

[Primary Care]

The Role of Mobility as a Protective Factor of Cognitive Functioning in Aging Adults: A Review

Emily Zhao, BS,[†] Michael J. Tranovich, DO,[†] and Vonda J. Wright, MD, MS*[†]

Context: Over 33 chronic disease states and health disorders, including obesity and type 2 diabetes, are grouped into what is known as *sedentary death syndrome*. All these conditions are positively affected by 30 minutes of brisk exercise daily. In addition, only 30% of aging is based on genetics, with 70% on lifestyle. Therefore, a large majority of aging is controlled by individual health behaviors. Exercise is a powerful tool for healthy aging of the body and the mind. Courses of short- and long-term exercise provide benefits to musculoskeletal and cardiovascular health and can prevent age-related brain structural and functional losses. This review examines the evidence in support of mobility as an inexpensive and effective protective factor in maintaining brain health and preventing cognitive decline in aging adults.

Evidence Acquisition: A PubMed search was performed for articles in English from 1990 to 2012. Reference lists were also reviewed and relevant articles obtained.

Level of Evidence: Level 4.

Results: Evidence suggests that maintaining a high level of cardiopulmonary fitness and mobility exhibits protective effects on structural changes that occur with aging in areas of the brain associated with memory, attention, and task completion. Chronic exercise is also associated with preservation of overall cognitive functioning and prevention of dementia.

Conclusion: In combination with other preventative measures, physical mobility can assist in preventing or slowing cognitive decline in aging adults.

Keywords: mobility; exercise; aging; master athlete; cognitive function

Regular exercise improves overall health; reduces weight; lowers cholesterol levels; protects against stroke, heart disease, and high blood pressure; increases immune health; and reduces stress.^{1,7,19} Throughout the past 20 years, the effects of physical mobility on brain structure and function have been explored. Many studies established a connection between exercise and increased cognitive function and a reduction in age-related cognitive decline.^{14,25} This is particularly relevant as the US baby boomer population reaches retirement age and the number of adults aged 60 years and older increases to more than 50 million people.³⁹

Now there is a great need to explore potential preventative health measures, such as exercise interventions, to prolong overall health and independence in the aging population. Doing so may reduce the need for complex and debilitating health interventions and thereby increase quality of life and lower overall health care costs. In this review, the evidence

implicating the role of mobility—specifically, regular and prolonged physical exercise—as a protective factor in cognitive function and its potential benefits within the aging population are summarized.

METHODS

A PubMed search was performed using the keywords “exercise AND cognition” for articles in English from 1990 to 2012. Articles were narrowed to retrospective, prospective, and cross-sectional studies, as well as randomized clinical trials that studied exercising frequency and fitness level in relation to brain structure and function. The studies summarized in this review pay particular attention to the role of exercise in the human brain rather than animal models, with special emphasis on the impact of exercise as a neuroprotective antidote to aging (Table 1).

From the [†]University of Pittsburgh, Pittsburgh, Pennsylvania

*Address correspondence to Vonda J. Wright, MD, MS, Department of Orthopaedic Surgery, University of Pittsburgh, 3200 South Water St, Pittsburgh, PA 15203 (e-mail: wrightj@upmc.edu).

The following authors declared potential conflicts of interest: Vonda J. Wright, MD, MS, received royalties from Dick's Sporting Goods and AMACOM Books.

DOI: 10.1177/1941738113477832

© 2013 The Author(s)

Table 1. Literature summary of mobility and exercise benefits on brain structure and cognitive function

