and abstract, 50 articles were selected for further evaluation. Of these, 37 were excluded for the following reasons: 4 evaluated caregivers of those with dementia, 17 had additional confounders representing a multimodal approach such as mental training, acute supplementation, and music for the intervention group (these included 2 studies investigating the impact of dance as well), 3 had duration of intervention less than 12 weeks or 3 months, 9 focused on mental health variables or only assessed cognitive impairment via the NPI (Neuropsychiatric Inventory), 2 were eliminated for the severity of dementia symptoms. One was excluded as they did not have a proper control group and another investigated mahjong and tai chi's impact rather than robust aerobic or anaerobic exercises regimens. This yielded 13 studies and, after reviewing the references, 4 additional studies were added as they met all the listed criteria. After an extensive electronic search, 17 studies were found that met eligibility criteria.

Demographics and characteristics of each study are outlined in Table 1. Table 2 depicts the results of the Cochrane Risk of Bias Tool. The largest takeaway from the risk bias tool assessment is that numerous studies had difficulty blinding participants from the exercise regimen. As a result, thirteen studies had concerns or unclear risk for bias secondary to insufficient blinding. No studies demonstrated high risk of bias in another category, but some were unclear in description of technique to limit bias. Six RCTs looked at cognitively intact adults,[15-20] 5 studies included participants with MCI,[21-25] and 6 included participants with a known diagnosis of mild to moderate dementia.[26-30] Yoon et al. included participants with a clinical dementia rating score (CDR) of .5 which is the equivalent of mild cognitive impairment and was categorized as such.[25] Morris et al. enrolled those with both MCI and early dementia.[31] The mean age of participants ranged from 64 to 85 years old and sample size varied between 23 to 494 participants. A formal, instructor-led aerobic exercise program was the most common intervention and consisted of supervised walking, stationary cycling, or elliptical training. Heart rate reserve (HRR), which calculates individual target heart rate zones, was used in 8 studies to objectively determine intensity of exercise, with goals ranging from 40-89% HRR.[16,21-24,27,28,31] The Borg Rating of Perceived Exertion Scale (RPE) was used as a subjective measurement of exertion in 7 studies.[15-17,27,28,32] In addition to aerobic exercise, 3 studies included a strength training program as part of the intervention.[17,26,28] Three additional studies looked at the effects of resistance exercise alone.[15,19,25] Lautenschlager et al. did not have a formal training program and participants were able to construct their own at-home aerobic or non-aerobic exercise program.[22] The duration of interventions lasted between 12 weeks to 12 months and all but 3 studies looking at aerobic exercise met the recommended guidelines of 150 minutes of moderate-intensity aerobic activity per week.[18,24,28]

Seventeen studies compared the intervention group to a non-aerobic control; however, there was significant variability in the prescribed activity for the control group.[33] Most studies compared the exercise group to an inactive, usual care control. Morris et al. compared 26 weeks of aerobic exercise to a non-aerobic control group that alternated between core strengthening, resistance training, and modified tai chi or yoga.[31] Varela et al implemented recreational activities, including playing cards or doing crafts and 2 studies compared the aerobic intervention to a stretching control.[21,27] Sanders et al. compared both low- and high-intensity training to a control group that performed flexibility exercises and recreational activities.[28] Martin-Willett et al. compared cognitive outcomes between 2 intervention groups, a moderate intensity continuous training plus high-intensity interval

Figure 1.

Flowsheet describing the search strategy.



training group (MICT + IT) and low-intensity continuous training group (LICT).[18] In the 3 RCTs that looked at the effect of resistance training on cognitive function, 1 study compared moderate resistance (50% of 1 repetition maximum) and high resistance (80% of 1 repetition maximum) training to a control group that did similar exercises without overload training[15] and the other 2 studies compared a resistance exercise protocol to a balance and tone or stretching program.[32,34] Most studies reported >60% adherence to exercise intervention. Muscari et al included participants with at least 50% compliance in endurance exercise training and 3 studies did not specify degree of adherence.[17,18,25] Strategies used to promote compliance included direct supervision, in-class attendance, and behavioral interventions (i.e., motivational telephone calls, target setting, visual reminders).

Table 3 depicts the primary cognitive outcome measures assessed in each study. Global cognitive functioning was assessed by the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) in 6 studies[22,23,26,27,29,30] and by the Mini-Mental State Exam (MMSE) in 6 RCTs.[17,20,24,28-30] Measures of memory included Rey Auditory Verbal Learning subdivision of Wechsler Adult Intelligence Scale (WAIS-III), Wechsler Memory Scale (WMS-IV) and Corsi's Block-Tapping Task of Revised Wechsler Memory Scale (WMS-R), Rey 15-Item Test, Rey-Osterrieth Complex Figure, Free and Cued Selective Reminding Test, Forward Digit Span, Story Recall, List Learning, Delayed Matching to Sample, Hopkins Verbal Learning Test-Revised, Visual Memory Span Forward and Backward, and the Second Edition of California Verbal Learning Test (CLVT-II). Tests of executive function and complex attention included EXIT-25, Executive Clock Drawing Task, Letter-Number Sequencing, Digit Span Backwards, Digit-Symbol Coding, and Similarities subdivisions of WAIS

Table 1.

