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Impact of aerobic exercise on neurobehavioral outcomes

Patrick J. Smith[*], **Guy G. Potter**, **Molly E. McLaren**, and **James A. Blumenthal**
Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC, USA

Abstract

Numerous studies have examined the relationship between physical activity and cognitive function, demonstrating that greater physical activity is associated with lower incidence of cognitive impairment in later life. Due to an increasingly large number of older adults at risk for cognitive impairment, the relationship between physical activity and cognition has garnered increasing public health relevance and multiple randomized trials have demonstrated that exercise interventions among sedentary adults improve cognitive performance in multiple domains of function. This article will examine the relationship between physical activity and cognitive function by reviewing several different areas of literature, including the prevalence of cognitive impairment, assessment methods, observational studies examining physical activity and cognition, and intervention studies. The present review is intended to provide a historical tutorial of existing literature linking physical activity, exercise, and cognitive function among both healthy and clinical populations.

Keywords

Physical activity; Neurocognition; Aerobic exercise

The impact of physical activity and cognitive function has been a topic of increasing interest over the past two decades. Numerous studies have shown that physically active individuals are less likely to experience cognitive decline and dementia in later life (Sofi et al., 2011) and that increasing physical activity is associated with improvements in cognitive function (Smith, Blumenthal, Babyak et al., 2010; Smith, Blumenthal, Hoffman et al., 2010). The impact of physical activity on cognition has garnered increasing interest as rates of physical inactivity (Wolf & Colditz, 1998) and cognitive impairment continue to increase rapidly (Graham et al., 1997; Luck, Luppa, Briel, & Riedel-Heller, 2010; Plassman et al., 2008). This article will examine the relationship between physical activity and cognitive function by reviewing several different areas of literature. First, we describe the prevalence of cognitive impairment; second, we discuss how cognitive function and cognitive impairment are assessed, as well as neuroimaging assessments of brain correlates of physical activity, including markers of connectivity, vascular function, and cortical volume; finally, we provide an overview of observational and interventional studies examining the relationship

[*]Corresponding author: smith562@mc.duke.edu (P.J. Smith).

of physical activity and cognitive function in healthy adults and in clinical populations. In order to identify studies included in the present literature review, we reviewed recent meta-analytic and review studies, as well as highly cited randomized trials, in order to provide an up-to-date assessment of the existing literature on physical activity and cognitive function. In order to identify all meta-analyses to date, we also performed a brief literature search through PubMed and Web of Science using the terms “exercise”, “physical activity”, “cognitive”, “meta-analysis”, and/or “review”. We also review highly cited observational studies if they utilized a prospective design and/or included important physiological measures that help to better understand the relationship between cardiovascular fitness and cognitive function. The present review is intended to provide a historical tutorial of existing literature linking physical activity, exercise, and cognitive function among both healthy and clinical populations.

1. Epidemiology of neurocognitive impairment

Cognitive impairment, including dementia, is a growing public health problem worldwide, with prevalence estimates in older adults ranging between 10% and 22% (Graham et al., 1997; Luck et al., 2010; Plassman et al., 2008). The burden of cognitive impairment is growing worldwide and the number of older adults living with Alzheimer’s disease (AD) is estimated to increase from the current 26.6 million to over 106 million by mid-century (Qiu, Kivipelto, & von Strauss, 2009). The impact of cognitive impairment is particularly burdensome in the United States, where an estimated 5.3 million Americans presently have Alzheimer’s (2010) disease (AD), and as many as 10 million ‘baby-boomers’ are presently at risk for cognitive decline (Hebert, Scherr, Bienias, Bennett, & Evans, 2004). In addition to the burden of AD, 15–20% of dementia cases are attributable to underlying vascular disease, making vascular dementia (VaD) the second most common cause of dementia worldwide (Roman, 2002; Roman et al., 2004) and approximately 30% of individuals with Parkinson’s disease will eventually develop dementia (Aarsland, Zaccai, & Brayne, 2005). In addition to these primary causes of late-life dementia, it has been estimated that an additional 5.4 million individuals have cognitive impairment that does not reach the threshold for dementia (cognitive impairment, not dementia [CIND]) (Plassman et al., 2008), and more than one million elderly adults in the United States experience post-stroke VaD (Roman, 2002). Taken together, cognitive impairment is becoming increasing common in the aging United States society and represents a significant public health problem.