	Brain Volume Increase ^a	Improved Cognitive Function		Decreased Risk ^b
		Reduced Cognitive Dysfunction	In Setting of Cognitive Decline	
Barnes et al ²		×		
Bixby et al ⁴		×		
Brown et al ⁵		×		
Coelho et al ⁹		×	×	
Colcombe et al ¹²	×			
Colcombe et al ¹³	×	×		
Erickson et al ¹⁷	×	×		
Fabre et al ¹⁸		×		
Gordon et al ²⁰	×	×		
Hamer et al ²¹		×		×
Hillman et al ²²		×		
Hopkins et al ²⁴		×		
Langdon and Corbett ^{27c}	×	×		
Laurin et al ²⁸		×		×
Lautenschlager et al ²⁹			×	×
Lindwall et al ³⁰		×		
Maki et al ³¹		×		×
Marks et al ³²	×			
Richards et al ³⁴		×		×
Rovio et al ³⁵				×
Siette et al ^{36c}	×		×	
Szabo et al ³⁸	×	×		
van Boxtel et al ⁴⁰		×		
Voss et al ⁴³	×	×		
Weuve et al ⁴⁴		×		×
Yaffe et al ⁴⁵				×

^aWith attenuated brain volume decrease.

^bDecreased risk of cognitive disorders and mental decline.

^cAnimal study.

RESULTS

Effects of Exercise on Brain Structure and Cognition

Chronic exercise imparts greater cardiovascular fitness, which is associated with physical changes in brain structure and measurable differences in brain function when compared with conditions of sedentary living and reduced physical activity.^{2,10,21} Animal studies demonstrated structural differences in parts of the brain used in cognitive tasks: there is an increase in size for areas involved with memory, such as the hippocampus,³⁶ which correlates with improved performance in cognitive tasks.⁴² Similar changes in brain structure and function were also noted during investigation of the human population.

Fitness and Structural Brain Changes

Examination of magnetic resonance images from 55 older adults (age range, 55-79 years; mean, 66.5 years) without cognitive impairment (Mini-Mental State Examination range, 24-30; mean, 28.6) exhibited a loss of gray and white matter that correlated with increased age, specifically in the prefrontal, superior parietal, and middle/inferior temporal cortices.¹² However, when these images were analyzed to assess the degree to which fitness level moderated the change in tissue loss, the same areas affected by age-related decline exhibited the greatest sparing effects due to cardiovascular fitness.^{12,20} Colcombe et al also demonstrated that older adults with high cardiovascular fitness, compared with those with low cardiovascular fitness, had greater activation in areas of the brain related to effective attentional control, which is important in successful task completion.¹³ Fitness level can be a valid parameter in predicting structural changes related to improved cognitive function in areas such as memory and task completion, emphasizing the significance of exercise's role in maintaining these functions.

Fitness and Increased Hippocampal Volume

One area of the brain that shows significant exercise-related size differences is the hippocampus, which is responsible for spatial navigation and the consolidation of short- to long-term memory. A cross-sectional investigation of older adults ($n = 158$; mean age, 66.49 years) showed that those with higher fitness levels also had greater preservation of hippocampal volume.³⁸ This leads to increased accuracy and speed of spatial memory and reduced forgetfulness. Increased hippocampal size, due to exercise, is thought to be the result of exercise-induced increases in levels of brain-derived neurotrophic factor (BDNF).⁴² Decreased levels of BDNF are linked to age-related hippocampal dysfunction and related memory impairment, whereas increased levels of BDNF owing to exercise slow or prevent hippocampal degeneration and improve memory function.¹⁶

BDNF and IGF-1 Mediate Exercise-Induced Structural Changes in the Brain

Exercise-induced increase in levels of BDNF is one of the primary mechanisms mediating improved cognitive function through its effects on increasing hippocampal size, improving

memory function, and reducing depression.^{16,41} Insulin-like growth factor 1 (IGF-1) plays a role in this protective BDNF-mediated mechanism. As with BDNF, levels of IGF-1 increase as a result of physical activity; IGF-1 interacts with BDNF, modulating downstream signaling and subsequent improvements in cognitive function associated with increased hippocampal size. Blocking IGF-1 receptors in the hippocampus resulted in a decrease in exercise-induced increase in BDNF levels and memory retention but not in learning acquisition; the blockade also reduced levels of downstream proteins related to cortical plasticity and memory processes, such as synapsin I, mitogen-activated protein kinase II, and calcium/calmodulin protein kinase II, which have been shown to be elevated as a result of exercise.¹⁵ Thus, exercise induces a biological change involving both BDNF and IGF-1, and these 2 proteins play important roles in mediating downstream effects of exercise-induced improvements in cortical plasticity, hippocampal size, and memory function.