Description of Randomized Controlled Trials.

Study	N (IG/CG)	Age (IG/CG)	Diagnosis	Primary Outcomes	Secondary Outcomes	Exercise Intervention	Duration	Control Group Activity	Results
Liu Ambrose (2016)	35/35	74.8/73.7	Mild SIVCI	ADAS-cog, EXIT-25, ADCS-ADL	Stroop test, trail making tests (part B minus part A),Verbal digit span, 6MWT, BMI, BP	1-hr thrice weekly instructor-led walking program with progression to 60-75% HRR	6 months	Usual care	Improvement in ADAS-CoG at 6 months (1.71 points), not significant at 12 months, improved 6MWT and DBP compared to CG. No change in EXIT-25 or ADCS-ADL
Langlois (2012)	36/36	Frail: 74.47/ 75.41 Nonfrail: 68.74/70.95	Cognitively intact	MMSE, similarities, digit-symbol coding, letter-number sequencing, digit span backwards (WAIS-III), TMT part A, stroop color-word test, rey auditory verbal learning, quality of life systemic inventory, grip strength, 6MWT, TUG, gait speed	None identified	1-hr thrice weekly supervised aerobic and strength training	12 weeks	Usual care	Improvement in functional capacity, processing speed (.24 and .35 z score increase), working memory (.35 and .13 z score increase), executive function (.36 and .24 z score increase), QoL at end of intervention, for frail and non-frail individuals, respectively
Lamb (2018)	329/165	76.9/78.4	Mild-mod dementia	ADAS-cog	Bristol ADL index, neuropsychiatric index, EQ-5D quality of life measure, ADAS-cog subscales, Zarit burden interview	60-90 min. Twice weekly supervised mod-high intensity aerobic and strength training, additional 1-hr/ week home exercise	12 months	Usual care	Improvement in physical fitness (mean improvement by 18.1 m in 6MWT) but no noticeable improvements in other outcome measures compared to CG

(continued)

Table 1. (continued)

Cassilhas (2007)	EMOD: 19 EHIGH: 20 CG: 23	EMOD: 69.01 EHIGH: 68.4 CG: 67.04	Cognitively intact	WAIS-III (similarities, digit span), WSM-R (Corsi's block-tapping task) Toulose-Pieron's, Rey-Osterrieth complex Figure, SF-36, GDS, POMS, blood viscosity, serum IGF-1, BMI	None identified	1-hr thrice weekly instructor-led resistance training (50% RM EMOD, 80% EHIGH)	24 weeks	Same exercises as IG without overload training	Significant improvements across all tests in measures of memory and executive function (increase by ~ .50 in forward digit span, ~.30 and ~.95 increase in corsis forward and backward, respectively) regardless of exercise intensity, increased IGF-1 concentrations in both IG
Chapman (2013)	18/19	64.0/64.0	Cognitively intact	Trails B-trails A, CVLT-II, WMS-IV, DKEFS-color word, backward digit span, weight, heart rate, VO2 max, RPE, rCBF	None identified	1-hr thrice weekly supervised aerobic exercise	12 weeks	Wait-list (i.e., no intervention)	Significant improvement (improvements by ~ 1 in CVLT-II, LM delayed and immediate recall tests), VO2 max, rCBF at intervention completion
Baker (2010)	19/10	65.3/74.6 (women) 70.9/ 70.6 (men)	Mild cognitive impairment	Symbol-digit modalities, verbal fluency, stroop, trails B, task switching, story recall, list learning, fasting insulin level, cortisol, BDNF, IGF-1	None identified	45-60 min sessions of high intensity aerobic exercise 4d/wk	6 months	Stretching	Sex-specific improvement (with the effect size magnitude being .67 for women and .29 for men on SDMT and .88 for women and .28 for men in category fluency) in executive function and glucoregulation, decreased cortisol and *BDNF* in IG women compared to men
Lautenschlager (2008)	85/85	68.6/68.7	Subjective memory complaints, mild cognitive impairment	ADAS-cog	Digit symbol coding test, verbal fluency (D-KEFS), beck depression inventory, SF-36	At least 150 min. Home aerobic exercise weekly, optional light strength training	24 weeks	Usual care + education	Improvement ADAS-cog by 1.3 points at the end of intervention, lessened to .69 at 6 month follow up compared to CG

(continued)

Table 1. (continued)