2. Assessment of cognition

2.1. Traditional neuropsychological testing

Neuropsychological testing is used to measure the strength and pattern of various cognitive abilities, including memory, concentration, and executive function, as well as to discriminate between normal brain aging and the development of dementia. One of the earliest standardized neuropsychological batteries designed to measure brain function was the Halstead–Reitan battery, first described by Halstead (1947) and later refined by Reitan (1955). In its original content, the battery consisted of 10 subtests including the Halstead (1947) Category test, Tactual Performance Tests, Rhythm test, Seashore Test, Speech-Sound Perception test, Finger Oscillating test, and Trail Making Test A and B. Although

subsequent refinements to this battery were made (Lezak, Howieson, & Loring, 2004), many research studies of physical activity continue to use subtests from this battery to assess neurocognitive function, particularly the Trail Making Test, and its validity has been well established (Russell, 1998).

Another well validated testing measure, the Wechsler (2008) Adult Intelligence Scale (WAIS), is the gold standard for the assessment of intellectual functioning in adults, and also has often been used to assess the presence and severity of neurocognitive impairment. First introduced in 1955, the WAIS has undergone several iterations. Currently on its fourth version (WAIS-IV), the core subtests of the WAIS include working memory tests (arithmetic, digit span, and letter–number sequencing), a verbal comprehension index (vocabulary, similarities, information, and comprehension), tests of perceptual organization (block design, matrix reasoning, and picture completion), and processing speed assessments (digit symbol coding and symbol search) (Wechsler, 2008). Wechsler (1987) has also designed one of the most frequently used tests of memory, the Wechsler Memory Scale (WMS). This scale, currently on its fourth edition, includes the logical memory, verbal paired associates, and visual reproduction subtests, among others, and is often used in conjunction with the WAIS-IV.

A fourth standardized test battery, the Luria–Nebraska neuropsychological battery, was initially published in 1980 based on the work of Luria and Christensen. This comprehensive battery consists of 14 subtests: motor function, rhythm, tactile function, visual function, receptive speech, expressive speech, writing, reading, arithmetic, memory, intellectual processes, pathognomonic, left hemisphere, and right hemisphere function (Golden et al., 1982). In addition to these general test batteries, there are numerous batteries that have been designed for assessment within specific populations, including HIV, neurotoxicity, traumatic brain injury, and dementia (Lezak et al., 2004). There are also published harmonization standards for test batteries among specific populations, comprised of different combinations of commonly used clinical tests. For example, existing harmonization standards include recommendations for tests used in the assessment of vascular cognitive impairment (Hachinski et al., 2006), mild cognitive impairment (Albert et al., 2011), and Alzheimer's disease (McKhann et al., 2011).

The majority of studies examining the impact of aerobic exercise on neurocognition has used subtests from these established clinical test batteries. Although test selection has varied widely, most evidence suggests that tests involving processing speed may be the most amenable to improvement with aerobic exercise training (Etnier, Nowell, Landers, & Sibley, 2006; Smith, Blumenthal, Babyak et al., 2010; Smith, Blumenthal, Hoffman et al., 2010). For example, clinical neuropsychological tests such as Trail Making test, Animal Naming test, and Digit Symbol Substitution test appear to be the most improved with exercise and all require efficient processing speed abilities (Smith, Blumenthal, Babyak et al., 2010; Smith, Blumenthal, Hoffman et al., 2010). As we reported in a meta-analysis (Smith, Blumenthal, Babyak et al., 2010; Smith, Blumenthal, Hoffman et al., 2010), the most commonly used measures have included the Digit Symbol Substitution and Digit Span tests from the WAIS, Simple and Complex/Choice Reaction Time tests, and the Stroop Interference test. In addition to established clinical tests, many studies have used measures of simple and

complex processing speed, such as Flanker tasks, as measures of overall brain function (Kramer, Erickson, & Colcombe, 2006). These tests assess both simple and complex processing abilities by testing reaction time under conditions requiring low and high levels of response inhibition, which may be important as data from some studies suggest that aerobic exercise may improve complex processing abilities but may have little impact on simple reaction time measures (Kramer et al., 1999).

Although cognitive testing has traditionally been used to measure cognitive abilities within various domains of function, neuroimaging assessments allow for a more sensitive assessment of brain activity. Whereas cognitive function provides a more accurate measure of cognitive performance or function on various tasks, neuroimaging allows for a more sensitive examination of the brain regions or neurophysiological mechanisms underlying these functions. Various neuroimaging measures have been employed to examine the relationship between exercise and cognitive function, including structural markers, measures of perfusion, tractography, and functional connectivity.