Mobility and Preservation of White Matter

In addition to increased hippocampal size and the preservation of specific areas of cortical gray matter, exercise helps to preserve white matter. Anterior white matter tract loss is associated with cognitive impairment, dementia, and Alzheimer disease³ and is one of the main mechanisms behind cognitive aging. Anterior white matter tracts experienced greater age-related decline than posterior and temporal regions, but this loss was spared by increased aerobic fitness.¹² The cingula, in particular, are white matter tracts that facilitate communication between areas of the limbic system involved in executive function and memory formation. (*Executive function* refers to cognitive processes such as planning, working memory, attention, problem solving, verbal reasoning, inhibition, and task monitoring.) A cross-sectional study of older adults (66 ± 6 years old) revealed that those with high physical fitness, as measured by maximal oxygen consumption, had greater white matter integrity in areas of the cingulum compared with older adults who were sedentary.³² Increased physical activity aids in the preservation of white matter tracts and is one mechanism that can help slow down the process of cognitive aging and prevent debilitating mental decline. (Another mechanism was seen through education effects: higher education was associated with preserved white matter in inferior frontal areas, which mildly differs from the effects seen with exercise.²⁰) While different levels of fitness and education can lead to different structural changes in the brain, they are both predictive of cognitive function preservation through the enhancement of white matter integrity.

Mobility and Improved Cognitive Function

Exercise-induced changes in brain structure are predictive of improved cognitive functions related to those areas.^{17,40,42} These effects on cognitive function are evaluated via neurocognitive and neuropsychological tests that measure parameters such as verbal memory, visual memory, reaction time, and information-

processing speed. Physically fit older adults perform better than their less-fit counterparts at simple cognitive tasks.¹⁰ A study on 42 women aged 50 to 90 years revealed that higher cardiorespiratory fitness was a significant predictor of increased overall cognitive function, cognitive speed, verbal memory, and attention.⁵ Higher levels of physical activity and increased maximal oxygen consumption scores were positively associated with tasks that reflected information-processing speed, such as the Stroop color-word and interference task⁴ and concept shifting test.⁴⁰ There is specificity to how physical activity can benefit cognitive function, particularly in the frontal lobe areas that mediate executive function. Also, increased aerobic capacity with increased age seemed to have the greatest influence on improved cognitive function, especially in areas related to memory and effortful cognitive processing.⁴⁰ These results correlate with structural changes seen in the hippocampus and areas mediating executive function. In addition, physical mobility improves executive control function in older adults by affecting the distribution of cortical signaling related to memory and attentional processes.²² Data indicate that exercise has a selective beneficial effect in those tasks requiring cognitive effort and that it demonstrates significant application in promoting healthy cognitive aging.

The effects seen in van Boxtel's study correlate with an earlier hypothesis by Chodzko-Zajko: tasks that require significant cognitive processing would be more sensitive to the effects of fitness than tasks that can be performed with or without minimal attention.⁶ To investigate this task-dependent association between physical fitness and cognitive performance, Chodzko-Zajko suggested investigating molecular level differences and responses to various cognitive challenges between individuals of high and low fitness as well as before and after a structured program of exercise training. In the past 20 years since Chodzko-Zajko's suggestion, a wealth of information has been gathered. Results from studies investigating individuals of high and low fitness show that the biological impact of exercise on the brain and cognition includes structural and cognitive changes that facilitate healthy brain aging.^{12,16,17,41,42}

Therapeutic Effects of Short-Term Exercise Interventions on Brain Structure and Cognition

The human brain gradually grows and develops through the second or even third decade of life and then slowly decreases in size upon the later years of life. Exercise and maintained physical activity are implicated in slowing down the gradual progression of brain structural and cognitive decline. A number of longitudinal studies and randomized control trials investigated the effects of varying lengths of exercise interventions on brain structure and neurocognitive function, as well as mood and depression status, which are major determinants of quality of life.^{8,17,21,29,31} Generally, these studies show that adding physical activity to one's daily routine can result in significant biological changes that can improve one's overall physical as well as mental health.