Morris (2017)	34/34	74.4/71.4	Very mild to mild dementia	Immediate and delayed recall, free and cued selective reminding test, digit span, category fluency, D-KEFS confirmed correct and free card sorting, letter number sequencing, stroop color-word interference	DAD, Cornell scale for depression, peak VO2, 6MWT, hippocampal and gray matter volume	Gradual increase to 150 min. Supervised aerobic exercise per week	26 weeks	Non-aerobic stretching and toning exercises	Improved cardiorespiratory fitness correlated with memory change (~10 mL per kg lead to a z score improvement of 1 for memory) change in VO2and hippocampal volume on secondary analyses
Varela (2011)	40% HRR: 17 60% HRR: 15 CG: 15	40% HRR:79.24 60% HRR: 76.44 CG: 79.40	Mild cognitive impairment	MMSE and TUG	None identified	30-min Thrice weekly supervised stationary cycling (40% or 60% HRR)	3 months	Non-aerobic recreational activities	No significant difference between cognitive decline and functional autonomy in either MOD or HIGH intensity compared to CG (MMSE improvements by less than 1 point)
Martin-Willett (2021)	MICT: 78 LICT: 64	MICT: 67.49 LICT: 68.12	Cognitively intact	Stroop, category switch, keep track task	None identified	30-min Thrice weekly supervised aerobic exercise of different intensities	12 weeks	None (intervention comparison)	Significant improvement in both exercise groups in stroop (~40% decrease in error) and 15-30% decrease in category switch reaction time with no difference between groups
Liu-Ambrose (2010)	RTx1:54 RTx2: 52 CG: 49	RTx1: 69.5 RTx2: 69.4 CG: 70.0	Cognitively intact	Stroop test	Trail-making tests a and B, verbal digit span forward/ Backward	60-min Instructor-led resistance exercise class once or twice weekly	12 months	Balance and toning exercises	Improvement in stroop test after 12-months of once- or twice-weekly resistance training. Task improvement by 10.9-12.6%. No difference in working memory or set shifting

(continued)

Table 1. (continued)

Muscari (2009)	60/60	68.8/69.6	Cognitively intact	MMSE	Blood pressure, BMI, waist circumference, cholesterol, CRP	60-min Thrice weekly aerobic endurance exercise	12 months	Usual care + education	Control group showed a significant decrease in MMSE score as compared to treatment group (P = .02). Exercise group 2.74x more likely to have stable cognitive status at end of intervention
Yoon (2018)	32/33	73.8/74.0	Mild cognitive impairment	Rey-15, trail-making A&B, digit span forward and backward, frontal assessment battery	None identified	1-hr thrice weekly independent resistance training	4 months	Balance and band stretching	Resistance training significantly improved processing speed (Cohen's d = .21 effect size) and cognitive function (Cohen's d = .45)
Sanders (2020)	39/30	81.7/82.1	Mild to moderate dementia	MMSE, digit span forward and backward, visual memory span forward and backward, stroop test, 6MWT	None identified	30-min Thrice weekly supervised low-intensity and high-intensity combined aerobic and resistance training	6 months	Flexibility and recreational activities	No significant effects in cognitive function between exercise and control groups. MMSE effect size 95% confidence interval [-.53-+.43]. No difference in outcomes between low and high-intensity training
Yu (2021)	64/32	77.4/77.5	Mild to moderate dementia	ADAS-cog	Wechsler memory scale-revised logical memory subtest, Hopkins verbal learning test-revised, TMT Part A and B, EXIT-25, executive clock drawing task, WAIS-r digit span and digit symbol, golden stroop, controlled oral word association, category Fluency, Boston Naming test	Up to 50-min thrice weekly supervised aerobic exercise	6 months	Stretching and range of motion exercises	Exercise reduced decline in global cognitive function after 6 months; 1 point for cyclists compared to 3.2 in ADAS-cog for natural disease progression. However, it was not superior to control group at 12 months. This pilot study was not powered to detect between-group differences

(continued)

Table 1. (continued)

Hoffman (2016)	107/93	70/71	Mild Alzheimer's dementia	Symbol-digit modalities	ADAS-cog, stroop color- word test, verbal fluency and MMSE	60 minute thrice weekly supervised sessions of primarily aerobic exercise	16 weeks	Usual care	Significant changes between groups or baseline from SDMT for those who were adherent to the protocol by 4.2 points. Other tests showed no statistical significance
Toots (2017)	93/93	84/86	Mild to moderate dementia	ADAS-cog, MMSE, verbal fluency	None identified	5 45-minute supervised sessions every 2 weeks, based upon the high intensity functional exercise model	4 Months	Structured non-exercise activities lead by OTs	No significant differences in global cognition or executive function. (MMSE -.27, ADAS-cog -1.0 however, both confidence intervals included no change

IG/CG = intervention group/control group; SIVCI = subcortical ischemic vascular cognitive impairment; EMOD/EHIGH = moderate resistance/high resistance; rCBF = resting cerebral blood flow; HRR = heart rate reserve; MICT/LICT = moderate-intensity continuous training/low-intensity continuous training; RTx1/RTx2 = once weekly resistance training/twice weekly resistance training.

