Aerobic Exercise and Neurocognitive Performance: A Meta-Analytic Review of Randomized Controlled Trials

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Objectives: To assess the effects of aerobic exercise training on neurocognitive performance. Although the effects of exercise on neurocognition have been the subject of several previous reviews and meta-analyses, they have been hampered by methodological shortcomings and are now outdated as a result of the recent publication of several large-scale, randomized, controlled trials (RCTs). **Methods:** We conducted a systematic literature review of RCTs examining the association between aerobic exercise training on neurocognitive performance between January 1966 and July 2009. Suitable studies were selected for inclusion according to the following criteria: randomized treatment allocation; mean age ≥18 years of age; duration of treatment >1 month; incorporated aerobic exercise components; supervised exercise training; the presence of a nonaerobic-exercise control group; and sufficient information to derive effect size data. **Results:** Twenty-nine studies met inclusion criteria and were included in our analyses, representing data from 2049 participants and 234 effect sizes. Individuals randomly assigned to receive aerobic exercise training demonstrated modest improvements in attention and processing speed (g = 0.158; 95% confidence interval [CI]; 0.055–0.260; $p = .003$), executive function (g = 0.123; 95% CI, 0.021–0.225; $p = .018$), and memory (g = 0.128; 95% CI, 0.015–0.241; $p = .026$). **Conclusions:** Aerobic exercise training is associated with modest improvements in attention and processing speed, executive function, and memory, although the effects of exercise on working memory are less consistent. Rigorous RCTs are needed with larger samples, appropriate controls, and longer follow-up periods. **Key words:** cognitive performance, aerobic exercise, neuropsychological performance, executive function, randomized controlled trial, meta-analysis.

ITT = intention-to-treat; **RCT** = randomized controlled trial.

INTRODUCTION

Strategies to enhance neurocognitive functioning have important public health implications as subclinical neurocognitive deficits are associated with increased risk of neurocognitive impairment (1), dementia (2), and mortality (3–7), independent of traditional risk factors. One such strategy that has gained increased attention is the use of aerobic exercise to improve neurocognitive functioning (8–12). Although the value of exercise has been critically examined in review articles (13) and meta-analytic syntheses (8–11), there has been a lack of agreement as to the magnitude of improvement in neurocognitive function associated with physical activity interventions. The current lack of consensus is due to differences in the evaluation of study methodologies, studies included in the analyses, data analytic approaches, and in the classification of various neurocognitive measures.

Cross-sectional studies have shown that physically active individuals tend to exhibit better neurocognitive function relative to inactive individuals (13–22). Prospective observational studies have reported similar findings, demonstrating that individuals who maintain greater levels of physical activity show improvements in neurocognitive function relative to their sedentary counterparts (1,23–28). However, randomized trials have provided inconsistent results, with some reporting cognitive gains (29,30) and others equivocal findings (31). Meta-analytic reviews of randomized controlled trials (RCTs) have also reported great variation in the magnitude of improvement in neurocognition associated with aerobic exercise (10–12), with some meta-analyses reporting moderate cognitive gains (9,10) and others reporting more modest improvements (8,11,32).

In several recent meta-analyses, including a Cochrane review (11), it was concluded that current data are insufficient to show that improvements in neurocognitive function associated with physical activity are due to improved cardiovascular fitness, and that larger studies are necessary (11,32). However, since the publication of this review, there have been several large-scale RCTs examining this relationship (30,31,33,34). In addition, although one previous systematic review (12) examined the effects of various forms of physical activity on boosting cognitive function (primarily general orientation) among individuals with dementia, no reviews have combined data from trials attempting to prevent dementia among vulnerable populations (i.e., individuals with cognitive impairment). The Cochrane review was limited, in this sense, as persons with neurocognitive impairments (e.g., mild cognitive impairment [MCI] and depression) were excluded (11). Furthermore, previous meta-analyses examining this relationship may have been influenced by the inclusion of two relatively large studies reporting substantial treatment effects that were not truly randomized (9,35,36), which may have overly influenced the reported effects. Therefore, we conducted a meta-analysis that included the most recent exercise intervention trials and addressed several issues including: 1) the effects of aerobic exercise training on specific domains of neurocognitive performance, including attention and processing speed, executive function, working memory, and memory; 2) the influence of specific dimensions of the exercise prescription, such as the mode, duration, and intensity of the exercise

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intervention; and 3) the issue of individual differences in response to exercise training, with a focus on baseline, pre-exercise level of cognitive functioning as a potential moderator of exercise effects (i.e., we compared individuals with MCI to cognitively intact samples), as well as the age of study participants.

METHODS

To determine the effects of aerobic exercise interventions on neurocognitive status, an extensive literature search was conducted, using the following databases between January 1966 and July 2009: MEDLINE, Pubmed, EMBASE, Gateway, CENTRAL, PsycINFO, Dissertation Abstracts International, Educational Research in Completion (ERIC), Sports Discus, Cochrane Register, PEDRO, Ageline, and CINAHL. The following search terms were used: cogniti*, cognitive performance, age*, elderly, mental performance, and neuropsychological in combination with fitness, aerobic, cardiovascular, VO_2, and physical activity. Additional titles were identified by a manual search of relevant journals and by identification of references included in previous meta-analyses. Unpublished dissertations and conference papers were also obtained, when possible.

Suitable studies were selected for inclusion according to the following criteria: 1) randomized treatment allocation; 2) mean age $\geq$18 years of age and nondemented; 3) duration of treatment $>$1 month; 4) involved aerobic exercise training (e.g., brisk walking, biking, or jogging). Age 18 years was selected as a lower age limit to control for developmental age differences in cortical thickness and myelination, which stabilize around the second decade of life (37). Studies utilizing walking interventions that were not aerobic were not included (e.g., slow walking with frequent breaks) to ensure that included trials incorporated some aerobic exercise component. Additional inclusion criteria included 5) the presence of a control group that did not engage in aerobic exercise; and 6) sufficient information to derive an estimate of effect size (ES).