Exercise-Induced Changes in the Brain

Exercise has an immediate biological effect on brain composition and structure. A regimen of physical activity for 2 hours per day at 5 days per week for either 4 or 8 weeks produced a significant increase in rat hippocampal BDNF, compared with only cognitive activity treatment.²⁷ Similarly in humans, 6-month and 1-year aerobic exercise interventions, resulting in increased fitness in participants, were associated with an increase in serum BDNF levels and hippocampal size,¹⁷ greater levels of task-related activity in attentional control areas of the brain,¹³ increased white matter integrity in the frontal and temporal lobes, and greater improvement in short-term memory.⁴³ Specifically, Erickson¹⁷ found that aerobic training for 1 year mediated hippocampal growth by 2%, which reversed age-related loss by 1 to 2 years. Also, higher preinterventional fitness was able to counter age-related hippocampal volume decline. Therefore, age-related loss of brain volume can be attenuated by high levels of lifelong fitness or starting and maintaining a chronic exercise regimen regardless of prior fitness level.

Exercise-Induced Improvements in Cognitive Tasks in Healthy Brains

Even short-term exercise interventions improved cognitive function. In older adults aged 60 to 77 years, 2 months of aerobic training significantly improved memory and learning ability, whereas the control group did not see such improvements.¹⁸ Walking 90 minutes once a week for 3 months was associated with improvements in frontal lobe function, perceived quality of life, and motor function compared with those who did not walk.³¹ Healthy young adults who exercised for 4 weeks improved in object recognition memory compared with those who did not exercise consistently or at all.²⁴ The results of these exercise interventions support the evidence that executive functions are selectively maintained or enhanced in humans who exercise regularly and thus have higher levels of fitness. Specific improvements are associated with exercise-induced neurogenesis in the frontal lobe and hippocampal regions of the brain.⁸

The conclusions of several meta-analyses on the wealth of research regarding the effect of exercise interventions on cognitive processes support the notion that exercise is beneficial and selective in which processes that experience the most age-related protection and improvement. Colcombe and Kramer's analysis of 18 interventional studies involving older adults (55 years and older) conducted between 1966 and 2001 showed that fitness training has strong and selective benefits for cognition: the largest fitness-induced benefits were seen in executive control processes, and the degree of fitness effects was moderated by length, type, and duration of fitness training.¹¹ A meta-analysis of 29 randomized control trials between 1982 and 2009 that included younger participants (18 years and older) demonstrated that individuals randomly assigned to aerobic exercise training had modest improvements in attention and processing speed, executive function, and memory.³⁷

Short-Term Exercise Can Improve Cognitive Function in Diseased States

In addition to reducing age-related declines in brain volume and cognitive function, exercise can reduce the risk of age-related neurologic disorders.²⁶ Randomized control trials involving 4 to 6 months of physical activity intervention showed improved frontal cognitive functions in elderly patients with Alzheimer disease⁹ and significant improvement in Alzheimer's Disease Assessment Scale–Cognitive subscale scores in older adults with memory problems²⁹ compared with those who did not engage in physical activity interventions. In a study investigating the dose-response relationship of self-reported exercise and mental health in individuals aged 16 years and older, increased mental health benefits were seen at as little as 20 minutes of exercise per week. A strong dose-response relationship was observed in individuals that participated in high-volume activities such as sports.²¹ In a randomized trial, individuals who had memory problems and were at risk for dementia started a 6-month physical activity regimen and followed it for 18 months; those who received the physical activity intervention demonstrated a mild but important improvement on cognitive functioning tests at 6 months compared with the control group. This improvement continued for another 12 months following the discontinuation of the intervention.²⁹