III, Toulouse-Pieron's Concentration and Attention test, Trail Making Test A and B, Trails B Minus Trails A, Stroop Color-Word test, Task Switching, Keep Track Task, Verbal Fluency, Symbol-Digit Modalities (SDMT), Frontal Assessment Battery, and Color-Word Interference and Free Card Sorting subtests of Delis-Kaplan Executive Function System (D-KEFS). The MMSE has demonstrated high sensitivity and specificity for detection of both MCI and dementia and is considered the reference standard. The ADAS-Cog has demonstrated improved sensitivity with modified scoring resulting in high predictive value for dementia.[31] The remaining tests focus on specific domains of memory or executive function which are impacted in MCI or dementia but do not measure global cognitive function.

Exercise and Global Cognition

The ADAS-Cog and MMSE are 2 common tests of global cognitive impairment. The ADAS-Cog is an 11-item assessment of memory, language, and praxis that is routinely used as the primary neuropsychological test in many AD drug clinical trials.[34] The MMSE, which is the most frequently used test to screen for dementia in primary care settings, is also comprised of 11-questions that assess various cognitive domains; however, it is more influenced by educational level and may be less sensitive and reliable than the ADAS-Cog.[35]

In studies that used the ADAS-Cog as the primary outcome measure, some showed superiority in global cognitive function among the aerobic exercise group over non-aerobic controls after completing the intervention; however, significance was lost by long-term follow-up.[36] Liu-Ambrose et al found a mean difference of 1.7 points on the ADAS-

Table 2.

Cochrane Risk of Bias Tool Results.

Study	Random Sequence Generation	Allocation Concealment	Selective Reporting	Blinding of Personnel and Participants	Blinding of Outcome Assessment	Incomplete Outcome Data	Other
Liu Ambrose (2016)	Unclear	Low	Low	Unclear	Unclear	Low	Low
Langlois (2012)	Unclear	Low	Low	High	Unclear	Low	Low
Lamb (2018)	Low	Low	Low	High	High	Low	Low
Cassilhas (2007)	Unclear	Low	Low	Unclear	Unclear	Unclear	Low
Chapman (2013)	Low	Low	Low	Unclear	Unclear	Unclear	Low
Baker (2010)	Low	Low	Low	Low	Low	Low	Low
Lautenschlager (2008)	Low	Low	Low	High	Low	Low	Low
Morris (2017)	Unclear	Unclear	Low	Low	Low	Low	Low
Varela (2011)	Unclear	Low	Low	High	Low	Low	Low
Martin-Willett (2021)	Low	Low	Low	High	Low	Low	Low
Liu-Ambrose (2010)	Low	Low	Low	Low	Unclear	Unclear	Low
Muscari (2009)	Unclear	Low	Low	Unclear	Unclear	Low	Low
Yoon (2018)	Unclear	Low	Low	High	Low	Low	Low
Sanders (2020)	Low	Low	Low	Low	Low	Low	Low
Yu (2021)	Low	Low	Low	Low	Low	Low	Low
Hoffman (2016)	Unclear	Unclear	Low	High	Low	Low	Low
Toots (2017)	Low	Low	Low	Low	Low	Low	Low

Random Sequence Generation: Adequately described the randomization process to allow assessment of whether it should produce comparable groups. Allocation Concealment: Described method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocation could have been foreseen before or during enrollment. Selective Reporting: Stated how the possibility of selective outcome reporting was examined by the authors and what was found. Blinding Participants and Personnel: Describes measures to blind study participants and personnel from which intervention a participant received. Blinding Outcome Assessment: Describes measures to blind outcome assessors from knowledge of which intervention participants received. Attrition Bias: Describes the completeness of outcome data including attrition and exclusions from analysis. Other: Any other important concerns about bias not addressed above.

Table 3.

Characterization of Cognitive Tests.

Domain	Global Cognitive Functioning	Memory (Short-Term/Long-Term, Immediate/Delayed Recall, Visual)	Executive function (Working Memory, Processing Speed, Verbal Reasoning, Inhibition)
Test	ADAS-cog	Rey auditory verbal learning (WAIS-III)	EXIT-25
	MMSE	Wechsler memory scale (WMS-IV)	Letter-number sequencing (WAIS-III)
		Corsi's block-tapping task (WMS-R)	Digit-span backwards (WAIS-III)
		Rey-Osterrieth complex Figure	Digit-symbol coding (WAIS-III)
		Free and cued selective reminding	Similarities (WAIS-III)
		Forward digit span	Toulouse-pieron's concentration/Attention test
		Story recall	Trail making test A and B
		List learning	Trails B minus trails A
		Delayed matching to sample	Stroop color-word
		CLVT-II	Task switching
		Hopkins verbal learning test- revised	Executive clock drawing task
		Rey-15	Keep track task
		Visual memory span forward/Backward	Verbal fluency
			Symbol-digit modalities
			Color-word interference (D-KEFS)
			Free card sorting (D-KEFS)
			Frontal assessment battery

WAIS-III = Wechsler Adult Intelligence Scale, Third Edition; WMS-IV = Wechsler Memory Scale, Fourth Edition; WMS-R = Wechsler Memory Scale-Revised; CLVT-II = California Verbal Learning Test, Second Edition; D-KEFS= Delis-Kaplan Executive Function System.