After initial identification and retrieval of studies, several were found to be quasirandomized studies (36) or used case-control methodologies (15,36,38–44), were of insufficient duration to include (45–47), were found not to be nonrandomized based on personal communication with the trial's principal investigator (36), or did not utilize a nonaerobic exercise control group (48,49). Another trial was conducted among adolescents and was, therefore, excluded (50). Several trials utilized "dual-task" interventions (e.g., walking and talking) (51–53) or balance and strength-training (54,55) and were, therefore, not included as it could not be ascertained whether exercise was of sufficient intensity to produce aerobic changes. Several trials were not included because they utilized physical activity interventions with exclusively nonaerobic exercise components among individuals with dementia (52,56–65). The few studies utilizing walking interventions were either explicitly nonaerobic (58) or allowed residents with limited mobility (e.g., using walkers) to rest as needed (52), thereby limiting their generalizability to more healthy samples. Accordingly, these studies were excluded from the current analyses. For two trials in which the method of randomization was unclear (39,66), we attempted to contact the respective authors and were able to confirm that one trial followed a true randomization scheme (39). Results were unchanged when the remaining study was excluded and we, therefore, included this trial in all analyses (66).

Assessment of Study Quality

Two raters (P.J.S., B.M.H.) independently extracted information from each article, using an identical review protocol, which included study identifiers (e.g., authors' names, year of publication, publishing journal), duration of treatment, intensity of exercise, modality of exercise, blinding of assessment personnel to treatment status, during assessments, intention-to-treat (ITT) analyses, and time of follow-up assessment. ESs were assessed independently. Interrater reliability was assessed for the outcome domains in question (i.e., in each cognitive domain as well as for study characteristics). For all areas, interrater reliability was found to be excellent ($r > .90$; Cohen's $\kappa = 0.75$).

Data Analysis

Neuropsychological test results were classified according to the cognitive domains described by Lezak and colleagues (67). We considered neurocognitive tests that could be classified in the following categories: attention and processing speed (the sustained focus of cognitive resources with selective concentration and rapid processing of information (67,68), executive function (a set of cognitive skills responsible for the planning, initiation, sequencing, and monitoring of complex, goal-directed behavior), working memory (short-term storage and manipulation of information), and declarative memory (retention, recollection, and recognition of previously encountered information, hereafter referred to only as "memory"). We considered including "complex processing speed" as a measure of executive function as in previous analyses (9), but results were unchanged regardless of the classification of this test.

Analyses were conducted, using Comprehensive Meta Analysis software (Biostat, Englewood, New Jersey). Data were analyzed, using both fixed and random effects models and Cohen's G for between-group differences (69). Fixed effects analysis assumes that all studies are drawn from the same population, such that differences in treatment effects across studies are attributed to sampling and methodological variability (i.e., error variance). In contrast, random effects analysis allows for the possibility that studies are drawn from different populations, such that differences across studies may be due to unidentified sources of variation and provides a more conservative estimate of treatment effects (70). However, because results did not differ between fixed and random effects analyses and because random effects are generally recommended for examining treatment effects in meta-analytic studies (70), we have presented the random effects findings only. In trials reporting multiple effect sizes within the same neurocognitive domain, data were collapsed by averaging all ESs within each neurocognitive domain for each study, such that each study produced no more than one ES per domain. For the purposes of the study quality analyses, treatment effects were collapsed for each study for all neurocognitive domains. In addition, two trials in our literature search produced multiple publications in either peer-reviewed journals (71–73) or book chapters (74,75) that were combined for the purposes of analysis. Homogeneity of treatment effects was assessed, using the Q statistic. Three trials collected neurocognitive data at multiple time points in which participants continued to receive treatment (30,73,76). However, in only one study were the effects of treatment uncontaminated by crossover between groups (30). For this study only (30), we chose data from the longest follow-up assessment for inclusion in our analyses, although results were unchanged when other time points were examined.

Exploratory sensitivity analyses (77,78) were conducted to investigate sample characteristics that may have moderated the effects of treatment on neurocognitive outcomes. Specifically, three trial characteristics were examined: duration, intensity, and mode of exercise intervention. We also examined two important methodological characteristics associated with methodological quality: blinding of assessors of neurocognitive outcomes and use of ITT analyses. As an additional analysis, we examined whether treatment effects varied by cognitive status of participants at baseline (i.e., "nonimpaired" or MCI; patients with dementia [Alzheimer's disease] were excluded) and age of study participants.

RESULTS

Our initial literature search yielded 5538 potentially relevant studies, 68 of which were retrieved for full-text review. Twenty-nine studies incorporating data from 2049 participants met inclusion criteria and were included in the present analyses (Table 1), including data for 1024 experimental participants and 997 controls. Two hundred thirty-four ESs were available for analysis. Trials ranged in duration from 6 weeks (79) to 18 months (30). As shown in Table 1, the primary exercise modality was brisk walking and/or jogging and control groups were typically assigned to a wait-list control, although

TABLE 1. Randomized Controlled Trials Examining the Effect of Aerobic Exercise on Neurocognitive Function