Exercise May Be Less Effective in Mood Disorders

Exercise seems to have less of a beneficial effect in improving cognition in individuals with mood disorders. In a recent study involving middle-aged and older adults with major depressive disorders who engaged in an exercise intervention for 4 months, no significant difference between the exercise group and control group was seen in performance on neuropsychological tests of executive function, verbal memory, verbal fluency, and working memory.²³ These results are in discordance with the depression reduction hypothesis, which states that depression suppresses cognitive ability but can be alleviated by physical activity, subsequently improving cognitive function.⁴¹ A depressive mood and emotional state may diminish the beneficial effects of exercise, but if exercise is able to reduce the depressive state, the beneficial effects on neurocognition may be more pronounced. A longer randomized clinical trial may be necessary for the effects of exercise on alleviating depression to be realized before improvements in neurocognition are examined.

Impact of Long-Term Exercise and Fitness on Executive Function

Higher Fitness in Older Age Mediates Improved Cognitive Function

Several studies have established that higher levels of activity and fitness over extended periods have positive effects on cognitive functioning in older adults. In a longitudinal study examining activity in more than 16,000 US women between the ages of 70 and 81 years, a higher level of self-reported

activity was associated with higher cognitive performance.⁴⁴ Individuals with the highest reported activity levels had a 20% lower risk of cognitive impairment than individuals with the lowest reported activity levels. Walking as little as 1.5 hours per week was associated with improved cognitive function.⁴⁴ A longitudinal study of individuals in their 70s examining predictors of maintaining cognitive function over 8 years found that weekly moderate to vigorous exercise predicted higher cognitive functioning at follow-up.⁴⁵ In addition to weekly exercise, younger age, white race, high school education level or greater, ninth-grade literacy level or greater, and not smoking predicted increased cognitive functioning,⁴⁵ suggesting that a variety of factors are at play but that exercise is still a significant contributor to neuroprotection. A cohort study of men and women enrolled in the MRC National Survey of Health and Development (the British 1946 birth cohort) that evaluated the relationship between physical exercise and spare-time activity with verbal memory at 36, 43, and 53 years demonstrated that physical exercise at 36 years predicted a slower rate of memory decline in ages 43 to 53, indicating that exercise conferred protection against cognitive decline.³⁴ In a cross-sectional study investigating the effects of exercise intensity and frequency on cognitive functioning, elderly adults that participated in light exercise several times per week during the preceding 12 months exhibited the highest cognitive function scores, whereas individuals that were largely inactive during the preceding 12 months had the lowest cognitive functioning scores.³⁰ While the authors were unable to confirm the cognitive effects of strenuous exercise on Mini-Mental Status Examination scores, this study did demonstrate the cognitive functioning benefits of participating in light exercise on a regular basis.³⁰

While the previous studies used subjective self-reported activity levels to determine fitness, other studies used objective measures such as peak oxygen consumption to establish individual cardiorespiratory fitness.^{2,30,34,44,45} In a 6-year study of healthy older adults, cardiorespiratory fitness, determined by baseline oxygen consumption testing, was associated with better performance on cognitive functioning tests at 6-year follow-up.² The strongest associations involved measures of global cognitive function and attention/executive function. Chronic exercise and maintained fitness over many years can help prevent neurocognitive decline and maintain cognitive processes.