Cog between the exercise and control groups at the end of the 6-month aerobic intervention ($P = .02$); however, this is less than the accepted minimal clinically relevant difference of 3. This difference lessened to .63 and was not statistically significant at 12-month follow up ($P = .46$). Lautenschlager et al found similar results with an improvement of 1.3 points on the ADAS-Cog in the exercise group relative to the non-aerobic control at the end of the intervention, which lessened to .69 at six month follow-up ($P = .04$). In a pilot randomized controlled trial by Yu et al (n = 96), participants who engaged in 6 months of aerobic exercise experienced a smaller within-group change in the ADAS-Cog score at the end of the intervention than would be expected for typical Alzheimer's disease progression, which was described as 3.2 +/− 6.3-point increase. There was not a significant difference in the change in ADAS-Cog score between the intervention and control groups at 6 and 12-months; however, this finding was expected as the pilot study was not powered to detect between-group differences. Given the heterogeneity within these studies, it is difficult to ascertain comprehensive conclusions. Further studies are needed to provide additional robustness to the current state of literature. Specifically, future studies should focus on the impact of a supervised exercise program for those with MCI. Liu-Ambrose et al demonstrated the largest effect size within the ADAS-CoG group and employed a supervised walking program. This suggests that despite its

lower intensity, benefits can be realized from an escalating in intensity supervised exercise regimen rather than a prescribed home exercise program with less accountability. Further studies should assess the benefit of higher intensity supervised exercise and its impact on this test amongst those with MCI.

The Dementia and Physical Activity (DAPA) trial, which is the largest study included in this review (n = 494), generated contrasting results. There was no improvement in ADAS-Cog following exercise intervention and the ADAS-Cog scores worsened at 12-month follow up in both trial arms. Notably, the participants in this study already had a diagnosis of dementia and had significantly higher ADAS-Cog scores at baseline (21.4 in control group, 21.2 in exercise group), which is indicative of worse global cognitive function.

Out of the 6 studies that used MMSE scores as primary outcome measures, 2 studies showed marginal improvements post-intervention in the exercise group as compared to the control; however, these differences similarly dissipated on long-term follow up.[17,24] Muscari et al found that healthy elderly participants had reduction in cognitive decline as assessed by the MMSE after 12-months of endurance exercise when compared to inactive controls. On immediate follow up, the intervention group had a 2.74 times higher likelihood of maintaining their cognitive status when compared to the control group; however, there is no long-term data to assess cognitive maintenance in this study population.[20] Of note, however, these 2 positive studies were performed on those who were deemed cognitively intact. Sanders et al compared MMSE scores of elderly adults who engaged in low- and high-intensity aerobic and resistance training to a flexibility control group and found no statistically significant between-group differences at the end of the 6-month intervention. Further long-term studies need to be conducted and the validity of the MMSE in varied levels of cognition needs to be more established. Out of the 6 studies that used MMSE scores to evaluate global cognitive function, 3 carried a diagnosis of mild to moderate dementia. All 3 of these studies showed that there was no statistically significant difference between baseline and post-intervention performances on MMSE for those with mild to moderate dementia.[28-30]

Exercise and Memory

Although there are several different types of memory, each can be broadly classified into short and long-term memory. Ten studies assessed components of memory through use of various neuropsychological tests as outlined in Table 3. Cassilhas et al demonstrated improvement in short-term and episodic, long-term memory after 24-weeks of moderate or high-intensity resistance training compared to non-overload controls.[15] This study also looked at serum IGF-1 levels as higher concentrations have been associated with improved cognitive function.[34] Both intervention groups had higher levels of IGF-1 following resistance training when compared to the control group, with no statistically significant difference in concentration when comparing moderate and high-intensity regimens.