Author / Year	Sample	Intervention	Instruments	Methodological Characteristics	Hedge's G
Bakken, 2001 (103)	15, older adults, ages 72 to 91	Duration: 8 wks Frequency: 30 min, 3/wk Intensity: - - - Combined Strength Training: Y MCI: N	Imaging (Verbal Fluency), Visual Discrimination, Raven's Progressive Matrices, Short-Term Retention, Addition, Perception of Ambiguous Stimuli	Attrition: 0% ITT: N Blinding: N	AT = .169
Blumenthal, 1989 (72) & Madden, 1989 (71)	101, sedentary, ages 60 to 83	Duration: 16 wks¥ Frequency: 40 min, 3/wk Intensity: 70% HRR Combined Strength Training: N MCI: N	Finger Tapping, Benton Revised Visual Retention Test, Digits Forward, Digits Backward, Selective Reminding Test, Randt Memory Test – Short Story, TMT-B, Digit Symbol, Ruff 2 & 7 Test, Stroop Color, Stroop Color-Word Interference, Nonverbal Fluency Test, Verbal Fluency Test	Attrition: 8% ITT:Y Blinding: Y	AT = .218 EX = −.025 WM = .114 ME = −.066
Emery, 1990 (110)	48, "inner-city cohort", ages 61 to 86	Duration: 12 wks Frequency: 60 min, 3/wk Intensity: 70% HRR Combined Strength Training: Y MCI: N	Digit Symbol, Digit Span, Word Copy, Number Copy	Attrition:10% ITT: N Blinding: N	AT = .028 EX = −.043 WM = .023
Emery, 1998 (111)	79, with stable COPD, age range not reported *M = 67*	Duration: 10 wks¥ Frequency: 45 min, 3/wk Intensity: - - - Combined Strength Training: Y MCI: N	Verbal Fluency, Digit Vigilance, Finger Tapping, TMT-A, TMT -B, Digit Symbol	Attrition: 5% ITT: N Blinding: N	AT = .075 EX = .325
Fabre, 2002 (112)	32, healthy elderly adults, ages 60 to 76	Duration: 8 wks Frequency: 45 min, 2/wk Intensity: - - - Combined Strength Training: N MCI: N	Wechsler Memory Scale	Attrition: 0% ITT: N Blinding: N	EX = −.188 WM = .878‡ ME = −.339
Hassmen, 1992 (39)	32, all women, ages 55 to 75	Duration: 12 wks Frequency: 20 min, 3/wk Intensity: 9–13 RPE Combined Strength Training: N MCI: N	Digit Span, Face Recognition, Simple Reaction Time, Choice Reaction Time	Attrition: 7% ITT: N Blinding: N	AT = .179 EX = .167 WM = .204 ME = −.145
Hawkins, 1992 (66)	40, sedentary, ages 63 to 82	Duration: 10 wks Frequency: 45 min, 3/wk Intensity: - - - Combined Strength Training: N MCI: N	Single-Task Reaction Time, Dual-Task Reaction Time, Difference Between Single-Task And Dual-Task Reaction Time	Attrition: 10% ITT: N Blinding: N	AT = −.243 EX = .047
Hoffman, 2008 (31)	153, sedentary and depressed, ages 41 to 87	Duration: 16 wks Frequency: 45 min, 3/wk Intensity: 70–85% HRR Combined Strength Training: N MCI: N	Logical Memory, Verbal Paired Associates, Digit Span, Animal Naming, COWAT, Stroop Color Word, Ruff 2 & 7 Test, Digit Symbol, TMT B-A	Attrition: 28% ITT: Y Blinding: Y	AT = .277 EX = .172 WM = −.031 ME = .072
Khatri, 2001 (113)	84, sedentary and depressed, ages 50 to 72	Duration: 17 wks Frequency: 45 min, 3/wk Intensity: 70–85% HRR Combined Strength Training: N MCI: N	Visual Reproduction, Stroop Color-Work Interference, Digit Span, TMT-A, Digit Symbol, Stroop Color, Stroop Word, TMT-B, Logical Memory	Attrition: 25% ITT: Y Blinding: Y	AT = .121 EX = .291 WM = −.047 ME = .186
Kramer, 1999 & 2002 (74, 75)	124, sedentary, ages 60 to 75	Duration: 26 wks Frequency: 40 min, 3/wk Intensity: 50–70% HRR Combined Strength Training: N MCI: N	Reaction Time Tests: Switching Trials, Non-Switching Trials, Incompatible Trials, Compatible Trials, Interference Effect (Difference Between Compatible Trials and Incompatible Trials), Stop Signal Trials, Simple Reaction-Time Trials	Attrition: 29% ITT:N Blinding: N	AT = .091 EX = .196 WM = −.101 ME = .156

(*Continued*)

TABLE 1. Continued

Author/Year	Sample	Intervention	Instruments	Methodological Characteristics	Hedge's G
Lautenschlager, 2008 (30)	170, elderly adults with MCI, age *M* = *69*	Duration: 72 wks¥ Frequency: 50 min, 3/wk Intensity: - - - Combined Strength Training: N MCI: Y	Word list recall (immediate and delayed), Digit Symbol, COWAT	Attrition: 19% ITT: Y Blinding: Y	AT = .083 EX = −.071 ME = .322**
Masley, 2008 (114)	56, adults, age *M* = *45*	Duration: 10 wks Frequency: 5/wk Intensity: 70–85% MHR Combined Strength Training: Y MCI: N	CNS Vital Signs (verbal memory, symbol digit coding, the Stroop test, shifting attention, continuous performance)	Attrition: 16% ITT: N Blinding: N (computerized)	AT = −.158 EX = .487‡
Moul, 1995 (115)	30, sedentary, ages 65 to 72	Duration: 8 wks Frequency: 35 min, 5/wk Intensity: 60–65% HRR Combined Strength Training: N MCI: N	Ross Information Processing Assessment Subtests: Organization, Auditory Processing, Immediate Memory, Recent Memory, Temporal Orientation, Problem Solving/ Abstract Reasoning	Attrition: 0% ITT: N Blinding: N	EX = .780‡ ME = .351
Munguia-Izquierdo, 2008 (116)	60, middle-aged women with fibromyalgia, ages 18 to 60	Duration: 16 wks Frequency: 50 min, 3/wk Intensity: 50–80% MHR Combined Strength Training: N MCI: N	Paced Auditory Serial Addition Task (PASAT)	Attrition: 12% ITT: Y Blinding: Y	AT = .922***
Oken, 2004 (117)	69, multiple sclerosis, *M* = *49*	Duration: 26 wks Frequency: 90 min, 1/wk Intensity: - - - Combined Strength Training: N MCI: N	Stroop Color-Word test, Simple Reaction Time, Complex Reaction Time, Attentional Shift Task, PASAT, Logical Memory, WAIS Similarities	Attrition = 12% ITT: N Blinding: Y	AT = .074 EX = .133 WM = −.354 ME = .000
Oken, 2006 (118)	135, healthy adults, ages 65 to 85	Duration: 26 wks Frequency: 60 min, 1/wk Intensity: 70% HRR Combined Strength Training: N MCI: N	Stroop Interference, Word List Recall, Letter-Number Sequencing, Covert Orienting, Divided Attention, Set Shifting, Simple Reaction time, Complex Reaction time	Attrition: 13% ITT: N Blinding: Y	AT = −.132 EX = −.034 WM = −.029 ME = −.055
Okumiya, 1996 (29)	42, healthy older adults, ages 75 to 87	Duration: 24 wks Frequency: 60 min, 3/wk Intensity: - - - Combined Strength Training: Y MCI: N	MMSE, Hasegawa Dementia Scale, Visuospatial Cognitive Performance Test	Attrition: 0% ITT: N Blinding: N	AT = .938**
Panton, 1990 (119)	39, healthy untrained older adults, ages 70 to 79	Duration: 26 wks Frequency: 45 min, 3/wk Intensity: 75% HRR Combined Strength Training: N MCI: N	Reaction time, Speed of Movement Time	Attrition: 14% ITT: N Blinding: N	AT = .111
Perri, 1984 (121)	42, healthy older adults, ages 60 to 79	Duration: 15 wks Frequency: 30 min, 3/wk Intensity: 40–50% HRR Combined Strength Training: N MCI: N	Rey Auditory Verbal Learning Task	Attrition: 41% ITT: N Blinding: N	ME = .261
Pierce, 1993 (120)	90, middle-aged adults with hypertension, ages 29–59	Duration: 16 wks Frequency: 50 min, 3/wk Intensity: 70% HRR Combined Strength Training: N MCI: N	Digit Symbol, Stroop Color Word test, Digit Span, TMT-B, Sternberg Memory Search Task (Slope and Y-intercept), Verbal Paired Associates, Logical Memory (immediate and delayed), Figural Memory (immediate and delayed)	Attrition: 7% ITT: Y Blinding: Y	AT = .249 EX = .126 WM = −.283 ME = .233