Chronic Exercise Can Reduce the Risk of Cognitive Disorders

In addition to preserved cognitive functioning and decreased levels of psychological distress, long-term exercise and higher activity levels can decrease the risk of dementia in older adults. In a 5-year longitudinal study of individuals aged 65 years and older, physical activity was associated with a decreased risk of cognitive impairment, Alzheimer disease, and dementia, and greater protection against dementia was found in individuals with the highest activity levels.²⁸ A 21-year longitudinal study

also found that physical activity of at least 2 times per week during midlife was associated with a reduced risk of dementia and Alzheimer disease at later ages.³⁵

Future Directions


Studies regarding the effects of exercise on cognitive function provide promising results and pave the way for future research, especially with applications to aging adults. However, there have been several criticisms regarding the methods of past studies and their attempts to establish a causal relationship between exercise and improved cognitive functioning.³³ More consistent measures and evaluations of cognitive functioning and a standard measure for exercise and fitness level would allow for study reproducibility among many different study populations. A more standardized approach to studying exercise and fitness level in relation to cognition would allow for a more quantitative evaluation of dose-response relationships.

A consideration for continued research includes directly studying a very physically active older population, such as masters athletes, and comparing them to a sedentary control group to determine the impact of high-level chronic exercise in preserving mental function. Examining the effects of physical activity in addition to other neurocognitive-

stimulating processes, such as mental and social activity, will help researchers determine the various combinations of modalities that are most effective at preserving brain function and mental capabilities. Both animal and human studies have found that physical and cognitive interventions in combination may be more beneficial to cognitive function than either type of intervention alone,^{18,27} but more specific details regarding which activities are more neuroprotective and which cognitive processes are more impacted have yet to be elucidated.

CONCLUSION

Chronic exercise exhibits positive effects on many areas of the human body, including the cardiovascular and musculoskeletal systems.⁷ Recent research demonstrates that participating in a chronic exercise regimen can improve an individual's cognitive functioning and reduce the risk of dementia and other neurodegenerative diseases. Maintaining mobility through exercise helps maintain brain fitness by preserving hippocampal volume and white matter tract integrity, which are important for memory processing, prevention of age-related cognitive decline, and even prevention of dementia.^{2,22,26,31,34,37} As we age, mobility is important not only for our bodies but for our minds as well.



Clinical Recommendations

SORT: Strength of Recommendation Taxonomy

A: consistent, good-quality patient-oriented evidence
B: inconsistent or limited-quality patient-oriented evidence
C: consensus, disease-oriented evidence, usual practice, expert opinion, or case series

Clinical Recommendation	SORT Evidence Rating
Engaging in regular exercise, especially during the later decades of life, is recommended for maintaining brain health by attenuating age-associated volume decline and white matter losses. ^{8,11,12,17,32,38}	A
Maintained regular exercise increases cardiopulmonary fitness and can help improve executive cognitive functions such as memory. ^{2,4,22,24,30,31,34,37,40,43-45}	A
Physical mobility is recommended in older adults to help reduce the risk of dementia and other age-associated cognitive disorders. ^{9,26,28,29,35,41}	A

REFERENCES

1. Ahlsgog JE, Geda YE, Graff-Radford NR, Peterson RC. Physical exercise as a preventive or disease-modifying treatment of dementia and brain aging. *Mayo Clin Proc.* 2011;86(9):876-884.
2. Barnes DE, Yaffe K, Satariano WA, Tager IB. A longitudinal study of cardiorespiratory fitness and cognitive function in healthy older adults. *J Am Geriatr Soc.* 2003;51(4):459-465.
3. Bartzokis G. Age-related myelin breakdown: a developmental model of cognitive decline and Alzheimer's disease. *Neurobiol Aging.* 2004;25(1):5-18.
4. Bixby W, Spalding T, Hauffler AJ, et al. The unique relation of physical activity to executive function in older men and women. *Med Sci Sports Exer.* 2007;39(8):1408-1416.
5. Brown AD, McMorris CA, Longman RS, et al. Effects of cardiorespiratory fitness and cerebral blood flow on cognitive outcomes in older women. *Neurobiol Aging.* 2010;31(12):2047-2057.
6. Chodzko-Zajko W. Physical fitness, cognitive performance, and aging. *Med Sci Sports Exer.* 1991;23(7):868-872.
7. Chodzko-Zajko W, Proctor D, et al. American College of Sports Medicine position stand: exercise and physical activity for older adults. *Med Sci Sports Exer.* 2009;41(7):1510-1530.
8. Churchill JD, Galvez R, Colcombe S, Swain RA, Kramer RF, Greenough WT. Exercise, experience and the aging brain. *Neurobiol Aging.* 2002;23(5):941-955.
9. Coelho FG, Andrade LP, Pedrosa RV, et al. Multimodal exercise intervention improves frontal cognitive functions and gait in Alzheimer's disease: a controlled trial. *Geriatrics Gerontol Int.* 2013;13(1):198-203.