Other components of memory that benefited from exercise included immediate recall[15] and delayed recall.[16,22] Cognitively intact adults who completed 12-weeks of 1 hour thrice weekly supervised aerobic exercise improved in immediate and delayed text-level memory when compared to usual-care controls.[16] In addition to memory function, Chapman et al also looked at changes in regional cerebral blood flow (rCBF), a biological indicator of brain health and preclinical biomarker for AD. After 3 months of aerobic exercise, the intervention group showed a selective increase of rCBF in bilateral anterior cingulate cortices on pseudo-continuous arterial spin labeling (pCASL) MRI compared to the control group. Improvements in immediate and delayed memory post-intervention were also associated with an increase in hippocampal rCBF mid-intervention. All studies that showed some improvement in memory included participants who were either cognitively intact or with MCI. Four studies that did not find a significant difference in tests of memory after exercise included participants with known diagnosis of mild to moderate dementia.[22,26,29,31] One of these studies, however, demonstrated a positive correlation on secondary analyses between peak VO2, a measure of cardiorespiratory fitness, bilateral hippocampal volume, and improvement in memory performance.[31]

Exercise and Executive Function

Executive function involves higher level cognitive skills that control organization, attention, working memory, and planning. Deficits in executive function are common in dementia and associated with more severe cognitive disease and worse functional impairment.[37] Out of eleven studies that looked at executive function as either a primary or secondary outcome measure, 6 showed statistically significant improvement following exercise intervention.[15,17,21,25] Cognitively intact elderly males who completed 24 weeks of moderate or high-intensity resistance training improved on tests of executive function when compared to controls.[15] These effects were not dependent on resistance intensity as there were no statistically significant differences between intervention

groups. Yoon et al similarly found improvements in executive function as measured by the Frontal Assessment Battery and Trail Making Tests following 4-months of high-speed resistance training. Baker et al randomized thirty-three adults with mild cognitive impairment into a high-intensity aerobic exercise group (75-85% HRR) or supervised stretching group. Six months of supervised aerobic exercise improved several domains of executive function, including: multitasking, cognitive flexibility, processing efficiency, and attention. In addition, this study showed sex-specific differences in almost all tests of executive function, with women demonstrating more pronounced improvement in executive control processes after aerobic intervention. Women randomized to the stretching control group experienced worsening performance on tests of executive function at the end of the study. Liu Ambrose et al randomized cognitively intact, community-dwelling women into one of three groups: once-weekly resistance training (RTx1), twice-weekly resistance training (RTx2), or twice weekly toning and balance control group. Women who participated in 12-months of weekly or twice weekly resistance exercises improved by 12.6% and 10.9%, respectively, on the Stroop test, which is a measure of selective attention and cognitive flexibility that requires individuals to name the color of a portrayed word and not the word itself (i.e., participants see the word "red" in yellow-colored font and are supposed to identify "yellow"). This is in contrast to women in the toning and balance group who regressed by .5% at the end of intervention. This study did not, however, find significant differences in tests of set shifting or working memory.

Martin-Willett et al randomized cognitively healthy adults into 2 exercise interventions and compared cognitive outcomes following 16-weeks of moderate-intensity exercise with high-intensity interval training (MICT + IT) to low-intensity continuous training (LICT). MICT + IT program started at 60% HRmax and progressed in intensity to include intervals at 85-85% HRmax. LICT group maintained 50% HRmax for all sessions during the intervention. Participants in both groups improved in Stroop effect on error and Category Switch effect reaction time when compared to their baseline, with no difference between exercise groups. Langlois et al found statistically significant improvements in working memory, processing speed and executive function in both frail and non-frail, cognitively intact adults after 12-weeks of moderate to high-intensity aerobic exercise (as measured by modified Borg Rating of Perceived Exertion Scale).

Discussion

This is a robust systematic review of 17 randomized controlled trials following the PRISMA framework that depicts the impact physical exercise has on cognition of cognitively intact adults and those with mild to moderate dementia. These studies were then evaluated for risks of bias, with the most prominent risk coming from inadequate blinding. In these studies where exercise is the intervention, there is an intrinsic difficulty to blind participants as they must actively participate in the prescribed physical activity. The other studies included in this review had no other attributes for high risks of bias. In evaluating this type of research, this is a required acceptable level of potential bias to make recommendations based on conclusions from studies on exercise and many lifestyle interventions.

After reviewing these studies, there is extensive heterogeneity within the current state of literature involving exercises impact on cognition. At present, there are a multitude of different exercise interventions and different objective tools to measure cognition, making integrated, global recommendations difficult. Despite these difficulties, studies consistently report that regular physical exercise results in modest improvement in global cognitive function during active participation among people without dementia. When compared to donepezil, a commonly prescribed acetylcholinesterase inhibitor used in the treatment of AD, physical activity results in similar effects on the MMSE and ADAS-Cog where direct comparisons are possible.[38] Donepezil does not prevent progression of cognitive decline. Effects of physical exercise diminish after study interventions ended, but it remains unclear if exercise might prevent progression if maintained over time as long-term exercise trials have not yet been conducted. In addition, the SDMT presents itself as interesting objective cognitive test, given that it was one of the most common and more tested functional capacity compared to other commonly used tests. Table 4 further describe the summation of findings from the 3 most used tests within the presented studies (ADAS-CoG, MMSE and SDMT). This test demonstrated some potential benefit for MCI and those with dementia after exercise. The SDMT may be more directly testing the benefits that could potentially be conferred from exercise and therefore should be further investigated.