(*Continued*)

TABLE 1. Continued

Author/Year	Sample	Intervention	Instruments	Methodological Characteristics	Hedge's G
Russell, 1982 (122)	45, sedentary older adults, ages 55 to 70	Duration: 16 wks Frequency: 45 min, 3/wk Intensity: - - - Combined Strength Training: N MCI: N	Simple Reaction Time, Complex Reaction Time	Attrition: 4% ITT: N Blinding: N	AT = .214 EX = .081
Scherder, 2005 (79)	43, elderly adults with MCI, ages 76 to 94	Duration: 6 wks Frequency: 30 min, 3/wk Intensity: - - - Combined Strength Training: N MCI: Y	Category Naming, TMT-A, TMT-B, Digit Span, Visual Memory Span, Rivermead Behavioral Memory Test (Faces and Pictures), Verbal Learning and Memory Test: Direct Recall, Delayed Recall, and Recognition	Attrition: 7% ITT: N Blinding: Y	EX = .441 WM = .037 ME = .413
Smiley-Oyen, 2008 (123)	57, older adults, ages 65–79	Duration: 40 wks Frequency: 25–30 min, 3/wk Intensity: 65–80% HRR Combined Strength Training: N MCI: N	Stroop Test, Go-No-Go Test, Simple Reaction Time, Choice Reaction Time, Wisconsin Card Sorting Test	Attrition: 7% ITT: N Blinding: N	AT = .234 EX = −.092
Stroth, 2009 (124)	28, young adults, age *M = 20*	Duration: 6 wks Frequency: 30 min, 3/wk Intensity: 70–100% aerobic threshold Combined Strength Training: N MCI: N	Digit Symbol Substitution Test, Rey Auditory Verbal Learning Test, Stroop Test	Attrition: 22% ITT: N Blinding: Y	AT = −.123 ME = .650‡
Wallman, 2004 (125)	61, adults with chronic fatigue syndrome, ages 16 to 74	Duration: 12 wks Frequency: increased progressively Intensity: based on target HR from treadmill testing Combined Strength Training: N MCI: N	Stroop Test (82 questions) Stroop Test (95 questions)	Attrition: 10% ITT: N Blinding: Y	EX = .479*
Whitehurst, 1991 (126)	14, sedentary older women, ages 61 to 73	Duration: 8 wks Frequency: 35 min, 3/wk Intensity: - - - Combined Strength Training: N MCI: N	Simple Reaction Time, Choice Reaction Time	Attrition: 0% ITT: N Blinding: N	AT = −.551 EX = −.609
Williams, 1997 (104)	187, all women, age *M = 72*	Duration: 42 wks Frequency: 35 min, 2/wk Intensity: - - - Combined Strength Training: Y MCI: N	Digit Span, Picture Arrangement, Cattell's Matrices	Attrition: 20% ITT: N Blinding: N	AT = .501** EX = .189 WM = .348*
Williamson, 2009 (34)	102, elderly adults, ages 70–89 years	Duration: 52 wks Frequency: 45 min, 1–2/wk Intensity: - - - Combined Strength Training: Y MCI: N	Digit Symbol, Modified Stroop Test, 3MSE, Rey Auditory Verbal Learning Test	Attrition: 10% ITT: N Blinding: Y	AT = .206 EX = .026 ME = .011
van Uffelen, 2008 (33)	152, elderly adults with MCI, age *M = 75*	Duration: 52 wks Frequency: 60 min, 2/wk Intensity: >3 METs Combined Strength Training: N MCI: Y	Digit Symbol, Stroop Color Word Test,Verbal Fluency, Auditory Verbal Learning Test	Attrition: 9% ITT: Y Blinding: Y	AT = −.10 EX = −.04 ME = −.03

*** $p < .001$; ** $p < .01$; * $p < .05$; ‡ $p < .10$; AT = attention and processing speed; EX = executive function; MET = metabolic equivalent, WM = working memory; MCI = Mild Cognitive Impairment, ME = memory; HRR = Heart Rate Reserve; MHR = maximum heart rate; RPE = Ratings of Perceived Exertion; TMT = Trail Mating Test; ¥ = indicates multiple time points of data.

TABLE 2. Effects of Aerobic Exercise Interventions Versus Controls on Neurocognitive Performance for Various Cognitive Indices

Cognitive Test	Studies	Domain	Hedge's G (95% CI) (Random Effects)	*p*
Digit Symbol Substitution	8	Attention/Processing Speed	0.146 (−0.002 to 0.294)	.052
Complex/Choice Reaction Time	8	Attention/Processing Speed	0.112 (−0.064 to 0.288)	.898
Simple Reaction Time	8	Attention/Processing Speed	0.088 (−0.118 to 0.295)	.116
Ruff 2 and 7 Test	2	Attention/Processing Speed	0.052 (−0.224 to 0.327)	.715
Trail Making Test Section A	2	Attention/Processing Speed	0.169 (−0.144 to 0.482)	.291
Stroop Interference	7	Executive Function	0.027 (−0.149 to 0.204)	.761
Trail Making Test Section B	5	Executive Function	0.234 (0.042 to 0.426)	.017
Animal Naming	4	Executive Function	0.275 (0.006 to 0.545)	.045
COWAT	2	Executive Function	−0.015 (−0.239 to 0.229)	.894
Logical Memory, Immediate Recall	5	Memory	0.151 (−0.050 to 352)	.140
Rey Auditory Verbal Learning Test	4	Memory	0.113 (−0.082 to 0.308)	.255
Digit Span	6	Working Memory	0.065 (−0.079 to 0.209)	.373
WAIS Letter-Number Sequencing	2	Working Memory	−0.134 (−0.469 to 0.202)	.435

CI = confidence interval; COWAT = Controlled Oral Word Association Test; WAIS = Wechsler Adult Intelligence Scale.