3. Neuroimaging assessments

The predominant approach for in vivo analysis of brain structure and function is magnetic resonance imaging (MRI). MRI uses manipulations of magnetic fields to produce contrasts between different types of body tissue, which results in highly detailed images of tissue structures. In the brain, structural MRI allows visualization and quantification of volumetric indices of specific brain regions, the prevalence and volume of white matter hyper-intensities, and regional markers of neuronal and white matter density. In addition to these conventional measures, more novel approaches relevant to assessing the effects of physical activities include: 1) diffusion tensor imaging (DTI), which is used to assess the integrity of specific white matter fiber pathways within the brain, 2) arterial spin labeling (ASL), which quantifies regional blood perfusion in the brain, and 3) cerebral blood volume (CBV), which may be a marker for neurogenesis in areas like the hippocampus (Pereira et al., 2007). Functional MRI (fMRI) uses related methods to detect changes in blood flow in the brain due to neural activity, which is referred to as the blood oxygenation level dependent (BOLD) signal. Functional MRI allows visualization and quantification of activity in specific brain regions in response to specific cognitive tasks, and well as of intrinsically connected networks of activity across the brain that are detectable when an individual is at rest. The most commonly studied intrinsic network is the default mode network, although other cognitive control networks have been studied.

4. Observational studies of physical activity and cognitive function

4.1. Cross-sectional relationship between physical activity, fitness, and cognitive function

Multiple cross-sectional studies have demonstrated that physical activity is associated with improved cognitive function. Beginning in the 1970s, Spirduso (1975), Spirduso and Clifford (1978) was the first to investigate this relationship, demonstrating that physically active older adults exhibit faster reaction time in comparison with their sedentary counterparts, a finding that spurred scientific interest in the role of physical activity in slowing the aging process. Epidemiological studies have generally supported these initial

cross-sectional findings, demonstrating that more physically fit and more physically active individuals tend to exhibit better cognitive function relative to their sedentary counterparts. Several different indices of physical activity and cardio-pulmonary function have been examined as they relate to cognitive function. These have included self-report measures of physical activity, objectively measured fitness levels (such as peak oxygen consumption [peak VO_2]) (Szabo et al., 2011), and markers of pulmonary function (such as forced expiratory volume) (Cerhan et al., 1998), among others.

Across various methods of assessment, higher levels of physical activity have been associated with greater cognitive function. Higher levels of self-reported physical activity have also been associated with quicker reaction times among community-dwelling volunteers, with greater physical activity correlating most strongly with measures of response inhibition and complex attentional processes (Hillman et al., 2006). Similar results have been demonstrated when more objective indices of fitness have been examined. A previous study among older adults (≥75 years of age), found a positive association between neuropsychological performance, particularly on tests of processing speed, and performance on the modified Physical Performance Test (Binder, Storandt, & Birge, 1999), independent of general intelligence. Colcombe et al. (2004) reported similar findings in a sample of 41 community-dwelling older adults. Estimated fitness level was derived using an index of peak VO_2 derived from the Rockport 1-mile test. Participants were then asked to perform a controlled reaction time test while undergoing functional brain imaging. Older adults with high cardiovascular fitness demonstrated performed better on a reaction time task compared to older adults with worse cardiovascular fitness, as well as showing greater activation in the medial frontal gyrus, superior frontal gyrus, and superior parietal lobe, and were associated with decreased activity in the anterior cingulate gyrus. Furthermore, these results were not significantly attenuated following post-hoc adjustment for regional gray matter volume, indicating that this effect was specific to the white matter integrity of these regions. Finally, Szabo et al. (2011) reported similar findings using path analysis, showing that greater peak VO_2 levels were associated with better memory performance and self-reported cognitive difficulties. In addition, the relationship between fitness and self-reported cognitive difficulties was mediated by hippocampal volume, providing a plausible mechanistic pathway by which improved fitness may result in better cognitive outcomes.

Several studies have also examined the relationship between leisure-time physical activity and cognitive function (Dregan & Gulliford, 2013). In contrast to measures of exercise, these indices attempt to measure the amount of physical activity engaged in during participants' routine, non-work, leisure time. For example, one large cross-sectional study of healthy, middle-aged and older adults study examining this relationship used a self-report measure of physical activity in which participants were asked about the frequency and duration of their participation in various leisure activities (e.g. walking, bicycling, housekeeping, gardening, etc.) (Angevaren et al., 2007). All activities were then coded and given a specific metabolic equivalent (MET) value. Greater intensity of reported physical activity was associated with better processing speed, memory, mental flexibility, and overall cognitive function, and this relationship remained after controlling for multiple markers of cardiovascular and metabolic function.

Although cross-sectional studies have generally found support for the association between greater physical fitness and enhanced cognitive function, cross-sectional study designs cannot provide causative inference. The fitness and cognition relationship is potentially confounded by a number of factors, such as differences in nutrition, educational factors, or personality characteristics. In addition, the combination of lifelong physical, social, and cognitive activities across the lifespan may increase cognitive reserve, acting as a protective factor against cognitive decline (Valenzuela & Sachdev, 2009). It is also possible that exercise may confer greater cognitive gains only after years of repeated behavior, such that cross-sectional studies assessing exercise and cognition at any one time point may not reflect the cumulative effect of physical activity due to variation in the assessment of fitness indices. Longitudinal studies provide greater insight into changes in cognitive function associated with physical activity over sustained periods of time.