10. Colcombe S, Kramer A, McAuley E, Erickson KI, Scalf P. Neurocognitive aging and cardiovascular fitness. *J Molec Neurosci*. 2004;24(1):9-14.
11. Colcombe S, Kramer AF. Fitness effects on the cognitive function of older adults. *Psychol Sci*. 2003;14(2):125-130.
12. Colcombe SJ, Erickson KI, Raz N, et al. Aerobic fitness reduces brain tissue loss in aging humans. *J Gerontol A Biol Sci Med Sci*. 2003;58(2):M176-M180.
13. Colcombe SJ, Kramer AF, Erickson KI, et al. Cardiovascular fitness, cortical plasticity, and aging. *Proc Natl Acad Sci U S A*. 2004;101(9):3316-3321.
14. Davenport M, Hogan D, Eskes GA, Longman RS, Poulin MJ. Cerebrovascular reserve: the link between fitness and cognitive function? *Exer Sport Sci Rev*. 2012;40(3):153-158.
15. Ding Q, Vaynman S, Akhavan M, Ying Z, Gomez-Pinilla F. Insulin-like growth factor I interfaces with brain-derived neurotrophic factor-mediated synaptic plasticity to modulate aspects of exercise-induced cognitive function. *Neuroscience*. 2006;140(3):823-833.
16. Erickson KI, Miller DL, Roecklein KA. The aging hippocampus. *Neuroscientist*. 2012;18(1):82-97.
17. Erickson KI, Voss MW, Prakash RS, et al. Exercise training increases size of hippocampus and improves memory. *Proc Natl Acad Sci U S A*. 2011;108(7):3017-3022.
18. Fabre C, Chamari K, Mucci P, Masse-Biron J, Prefaut C. Improvement of cognitive function by mental and/or individualized aerobic training in healthy elderly subjects. *Int J Sports Med*. 2002;23(6):415-421.
19. Gleeson M. Immune function in sport and exercise. *J Appl Physiol*. 2007;103(2):693-699.
20. Gordon BA, Rykhlevskaia EI, Brumback CR, et al. Neuroanatomical correlates of aging, cardiopulmonary fitness level, and education. *Psychophysiology*. 2008;45(5):825-838.
21. Hamer M, Stamatakis E, Steptoe A. Dose-response relationship between physical activity and mental health: the Scottish Health Survey. *Br J Sports Med*. 2009;43(14):1111-1114.
22. Hillman C, Belopolsky A, Snook EM, Kramer AF, McAuley E. Physical activity and executive control: implications for increased cognitive health during older adulthood. *Res Q Exer Sport*. 2004;75(2):176-185.
23. Hoffman B, Blumenthal J, Babyak MA, et al. Exercise fails to improve neurocognition in depressed middle-aged and older adults. *Med Sci Sports Exer*. 2008;40(7):1344-1352.
24. Hopkins ME, Davis FC, Vantighem MR, Whalen PJ, Bucci DJ. Differential effects of acute and regular physical exercise on cognition and affect. *Neuroscience*. 2012;215:59-68.
25. Kraft E. Cognitive function, physical activity, and aging: possible biological links and implications for multimodal interventions. *Aging Neuropsychol Cogn*. 2012;19(1-2):248-263.
26. Kramer AF, Colcombe SJ, McAuley E, Scalf PE, Erickson KI. Fitness, aging and neurocognitive function. *Neurobiol Aging*. 2005;26(1)(suppl):124-127.
27. Langdon KD, Corbett D. Improved working memory following novel combinations of physical and cognitive activity. *Neurorehabil Neural Repair*. 2012;26(5):523-532.