TABLE 3. Classification of Neurocognitive Tests by Domain

Neurocognitive Domain			
Attention	Executive Function	Working Memory	Memory
Accuracy Index	Attentional Flexibility	Digit Span	ADAS Word List Recall
Complex/Choice RT	Categorical Fluency (Animal Naming)	N-Back Spatial Task	Auditory Verbal Learning Test
d2 Test of Attention	Cattell's Matrices	N-Back Task	Benton Visual Retention Test
Digit Matching RTe	Cognitive Flexibility	Self-Ordered Pointing	CERAD delayed recall
Digit Symbol Substitution Test	Covert Orienting of Attention Task	Visual Memory span	RAVLT
Mental Speed	Go-No-Go Test	WAIS Letter Number Sequencing	RAVLT Delay
Paced Auditory Serial Attention Test (PASAT)	Mental Control		RAVLT, Temporal Order
Picture Arrangement	Nonverbal Fluency Test		RBMT faces
Premotor Time	Number Copying Speed		RBMT pictures
Response Compatibility RT	RIPA Organization		RIPA Auditory Processing
Ruff 2 and 7 Test (Letters)	RIPA Problem Solving		RIPA Immediate Memory
Simple RT	RIPA Abstract Reasoning		RIPA Recent Memory
Single/Choice Time Sharing	Ruff 2 and 7 Test (Digits)		Sternberg Memory Search Task, Y-intercept
Spatial Attention Task	Selective Reminding Intrusions		Sternberg Memory Search Task, Slope
Speed of Movement	Set Shifting Ability		Visual and Verbal Memory Test
Stopping Task RT	Stopping Task		Visual Reproduction, Immediate
Stroop Color	Stroop Color/Word or Interference		Visual Reproductions
Stroop Word	Trail Making Test Part B		VLMT Delayed Recall
Task Switching RT	Useful Field of View		VLMT Direct Recall
Trail Making Test Part A	Verbal Fluency Test (FAS)		VLMT Recognition
Visuospatial Cognitive Performance Test	WAIS Similarities		WMS Facial Recognition
Word Copying Speed	Wisconsin Card Sorting Task		WMS Figural Memory, Immediate
			WMS Figural Memory, Delayed
			WMS Logical Memory, Immediate
			WMS Logical Memory, Delayed
			WMS Verbal Paired Associates
			WMS Visual Reproduction

ADAS = Alzheimer's Disease Assessment Scale; RT = reaction time; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; RAVLT = Rey Auditory Verbal Learning Task; WAIS = Wechsler Adult Intelligence Scale; PASAT = Paced Auditory Serial Attention Test; RBMT = Rivermead Behavioral Memory Test; RIPA = Ross Information Processing Test; VLMT = Verbal Learning and Memory Test; WMS = Wechsler Memory Scale.

stretching and toning, health education, and relaxation exercises were also used. Rates of attrition varied widely (range, 0%–41%; mean attrition, 12.2%). Only 13 (44.8%) studies utilized blinded assessments and only seven (24.1%) studies utilized ITT analyses. The effects of exercise on individual neurocognitive measures are presented in Table 2. Due to the substantial number and heterogeneity of neurocognitive tests (Table 3), only those tests used in more than one study are presented.

Attention and Processing Speed

Twenty-four studies examined the effects of aerobic exercise on attention and processing speed. Exercise training was

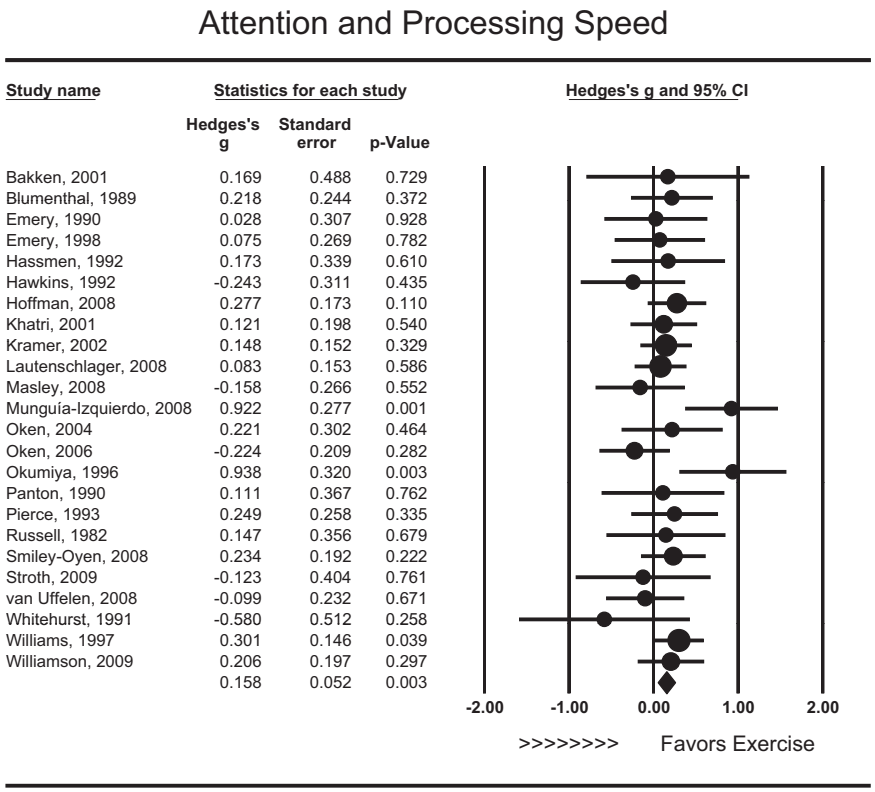

Figure 1. Effect of aerobic exercise on attention and processing speed (n = 24). Individuals randomized to aerobic exercise treatment exhibited improved attention and processing speed relative to controls (g = 0.158; 95% confidence interval [*CI*], 0.055–0.260; p = .003). Each study is denoted with a *circle*, with larger sample sizes corresponding to *larger marks*.

associated with modest improvements in attention and processing speed (g = 0.158; 95% confidence interval [CI], 0.055–0.260; p = .003) (Fig. 1) and this effect was consistent across studies (Q_{23} = 26.249, p = .289). Moderator analyses demonstrated that trials of greater duration did not improve attention and processing speed to a greater extent than briefer interventions (r = .17, Q_1 = 3.555, p = .399). Similarly, intensity was not associated with variations in attention and processing speed outcomes (r = −.375, Q_1 = 1.41, p = .235). Results did not differ between individuals with MCI (g = 0.028, p < .001) and other samples (g = 0.181, p = .825) (Q_1 = 1.228, p = .268). Combined interventions improved attention and processing speed to a greater extent (g = 0.350; 95% CI, 0.042–0.658; p = .026) than aerobic only interventions (g = 0.098; 95% CI, −0.012 to 0.208; p = .152) (Q_1 = 4.373, p = .037). There was no observed association between the mean age of study participants and improvements in attention and processing speed (r = −.047, p = .817).