4.2. Prospective studies of physical activity, fitness, and cognitive impairment

Multiple prospective studies have examined the protective effect of physical activity on cognitive functioning (Barnes, Whitmer, & Yaffe, 2007; Scarmeas & Stern, 2003) and have generally supported the positive relationship demonstrated in cross-sectional studies, demonstrating that sustained levels of aerobic exercise may be associated with improved cognitive reserve (Dik, Deeg, Visser, & Jonker, 2003), processing speed (Richards, Hardy, & Wadsworth, 2003), and memory (Broe et al., 1998; Laurin, Verreault, Lindsay, MacPherson, & Rockwood, 2001). Moreover, regular physical activity confers a decreased risk of cognitive impairment (Scarmeas, Levy, Tang, Manly, & Stern, 2001) and dementia (Singh-Manoux, Hillsdon, Brunner, & Marmot, 2005). Prospective studies have generally explored the total amount of time spent exercising, or exercise habits, as predictors of cognitive function, largely ignoring the effects of exercise intensity. Sturman et al. (2005) investigated the relationship between physical activity and cognitive decline in a sample of 4055 community-dwelling individuals, finding that each additional hour of physical activity per week was associated with a slower rate of cognitive decline, in a dose–response fashion. However, these effects were attenuated after controlling for participation in cognitive activities, depression, and vascular disease. This effect was also attenuated when individuals with compromised cognitive function at baseline (i.e. whose global cognitive score ≤10th percentile) were excluded, indicating that the effects of physical activity may have been more beneficial among those with lower cognitive performance. These findings have been replicated in several large, epidemiological studies: self-reported walking was associated with decreased risk of cognitive decline among 5925 older women (Yaffe, Barnes, Nevitt, Lui, & Covinsky, 2001) and, in a study of 19,000 women participating in the Nurses' health study, total energy expenditure was associated with less cognitive decline (Weuve et al., 2004). In an interesting study utilizing path analysis, Albert et al. (1995) found that greater levels of objectively measured aerobic fitness, indexed by peak expiratory flow rate, was the best predictor of cognitive function second only to level of education. The authors also found a direct association between strenuous levels of activity and change in cognitive performance, as well as an indirect association mediated by peak expiratory flow rate. However, moderate rates of physical activity were not significantly associated with cognitive change, suggesting a possible threshold effect of the influence of physical activity on cognitive function.

These findings have been extended to study the effects of physical activity as a means of protecting older adults against dementia in later life. Similar to the results above, greater frequency of vigorous exercise has been associated with reduced risk of cognitive decline among older adults (aged ≥ 75) (Stewart, Prince, & Mann, 2003). Leisure-time physical activity has also been associated with reduced risk of cognitive decline (Richards et al., 2003), with some studies finding reduced rates of dementia of approximately 35–50% even after accounting for demographic factors, vascular comorbidities, and, in some cases (Rovio et al., 2005), APOE genotype (Larson et al., 2006; Laurin et al., 2001). In several studies, a graded relationship was reported between increasing levels of physical activity and reduced risk of cognitive impairment. Andel et al. (2008) reported that regular physical exercise was associated with reduced risk of dementia in a sample of 2870 individuals from the Swedish Twin Registry. The authors found that 'light' exercise (i.e. low frequency) was associated with a 37% reduced risk of dementia, whereas more 'regular' exercise reduced the risk of dementia by 66%. Notably, this study was strengthened by incorporating a substantially longer follow-up period of 31 years. When analyses were limited to co-twin control analyses, the relationship between exercise and dementia was similar with a 50% reduced risk associated with exercise, but did not reach statistical significance, possibly due to the vastly limited sample size of this subset analysis.

Several studies have examined the longitudinal association between cognition and objective measures of physical fitness, reducing the influence of self-report biases. Although self-reported physical activity practices are associated with physical fitness, objective measures provide a more accurate index of cardiovascular health and reduce self-report bias. Barnes, Yaffe, Satariano, and Tager (2003) investigated the relationship between cardiorespiratory fitness and cognitive function in a sample of 349 individuals without evidence of cardiovascular disease, musculoskeletal disability, or cognitive impairment. In the course of their six year follow-up, those participants with poorer peak VO_2 performance at baseline showed a more rapid cognitive decline. Furthermore, after adjusting for demographic and health-related covariates, peak VO_2 showed the strongest association with global measures of cognitive function and attention/executive functions.