Previous work has indicated that epigenetic changes may occur following sustained physical exercise, particularly in mechanisms involved in *BDNF* synthesis, that

might lead to sustained brain health benefits from a lifetime of physical activity.[39] There are few prospective studies that examine the effect of sustained physical exercise on cognitive function later in life. The Caerphilly Cohort study followed health behaviors of over 2000 men in Wales for 30 years. Regular physical activity, defined in the study as walking 2 or more miles or cycling at least ten miles per day, had the greatest effect on reducing risk of cognitive impairment (OR .64) and dementia (OR .41) when compared to other behaviors like healthy diet, tobacco avoidance, and moderate alcohol consumption.[40] As part of the Prospective Population Study of Women (PPSW), Hörder et al tracked dementia incidence over a period of 44 years and found risk of dementia to be lowest in those with high cardiovascular fitness in mid-life.[41] Studies in this review found decay in global cognitive improvements within 6 months after participants stopped participating in physical activity interventions, suggesting that permanent changes in cognition and brain health are unlikely in this age group following moderate duration interventions. This suggests that interventions to support ongoing lifestyle change are likely to have greater impact for global cognition than time-limited physical exercise interventions that depend on external motivation.

Improvements in specific components of memory and executive function were observed in response to exercise in many studies, although the strength of these findings was variable. The strongest effects were seen in short- and long-term memory and processing speed. The most beneficial effects were seen in studies that included cognitively intact participants or those with MCI, suggesting that physical exercise may have the greatest impact before people reach the stage of active dementia. However, 1 study did suggest that there may be a dose-response component to improvements in those with dementia with exercise.[28] Hoffmann et al showed that the per protocol analysis showed improvements while intention-to-treat analysis did not show statistically significant improvements in SDMT.[29] The majority of studies have not replicated this finding. This finding aligns with a prior systematic review that found more pronounced cognitive benefits after physical exercise in participants with MCI as compared to those with more advanced disease.[42] Additionally, the SDMT does suggest, however, that it could be more sensitive in detecting functional changes in cognition due to exercise compared to the other common cognitive tests (ADAS-CoG and MMSE) [Table 4]. Further studies should investigate the relative validity within this battery of tests amongst different levels of cognition. In the few studies that also looked at structural and biochemical changes in the brain, physical exercise augmented cerebrovascular blood flow, increased levels of peripheral IGF-1, and lessened hippocampal atrophy, all of which were associated with improved cognitive performance.

Most research has been done with aerobic exercise as the primary intervention. This work has not demonstrated a correlation between intensity of aerobic exercise and degree of cognitive benefit to date. Only 5 studies incorporated strength training as part of the exercise program, making it difficult to draw conclusions about impact. Four studies included group classes in their exercise intervention which could contribute to cognitive benefit by introducing social aspects similar to team and competitive sports. A 2022 meta-analysis by Balbim et al demonstrated no significant effects on cognitive function in individuals with all-cause dementia when exploring treatment-level moderators, including type of intervention (i.e., aerobic, resistance, or multimodal), intensity of exercise, or weekly exercise volume.[42] This study did, however, find an association between higher adherence to exercise intervention and improved cognitive performance.[1] Although multicomponent exercise is the current general health recommendation for physical activity in adults, more research is needed to determine the optimal exercise regimen for cognitive function and brain health over the lifespan.

The studies included in this review were all designed to evaluate the cumulative benefit of regular exercise over a period of exercise intervention. The response-decay cycle of changes in cognitive function around individual exercise sessions was not evaluated.[43] Previous research has demonstrated that peak metabolic and cognitive effects of physical exercise decay over hours to days.[44] The time course to optimal cognitive functioning following exercise is not well understood and may include both cumulative and peak effects.[45] Therefore, the temporal relationship between exercise sessions and cognitive testing could have impacted findings.

Current research on the effects of physical exercise on cognitive function in older adults is limited by small sample sizes and considerable heterogeneity in exercise intervention and primary outcome measures. There is also significant variability in the baseline physical activity of included participants. Although many studies only included participants who were considered underactive or frail, some did not outline specific exclusion criteria for baseline fitness level and may have included participants who were already regularly physically active. The MMSE and ADAS-Cog may not have the

Table 4.

Evidence Summary of the Impact of Exercise on Cognition.