Executive Function

Nineteen studies assessed the effects of aerobic exercise on executive function. Aerobic exercise was associated with modest improvements in executive function (g = 0.123; 95% CI, 0.021–0.225; p = .018) (Fig. 2), and effects were of similar magnitude across studies (Q_{18} = 13.418, p = .766). Neither duration (r = −.436, Q_1 = 3.627, p = .057) nor intensity (r = −.203, Q_1 = 0.413, p = .520) were related to improved executive function. Improvements in executive function were smaller among individuals with MCI (g = −0.004, p = .973) relative to other samples (g = 0.153, p = .008) (Q_1 = 1.377, p = .241), and findings did not differ between studies that included only aerobic exercise (g = 0.109, p = .074) or combined aerobic exercise with other exercises (e.g., strength training) (g = 0.163, p = .106) (Q_1 = 0.214, p = .644). Finally, there was no observed association between the mean age of study participants and improvements in executive function (r = −.348, p = .130).

Working Memory

Twelve studies examined the effects of aerobic exercise on working memory. Exercise did not seem to improve working memory performance (g = 0.032; 95% CI, −0.103 to 0.166; p = .642) (Fig. 3) and this effect was relatively consistent across trials (Q_{11} = 12.241, p = .346). Similar to other cognitive domains, neither the duration of the intervention (r = .346, Q_1 = 1.438, p = .230) nor the intensity of exercise (r = .109, Q_1 = 0.123, p = .725) seemed to moderate the effects of treatment. Only one study examined the effects of working memory among individuals with MCI and test for moderation was, therefore, not examined. Combined interventions (n = 2) seemed to improve working memory (Q_1 = 4.817, p = .028) (g = 0.288; 95% CI, 0.030–0.546; p = .028) relative to aerobic only interventions (g = −0.042; 95% CI, −0.184 to 0.101; p = .567). In

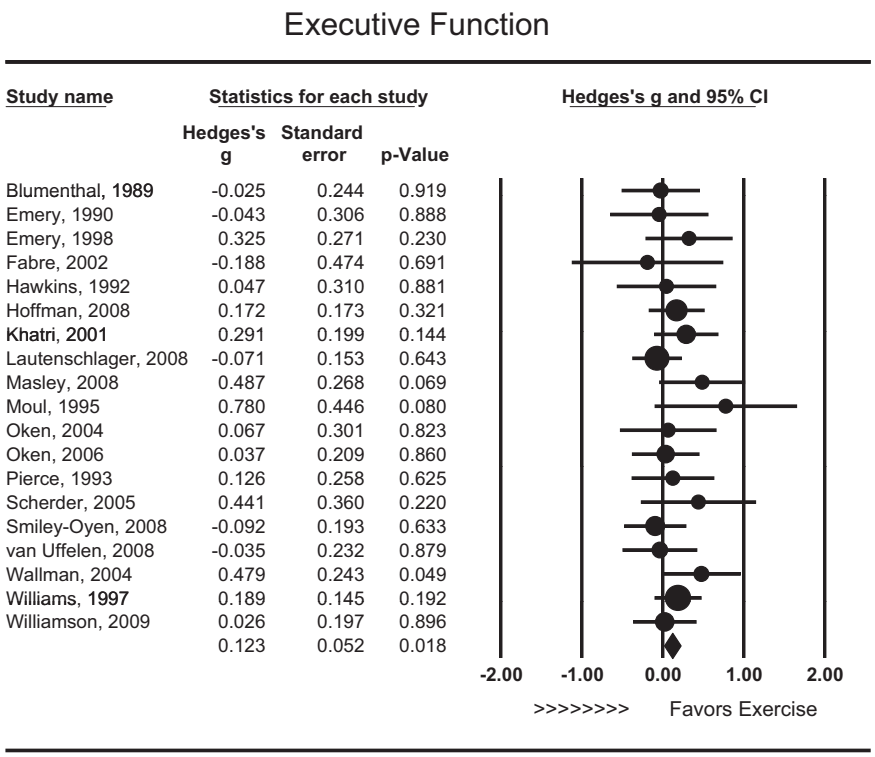

Figure 2. Effect of aerobic exercise on executive function ($n = 19$). Individuals randomized to aerobic exercise treatment exhibited improved executive function (g = 0.123; 95% confidence interval [*CI*], 0.021–0.225; $p = .018$). Each study is denoted with a *circle*, with larger sample sizes corresponding to *larger marks*.

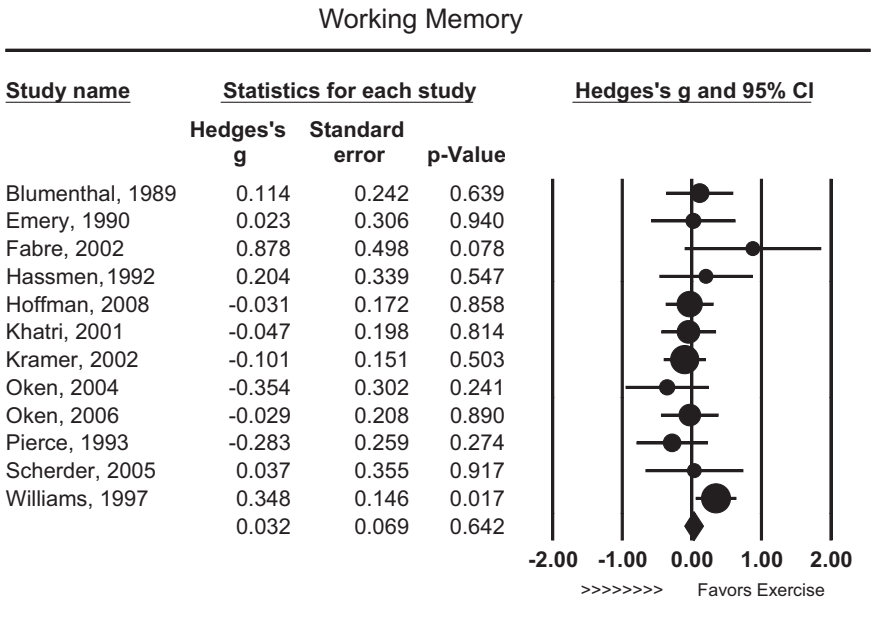

Figure 3. Effect of aerobic exercise on working memory ($n = 12$). Individuals randomized to aerobic exercise treatment did not exhibit significant improvements in working memory relative to controls (g = 0.032; 95% confidence interval [*CI*], −0.103 to 0.166; $p = .642$). Each study is denoted with a *circle*, with larger sample sizes corresponding to *larger marks*.

addition, a significant association was observed between mean age of study participants and improvements in working memory, with older samples demonstrating greater improvements relative to younger samples ($r = .564$, $p = .051$).