28. Laurin D, Verreault R, Lindsay J, MacPherson K, Rockwood K. Physical activity and risk of cognitive impairment and dementia in elderly persons. *Arch Neurol*. 2001;58(3):498-504.
29. Lautenschlager NT, Cox KL, Flicker J, et al. Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. *JAMA*. 2008;300(9):1027-1037.
30. Lindwall M, Rennemark M, Berggren T. Movement in mind: the relationship of exercise with cognitive status for older adults in the Swedish National Study on Aging and Care (SNAC). *Aging Mental Health*. 2008;12(2):212-220.
31. Maki Y, Ura C, Yamaguchi T, et al. Effects of intervention using a community-based walking program for prevention of mental decline: a randomized controlled trial. *J Am Geriatr Soc*. 2012;60(3):505-510.
32. Marks B, Katz L, Styner M, Smith JK. Aerobic fitness and obesity: relationship to cerebral white matter integrity in the brain of active and sedentary older adults. *Br J Sports Med*. 2011;45(15):1208-1215.
33. Miller DI, Taler V, Davidson PS, Messier C. Measuring the impact of exercise on cognitive aging: methodological issues. *Neurobiol Aging*. 2012;33(3):622-643.
34. Richards M, Hardy R, Wadsworth ME. Does active leisure protect cognition? Evidence from a national birth cohort. *Soc Sci Med*. 2003;56(4):785-792.
35. Rovio S, K areholt I, Helkala EL, et al. Leisure-time physical activity at midlife and the risk of dementia and Alzheimer's disease. *Lancet Neurol*. 2005;4(11):705-711.
36. Siette J, Westbrook RF, Cotman C, et al. Age-specific effects of voluntary exercise on memory and the older brain [published online July 13, 2012]. *Biol Psychiatry*.
37. Smith PJ, Blumenthal JA, Hoffman BM, et al. Aerobic exercise and neurocognitive performance: a meta-analytic review of randomized controlled trials. *Psychosomat Med*. 2010;72(3):239-252.
38. Szabo AN, McAuley E, Erickson KI, et al. Cardiorespiratory fitness, hippocampal volume, and frequency of forgetting in older adults. *Neuropsychology*. 2011;25(5):545-553.
39. US Census Bureau. *US Summary: 2010*. Washington, DC: US Census Bureau; 2010.
40. van Boxtel MP, Paas FG, Hous PJ, Adam JJ, Teeken JC. Aerobic capacity and cognitive performance in a cross-sectional aging study. *Med Sci Sports Exer*. 1997;29(10):1357-1365.
41. Vance D, Wadley V, Jolles J. The effects of physical activity and sedentary behavior on cognitive health in older adults. *J Aging Phys Act*. 2005;13(3):294-313.
42. Vaynman S, Ying Z, Ball KK, Roenker DL, Rizzo M. Hippocampal BDNF mediates the efficacy of exercise on synaptic plasticity and cognition. *Euro J Neurosci*. 2004;20(10):2580-2590.
43. Voss MW, Heo S, Prakash RS, et al. The influence of aerobic fitness on cerebral white matter integrity and cognitive function in older adults: results of a one-year exercise intervention [published online June 5, 2012]. *Hum Brain Mapp*.
44. Weuve J, Kang J, Manson JE, Breteler MM, Ware JH, Grodstein F. Physical activity, including walking, and cognitive function in older women. *J Am Med Assoc*. 2004;292(12):1454-1461.
45. Yaffe K, Fiocco A, Lindquist K, et al. Predictors of maintaining cognitive function in older adults: the Health ABC Study. *Neurology*. 2009;72(23):2029-2035.