In addition to the positive findings demonstrated among healthy, older adults, several studies have replicated this relationship in clinical populations. Etnier et al. (1999) examined the association between cognitive function and several indices of aerobic capacity in a sample of 98 older adults with chronic obstructive pulmonary disease (COPD). Specifically, the authors investigated whether measures of fluid intelligence, processing speed and working memory, or processing speed and inhibition were associated with different indices of cardiovascular and cardiopulmonary function, including the 6-min walk test, peak VO_2, and FEV_1. Across cognitive domains, greater 6-min walk distance was associated with better cognitive performance, although other indices of cardiopulmonary function were not. It should be noted, however, that markers of cardiovascular fitness, such as peak VO_2, may not be associated with pulmonary function. Etnier and Berry (2001) reported similar findings in an 18-month longitudinal study of COPD patients, in which decreased cardiorespiratory ventilation capacity (V_E) measured during the peak VO_2 from a treadmill test was predictive of fluid intelligence.

Although greater aerobic fitness appears to be associated with better cognitive performance among some medical populations, not all have shown benefits. For individuals with multiple sclerosis (MS), for example, this relationship is less clear. MS is a common neurological disease typified by diffuse white matter damage which primarily afflicts middle-aged and younger adults, resulting in decreased neuronal conduction capacity. Prakash et al. (2007) examined the association between peak VO_2, cognitive performance, and functional brain activation in a sample of 24 individuals with MS, assessing a range of cognitive functions including memory, psychomotor sequencing, verbal fluency, and executive function. In addition, participants underwent functional brain imaging while completing the Paced Visual Serial Addition Test (PVSAT). During the PVSAT, participants exhibited increased activation in the inferior and medial frontal gyri, and the level of activation in this area correlated significantly with higher levels of aerobic fitness. Furthermore, participants with better aerobic fitness showed decreased activation in the anterior cingulate gyrus during periods of increased frontal activity. However, none of the other seven cognitive tests were associated with aerobic fitness in this study.

Finally, several studies have examined whether individual differences may moderate the effects of exercise on cognitive performance. Several studies have examined whether APOE genotype may act as a moderator of the relationship between physical activity and cognitive function (Blair et al., 2005; Podewils et al., 2005). Podewils et al. (2005) examined this association among 3375 older men and women, investigating the association between leisure-time energy expenditure and the development of cognitive disorders over a 4.5-year follow-up. Individuals in the highest quartile of energy expenditure demonstrated a 15% reduced risk of incident dementia compared with individuals in the lowest quartile. Furthermore, individuals engaging in >4 leisure activities on a regular basis demonstrated a 39% decreased relative risk of dementia, as well as reduced risk for AD and vascular dementia (VaD). Notably, examination of APOE genotype showed that ε4 carriers experienced the greatest benefit with exercise, whereas a non-significant association was evident in non-carriers. These findings have since been extended to show that exercise engagement may moderate the impact of APOE ε4 genotype on amyloid deposition, with more active individuals showing an attenuation of Pittsburgh compound B binding (Brown et al., 2012; Head et al., 2012; Smith, Nielson, Woodard, Seidenberg, & Rao, 2013).

Despite these positive findings, several notable negative findings deserve further mention. In a meta-analysis examining the relationship between cardiovascular health and cognitive function, Etnier et al. (2006) found no association between greater aerobic fitness and enhanced cognitive function when data from eight separate cross-sectional studies were combined, including 27 effect sizes representing data from 214 subjects. Several prospective studies have also failed to demonstrate a protective effect of physical activity on cognitive function (Wilson et al., 2002; Yamada et al., 2003) and two large-scale prospective trials reporting that regular exercise protects against the development of AD did not find evidence that this relationship was moderated by APOE genotype (Lindsay et al., 2002; Schuit, Feskens, Launer, & Kromhout, 2001). Nevertheless, the vast majority of extant data indicates that greater physical activity and cardiovascular fitness are associated with better neurocognitive function.

Four meta-analytic studies have attempted to combine results across prospective studies in order to provide a quantitative synthesis for the relationship between physical activity and the development of cognitive impairment in later life (Table 1). In a meta-analysis of 24 studies conducted among older adults, incorporating results from 1378 cases and 10,108 controls, Aarsland, Sardahaee, Anderssen, and Ballard (2010) found that greater physical activity was associated with a significantly reduced risk for the development of VaD (OR = 0.62) over a 4–7 year follow-up period. Sofi et al. (2011) reported similar findings in a meta-analysis of 33,816 non-demented older adults over an approximate 5-year follow-up period (range 1–12 years). Individuals reporting 'high' levels of physical activity 38% less likely to experience cognitive decline compared with their 'low' activity counterparts. Perhaps more importantly, individuals participating in low-to-moderate physical activity had a 35% reduced risk of cognitive decline. Similarly, Hamer and Chida (2009) found a 28% reduced risk for all-cause dementia in a meta-analysis of 3219 individuals from 16 prospective studies. The effects of physical activity appeared to be strongest for AD (RR = 0.55), although a protective effect was also noted for Parkinson's disease (RR = 0.82). Finally, Morgan et al. (2012) examined the relationship between leisure-time and work-related physical activity on the development of dementia. The authors found that greater physical activity was associated with significantly lower risk of cognitive impairment (OR = 0.66) and dementia (OR = 0.78) and that results were consistent across varying lengths of follow-up.