Memory

Sixteen studies assessed the effects of aerobic exercise on memory function. Aerobic exercise was associated with modest improvements in memory relative to controls (g = 0.128;

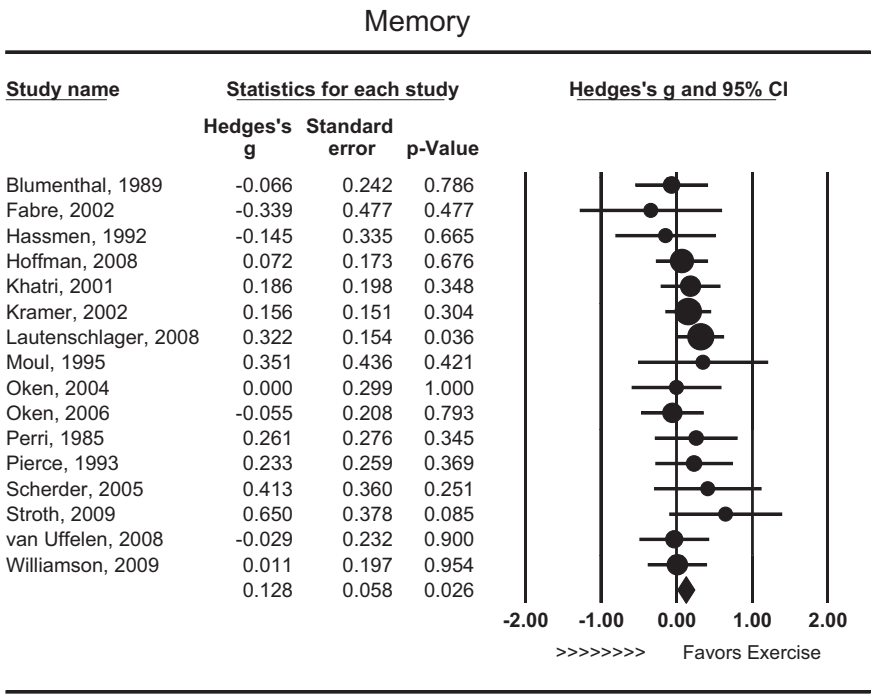

Figure 4. Effect of aerobic exercise on memory (n = 16). Individuals randomized to aerobic exercise treatment exhibited improved memory relative to controls (g = 0.128; 95% confidence interval [*CI*], 0.015–0.241; p = .026). Each study is denoted with a *circle*, with larger sample sizes corresponding to *larger marks*.

95% CI, 0.015–0.241; p = .026) (Fig. 4) and effects were of similar magnitude across studies (Q_{15} = 9.030, p = .876). Neither intensity (r = −.051, Q_1 = 0.026, p = .871) nor duration (r = .373, Q_1 = 1.381, p = .240) seemed to moderate the observed effects on memory. Sensitivity analyses demonstrated that the effects of exercise were stronger among individuals with MCI (g = 0.237; 95% CI, 0.000–0.474; p = .050) relative to noncognitively compromised individuals (g = 0.096; 95% CI, −0.032 to 0.224; p = .143), although the statistical test for moderation did not achieve significance (Q_1 = 1.055, p = .304). Only one study assessing memory utilized a combined intervention, so this was not examined as a potential moderator. In addition, there was no observed association between the mean age of study participants and improvements in memory (r = −.222, p = .175).

Study Quality

In order to assess whether methodological quality moderated the observed pattern of results, we examined whether treatment effects varied by 1) blinding of assessors and 2) use of ITT analyses. Studies did not differ in neurocognitive treatment effects whether they did (g = 0.143, p = .013) or did not use (g = 0.185, p = .012) blinded assessments (Q_2 = 0.204, p = .651). Similarly, the effects of treatment on neurocognitive performance did not differ between those studies that did (g = 0.161, p = .004) or did not (g = 0.166, p = .087) utilize ITT analyses (Q_2 = 0.002, p = .964).

DISCUSSION

Results indicate that aerobic exercise training confers modest improvements in neurocognitive function among healthy older adults, including improvements in attention and processing speed, executive function, and memory. Aerobic exercise did not seem to benefit working memory, however. Moderator analyses demonstrated that studies utilizing combined aerobic exercise and strength training interventions improved attention and processing speed and working memory to a greater extent than aerobic exercise alone. In addition, we found preliminary evidence that trials among individuals with MCI may be associated with greater improvements in memory relative to those among noncognitively compromised samples. In contrast, neither training characteristics, such as study duration and intensity, nor methodological quality were associated with differential improvements in neurocognition.

Although previous meta-analytic reviews have reported that exercise may improve neurocognitive performance (8–12,32), ours is one of the largest reviews to date demonstrating that aerobic exercise improves neurocognition among nondemented adults and the first to show that physical activity may enhance memory performance among individuals with MCI, a group at elevated risk for Alzheimer's disease (24). Several previous meta-analytic studies have examined the relationship between physical activity and cognitive function (8–12,32). Colcombe and Kramer (9) reported that RCTs of exercise are associated with clinically meaningful improvements in executive function, processing speed, memory, and motor function. Our findings showed markedly weaker effects relative to this review, most likely as a result of excluding two decidedly positive studies trials included in the meta-analysis of Colcombe and Kramer (35,36) which, on closer examination, were not truly RCTs. In a Cochrane review, Angevaren and colleagues (11) concluded that,