Cognitive State	Cognitive Test	Evidence Summary	Benefit
MCI	ADAS-cog	For those with mild cognitive impairment, an exercise regimen lead to improvements in ADAS-CoG between .69-1.71 compared to control groups at 6 months. There was a loss of statistical significance with greater than 6-month time periods. The study with a supervised walking program had greater impact on ADAS-CoG at 6 months than a home aerobic routine. A study comparing the benefits of supervised exercise vs home exercise programs on cognition is warranted	=
DM	ADAS-cog	There were no statistical significant differences in ADAS-CoG for those with dementia, despite different exercise regiments. One study showed a possible slowing of degenerative symptoms; however, the study was not sufficiently powered to detect in group differences. This study looked at aerobic exercises and noted that the cyclists had slower disease progression. Further studies should be adequately powered with an adequate number of cyclists to truly understand the possible effect size and its potential statistical significance	=
MCI	MMSE	Three studies were done on those with zero to mild cognitive impairment. Of those, the 2 completed on cognitively intact individuals showed mild to moderate benefit from an exercise program or at least maintenance of cognition during the duration of the intervention. The last study did not show any statistical differences between the MCI and control group. Further studies need to be completed on the long-term effect measured by MMSE and could be related to differing sensitivities within different populations	+
DM	MMSE	There were no statistical different changes after exercise intervention detected by MMSE for those with mild to moderate dementia. The validity of the test amongst those with already established dementia should be considered as well	=
MCI	SDMT	There were sex-specific improvements with women having an increased impact in SDMT testing; however, further studies should validate this finding. There were demonstrations in increased functional capacity and relates to a central theme that with exercise comes improved ability to function. SDMT more directly tests this phenomenon which could impact effect size. However, the data is not conclusive as 1 study detected no difference after exercise	=
DM	SDMT	Of the 2 studies using SDMT, 1 showed statistically significant change and 1 did not. In the study that showed statistical significance, all other tests were negative. Given that few other tests have shown improvements in testing for those with dementia suggests that SDMT may be more sensitive to improvements in function from exercise; however, further studies need to be completed to assess this claim	=

MCI: Mild Cognitive Impairment; DM; Dementia; ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive Subscale; MMSE: Mini-Mental State Exam; SDMT: Symbol-Digits Modalities Test; + indicates positive impact, - indicates negative impact, = indicates inconclusive or needs more evidence.

sensitivity and responsiveness to detect changes in higher order cognitive functions. The diversity of neuropsychological tests selected to assess cognitive performance make it difficult to synthesize the data and understand the significance of the results. Similarly, there is a lack of evidence evaluating the relative benefit of specific exercise interventions in preventing cognitive decline as the existing RCTs vary significantly on the type, duration, and frequency of exercise utilized as the primary intervention and many common types of exercise (e.g., team sports) have not been evaluated.

Limitations

The limitations of this study are intrinsic to the nature of the studies that were analyzed in our systematic review. Of our 17 studies, 12 had concerns for inadequate explanations of blinding or concerns for inadequate blinding. When studying lifestyle interventions, it is difficult to blind individuals to their lifestyle changes. Additionally, there are lifestyle changes beyond the scope of the study that can impact the results of our study. With increased exercise, there could be changes to diet and other healthy lifestyle choices that could be unaccounted during the course of intervention in our included studies. Furthermore, the category of exercise is so broad that it is difficult to provide comprehensive or universal results that could be expected after these interventions. From the type of exercise, level of coaching or supervision and varied intensity it is difficult to recommend a single exercise regimen based on an individual's level of cognition. Furthermore, the presented studies have such a wide battery of objective measurement tools that it is difficult to determine the ultimate effect size of the interventions. Within the presented studies 2 different tests were used for global function, 13 were used for memory, and 17 were used to measure executive function.

While previous systematic reviews exist detailing how multicomponent exercise impacts cognition,[46,47] our review differs in that our study only is analyzing studies that have at least the recommended 150 minutes of exercise per week. It has been demonstrated that that level of activity is safe for older adults and the authorship felt that it was important to make sure that participants had adequate dose of either aerobic or strength training exercise to determine the possible effect exercise can have.

Conclusion

We found the strongest evidence for improvements in components of memory in response to exercise among people who were cognitively intact or diagnosed with MCI, with weaker evidence of improvements in global cognition and executive function. Physical fitness and cognitive gains were associated with increases in regional brain volume or blood flow in some studies. Improvements tended to decay after interventions were completed. Less meaningful cognitive improvements were demonstrated in those with diagnoses of dementia rather than mild cognitive impairment.

Of note, this review necessitated studies had at least 150 minutes of exercise, the defined minimum for regular exercise per the Physical Activity Guidelines issued by the U.S. Department of Health and Human Services and 12 weeks of duration, which is unique compared to previous reviews. These findings suggest that sustained physical exercise can have a clinically meaningful impact on cognition and brain health among older adults prior to onset of dementia that decays when people stop exercising. This "on-off" phenomenon strengthens the association of cognitive function with current physical activity. Therefore, interventions to support ongoing physical activity may have the greatest potential for cognitive preservation and brain health in older adults in future research.

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