As demonstrated above, longitudinal studies have generally demonstrated a relationship between physical activity and enhanced cognitive function. Discrepant findings are not uncommon, however, and the majority of those studies examining other leisure-time activities (e.g. cognitive activities) has demonstrated that these are also associated with improved cognition, in some cases mediating the physical activity and cognition relation. This suggests that individual differences may explain some of the observed relationship between exercise behavior and cognitive function. Importantly, causality cannot be inferred from observational studies, as many factors, measured and unmeasured, may account for the relationship between physical activity and cognition. Randomized controlled trials (RCTs), therefore, offer the best experimental design for assessing the relationship between physical activity and cognitive function in a controlled setting.

5. Interventional studies of exercise on cognitive function

5.1. Healthy adults

The majority of existing studies has examined the impact of aerobic exercise on neurocognitive function among cognitively normal adults (Angevaren, Aufdemkampe, Verhaar, Aleman, & Vanhees, 2008). Most of these studies have been conducted among sedentary but otherwise healthy older adults, although there are numerous trials among individuals with various medical conditions as well.

In their seminal work, Dustman et al. (1984) conducted a 12-week trial consisting primarily of jogging/running, among 40 sedentary adults. Exercise participants demonstrated improvements on tasks associated with complex sequencing compared with controls subjects, although complex reaction time was unchanged in either group. Although this

study used alternating treatment assignment, it nevertheless generated interest in the use of randomized trials to investigate the aerobic fitness and cognition relationship. Among non-clinical populations, the effects of exercise have been most extensively examined among sedentary and/or elderly adults. Results have varied widely between studies, underscoring the need to investigate mediators of cognitive improvement, as well as to rigorously study the influence of type, intensity and duration of exercise in future research.

Following this early publication, approximately 30 trials have been published examining the impact of aerobic exercise on cognitive function among healthy adults. The majority of existing trials has used walking and/or jogging as the primary treatment modality, with durations ranging from several weeks to 18 months (Smith, Blumenthal, Babyak et al., 2010; Smith, Blumenthal, Hoffman et al., 2010). For example, a large 12-month Australian trial found that aerobic exercise improved reaction time and working memory performance among 187 community-dwelling older adults (Williams & Lord, 1997). In addition, a highly cited study by Kramer et al. (1999) found improvements on an executive-control process following a 6-month randomized walking trial among 124 older adults. Discrepant findings have been reported, however, with many individual trials reporting equivocal findings (Blumenthal et al., 1989). For example, Blumenthal et al. (1989) did not find improvements in cognitive function following a 4-month exercise intervention among 101 sedentary, older adults, despite physiological improvements in peak VO_2, as well as reduced lipids, weight, and blood pressure (BP). This study may have been underpowered due to a relatively smaller sample size, however. Nevertheless, when results have been combined across trials, meta-analytic studies have consistently reported cognitive benefits from aerobic exercise interventions (Angevaren et al., 2008; Colcombe & Kramer, 2003; Smith, Blumenthal, Babyak et al., 2010; Smith, Blumenthal, Hoffman et al., 2010). In one of the most comprehensive meta-analyses to date, Angevaren et al. (2008) examined the effects of exercise on cognitive function among adults without cognitive impairment, identifying 11 studies for inclusion. Among studies using oxygen uptake as their marker of fitness, improvements in fitness were associated with cognitive gains, with the largest benefits observed for motor function and auditory attention. Our meta-analysis reported similar gains in executive function, memory, working memory, and attention/processing speed among healthy adults participating in aerobic exercise interventions, and these findings did not appear to vary significantly by training paradigm, mean age of study participants, or study quality, suggesting a modest, but consistent impact of exercise on cognition (Smith, Blumenthal, Babyak et al., 2010; Smith, Blumenthal, Hoffman et al., 2010).