although RCTs of aerobic exercise among individuals without cognitive impairment were associated with modest improvements in attentional processes, cognitive speed, and motor function, the existing data were insufficient to show that improvements in cognition were attributable to changes in cardiovascular fitness. Similarly, Etnier and colleagues (32) have demonstrated that, although higher levels of fitness were associated with better neurocognitive performance among cross-sectional study designs, studies examining pre and post comparisons found that larger gains in aerobic fitness were associated with lesser improvements in cognitive performance (32). Etnier and colleagues (8) have also noted that methodological limitations contributed to significant variability in treatment effects, with higher-quality studies tending to show smaller effects, and studies with the highest-quality rating demonstrating no effect of exercise on neurocognition. Most recently, van Uffelen and colleagues (12) reported that physical activity interventions among individuals without cognitive decline, on average, tended to report improved neurocognitive function. However, van Uffelen and colleagues (12) did not attempt to statistically combine treatment ESs across studies, reported that the majority of existing trials examining this question have failed to demonstrate a treatment benefit, and found that the extant literature is marked by a lack of high-quality studies. The present analyses address many of the issues raised by this previous review by including several large, high-quality RCTs not previously incorporated in systematic literature syntheses (30,31,33,34).

The finding that exercise may produce larger improvements in memory for individuals with MCI than other patient groups is novel and warrants further investigation, although this must be viewed as preliminary. Although Heyn and colleagues (10) demonstrated that physical activity is associated with improvements in mental status among individuals with dementia, the majority of these trials were conducted among institutionalized adults with dementia and utilized balance and isometric exercises and did not examine the effects of aerobic exercise, specifically, on neurocognition. The finding that aerobic exercise improves memory is consistent with several animal studies, which have indicated that physical activity increases brain-derived neurotrophic factor expression (80) in the hippocampus and perihippocampal structures (81,82). In an important examination of mediators, Pereira and colleagues (83) demonstrated that increased brain-derived neurotrophic factor in the dentate gyrus, an area of the brain proximal to the hippocampus, was associated with dose-response improvements in memory performance among younger adults participating in an exercise intervention. In addition to plausible neurotrophic mediators, it is also possible that individual differences influenced the present findings. For example, it is possible that the MCI samples in our study were composed of a greater number of individuals with the apolipoprotein E type 4 allelic genotype, which has been associated with an increased risk for incident MCI and Alzheimer's disease (84). In addition, evidence (85–87) suggested that individuals with this genotype may exhibit relatively greater neurocognitive improvements with physical activity compared with healthy, older adults.

The finding that aerobic exercise alone did not improve working memory performance is an interesting and unpredicted finding. Although it is unclear why aerobic exercise improved other cognitive functions but did not seem to benefit working memory, this finding is consistent with previous brain imaging studies of aerobic exercise. Previous studies have demonstrated that cerebral alterations associated with exercise are preferentially in the perihippocampal region (83), anterior white matter tracks (88), and anterior cingulate (89). Although there is substantial overlap in the brain circuitry for carrying out complex cognitive processes, such as working memory, no imaging studies have demonstrated volumetric changes in the dorsolateral prefrontal cortex, which is primarily subserved by white matter projections from the corpus callosum and most consistently associated with working memory performance (90,91). The finding that combined aerobic exercise and strength training interventions improved attention and working memory to a greater extent than aerobic exercise alone is consistent with previous reviews (9), as well as mechanistic studies demonstrating that strength training may improve neurocognitive function by increasing insulin growth factor, which has been implicated as a mediator of the exercise and neurocognition relationship (92–94). It is also possible that interventions utilizing both aerobic exercise and strength training were more effective in reducing cerebrovascular risk factors (e.g., high blood pressure) (95) and improving aerobic fitness relative to aerobic training alone (96). These improvements in cardiovascular function may reduce the white matter degradation and cerebral ischemia that often result from these conditions (97–99). Alternatively, it is also possible that combined interventions may result in greater improvements in vascular health (100) and basal levels of inflammation (101,102), although these relationships have yet to be investigated.

The present meta-analysis has several limitations. First, the literature is marked by a lack of high-quality trials examining the effects of aerobic exercise on cognitive end points. Trials included in our analyses differed substantially in their use of blinded evaluations, ITT analyses, and clinically validated cognitive assessment tools. Second, RCTs are limited by logistical constraints in their ability to sustain interventions over prolonged periods of time. Accordingly, the majority of studies examining cognitive end points have done so after several months of aerobic training (79,103) or, in some instances, incorporated follow-ups several years later (33,104). There are limited data regarding how physical activity sustained over the course of several years may affect cognitive end points (2,105), despite observational data indicating that physical activity and cardiovascular health may take years to affect brain health (106,107). In addition, RCTs that have examined the neurocognitive effects of aerobic exercise over an extended time period have demonstrated greater improvements in memory over longer follow-up periods (30,73). Third, the majority of extant studies have utilized interven-

tions with frequency and intensity prescribed in accordance with the American Heart Association recommendations for cardiac rehabilitation (i.e., heart rates at 70% peak oxygen consumption three times per week). It is, therefore, possible that there was not enough of a range in exercise prescriptions to observe an effect on neurocognition. Finally, there is a lack of consensus as to which neurocognitive measures are most appropriate to examine changes in neurocognitive function associated with exercise. As shown in Table 2, there is substantial heterogeneity in treatment effects among neurocognitive measures. Accordingly, future studies would benefit from the identification of a standardized neurocognitive battery with the appropriate psychometric characteristics to examine neurocognitive measures associated with aerobic exercise.

In conclusion, aerobic exercise training results in modest improvements in cognitive performance among nondemented adults. Trials utilizing longer interventions were associated with greater gains in attention and processing speed, whereas trials conducted among individuals with MCI tended to demonstrate greater improvements in memory relative to non-MCI samples. Additional randomized trials are needed with larger samples, more extensive follow-up periods, appropriate controls, and more extensive measurement of potential mediators of cognitive change. Accordingly, future studies would benefit from the assessment of subclinical vascular health as a potential mediator of the exercise and neurocognition relationship, as this has been associated with improvements in aerobic capacity (100) and neurocognitive performance in other samples (108,109). Future studies should also collect functional magnetic resonance imaging or diffusion tensor imaging measures to track cerebral alterations post exercise, as several previous studies have demonstrated that exercise and improved fitness may increase cerebral blood flow (16) and alter blood oxygen level dependent response patterns to cognitive tasks (89), as well as improve structural brain health, such as by increasing white (88) and gray matter integrity (22) and brain volume (88). Finally, more rigorous studies should examine the effects of aerobic exercise training among individuals with MCI to determine whether this is a plausible strategy to delay or prevent incident dementia (101).

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