5.2. Clinical populations

5.2.1. Cardiovascular disease—The effects of aerobic exercise have also been examined among clinical populations. Several RCTs conducted at Duke University have examined the influence of exercise on cognitive function among individuals with hypertension (Pierce, Madden, Siegel, & Blumenthal, 1993; Smith, Blumenthal, Babyak et al., 2010; Smith, Blumenthal, Hoffman et al., 2010). Pierce et al. (1993) examined this in a 16-week RCT in which participants were randomized to receive aerobic exercise, strength training, or flexibility exercises. Aerobic exercise training was associated with improved fitness among hypertensive patients but did not improve cognitive functioning, although

participants reported improvements in *perceived* change in cognitive performance, suggesting that participants felt their cognitive function had improved, despite the fact that no group differences were found for cognitive variables. In a randomized trial among overweight adults with hypertension, we have demonstrated that a combined aerobic exercise and dietary modification intervention was associated with improvements in executive function, memory, and psychomotor speed (Smith, Blumenthal, Babyak et al., 2010; Smith, Blumenthal, Hoffman et al., 2010). Interestingly, improvements in peak VO_2 and weight loss were associated with improvements in neurocognitive functioning, whereas changes in BP were not.

Several quasi-randomized studies have also been conducted among cardiac patients, which have generally reported positive results. Gunstad et al. (2005) examined changes in psychomotor sequencing and executive function among 18 cardiac patients participating in a structured cardiac rehabilitation program. Participants were administered several tests of psychomotor sequencing, such as Trail Making Test A and WAIS Digit Symbol Substitution, as well as the Animal Naming Test. Following the 12-week rehabilitation program, participants experienced improvements on Trail Making A and the WAIS Digit Symbol Substitution, both tasks of psychomotor sequencing. In addition, exercisers exhibited improved cardiovascular fitness as indexed by peak metabolic equivalents (METs) and these gains were associated with improvements in psychomotor sequencing and, to a lesser extent, improved executive function performance. In addition, Tanne et al. (2005) conducted an important trial among 25 individuals with congestive heart failure. Control patients were those that could not participate in the exercise program due to lack of medical insurance and/or because they lived too far from the exercise facility, introducing a possible source of selection bias. Participants completed neuropsychological assessments, a test of cerebral vasomotor reactivity to hypercapnia, and exercise capacity assessments before and after the intervention. Following the 18-week trial, exercisers showed improvements in tasks associated with simple and complex psychomotor sequencing. These changes were not associated with vasomotor reactivity, however, which did not improve despite improved exercise capacity. While this may be understandable given the advanced cardiovascular disease in this population, this finding suggests that improved cardiovascular fitness does not necessarily improve cerebrovascular oxygenation efficiency.

5.2.2. Other chronic medical conditions—Extending work from the cardiac rehabilitation literature, several investigators have conducted aerobic trials among specific health populations such as chronic obstructive pulmonary disease (COPD) (Emery, Schein, Hauck, & MacIntyre, 1998), multiple sclerosis (Oken et al., 2004), and major depressive disorder (MDD) (Khatri et al., 2001). Emery et al. (1998) found that a 16-week combined exercise, education, and stress management intervention among COPD patients were associated with improvements in verbal fluency. In addition, COPD patients who continued to exercise did not experience a decline in cognitive function following the intervention, which was observed in control participants during a one-year follow-up assessment (Emery, Shermer, Hauck, Hsiao, & MacIntyre, 2003). Similar modest improvements in memory and executive functioning were observed among depressed adults following 4 months of exercise (Khatri et al., 2001). Despite these positive findings, aerobic exercise was not

associated with cognitive improvements among individuals with multiple sclerosis during a 6-month intervention (Oken et al., 2004).

5.2.3. Mild cognitive impairment—During the past ten years, several randomized controlled trials have been conducted examining the effects of aerobic exercise on cognitive function among older adults with mild cognitive impairment (MCI). Heyn et al. (2004) conducted a meta-analytic review examining the effects of physical activity on cognitive function among adults with cognitive impairment, examining the effects of both aerobic and milder forms of physical activity. Although the authors included both MCI and also dementia patients, their findings suggested that exercise improved cognitive function as well as a number of fitness indices. Lautenschlager et al. (2008) examined the effects of a 24-home based exercise program on cognitive function among adults with MCI. Participants in the exercise group showed improvements on the Alzheimer Disease Assessment Scale – Cognitive Subscale at 6 months and continued to show improvements in memory performance at 18 months. Two more recent, smaller trials have since replicated these findings, demonstrating that aerobic exercise (Baker et al., 2010) or resistance training (Nagamatsu et al., 2013) interventions improve cognitive function among individuals with MCI. In addition to these individual trial findings, we reported that the effects of exercise on cognitive function tended to be larger among individuals with MCI in a meta-analytic review (Smith, Blumenthal, Babyak et al., 2010; Smith, Blumenthal, Hoffman et al., 2010). Although we found that aerobic exercise was associated with modest improvements in executive function, memory, and processing speed across all studies, improvements in memory were particularly strong among individuals with MCI. Similarly, a meta-analysis among individuals with cognitive impairment reported that physical activity interventions, both aerobic and non-aerobic (e.g. isometric exercises, resistance training, etc.) were associated with improved cognitive performance (Heyn et al., 2004). However, a recent systematic review examining the impact of aerobic exercise (thereby excluding many of the studies included in the Heyn meta-analysis, above) concluded that there is limited data to support the use of aerobic exercise to improve cognition in adults with neurological illness due to the relatively small number of studies examining this issue and the poor methodological quality of many existing studies (McDonnell, Smith, & Mackintosh, 2011).

Results from clinical populations suggest that exercise improves cognitive function to a comparable extent as seen among healthy older adults, although there is a relative lack of high-quality studies among individuals with certain neurological illnesses (e.g. traumatic brain injury). Findings from patients with cardiovascular disease, pulmonary disease, depression, and MCI all support the notion that exercise improves cognitive function. Although the precise mechanisms linking exercise to improved cognition in these populations remain unclear, it is likely that beneficial effects are secondary to improvements in cardiovascular risk factors and not necessarily due to a reversal of the primary disease process.

5.3. Meta-analytic studies

The impact of exercise on cognitive function has been the focus on multiple meta-analyses and systematic reviews (Erickson et al., 2011; Lautenschlager & Almeida, 2006; Lee et al.,

2010; Littbrand, Stenvall, & Rosendahl, 2011; McDonnell et al., 2011; Rasberry et al., 2011; Snowden et al., 2011; Tomporowski, 2003; van Uffelen, Chin, Hopman-Rock, & van Mechelen, 2008). Fifteen previous meta-analyses have examined the relationship between physical activity, exercise, and cognitive function (Table 1). These have included several lines of inquiry: the association between chronic physical activity and cognitive decline from prospective studies (reviewed in the Prospective Studies section above) (Sofi et al., 2011), the impact of acute bouts of exercise on cognition (Lambourne & Tomporowski, 2010), the impact of chronic exercise interventions among healthy adults or adults at risk for cognitive impairment (Angevaren et al., 2008; Smith, Blumenthal, Babyak et al., 2010; Smith, Blumenthal, Hoffman et al., 2010), and the impact of exercise among individuals with cognitive impairment (Heyn et al., 2004).

Although not the focus of the present review, multiple studies and several meta-analyses have examined the impact of acute bouts of exercise on cognitive performance. The majority of existing studies has found that brief bouts of exercise improve working memory and attention both during and after exercise among children (Chang, Labban, Gapin, & Etnier, 2012; Lambourne & Tomporowski, 2010) and/or healthy adults (McMorris, Sproule, Turner, & Hale, 2011). Results have generally shown small but consistent benefits of acute exercise bouts on cognitive function both during and after exercise, particularly with respect to cognitive tests involving efficient processing speed.

Six previous meta-analyses have investigated the effects of chronic aerobic exercise interventions on cognitive function. Etnier et al. (1997) examined the effect of acute and long-term exercise on cognition, combining nearly 200 studies and 134 effect sizes among participants aged 6–90 years. Exercise was associated with small improvements cognitive performance (ES = 0.25) and this effect appeared to be strongest among middle-aged adults (aged 45–60), although higher quality studies tended to report smaller cognitive gains following treatment. More recently, Etnier et al. (2006) conducted meta-regression analyses to examine whether changes in aerobic fitness were associated with corresponding changes in cognitive performance. Among RCTs, 24 studies were examined, yielding 78 effect sizes from 934 participants. Interestingly, changes in fitness were not associated with changes in cognitive function, and this effect did not vary significantly across studies.

Colcombe and Kramer (2003) conducted a meta-analytic study of RCTs investigating the effects of aerobic exercise training on cognition. Eighteen studies and 197 effect sizes were included in the analyses. Aerobic exercise trials were associated with improved cognitive performance in executive-control processes, spatial performance, and speed tasks. Furthermore, aerobic training trials that combined strength training were associated with greater improvements compared to aerobic training alone and trials among participants aged 66–70 appeared to show the greatest improvements.

Heyn et al. (2004) conducted a meta-analysis of randomized trials evaluating the effects of both aerobic and non-aerobic exercise in persons 65 years of age or older with cognitive impairment. Specifically, the effects of exercise were investigated on multiple outcomes, including strength, physical fitness, functional performance, cognitive performance, and behavior. Thirty studies were included in the analyses, incorporating data from 2020

participants, although only 12 effect sizes from 10 studies were available for cognitive outcomes. Studies examining cognitive function found that exercise was associated with moderate improvements in cognitive function (ES = 0.57).

In the most rigorous meta-analytic study to date, Angevaren et al. (2008) examined the effects of aerobic exercise trials on cognitive function among adults 55 years of age or older without cognitive impairment. Similar to Etnier et al. (2006) analyses, improvements in aerobic fitness were examined as a potential moderating effect. In contrast to the graded relationship between improved fitness and cognition used in the Etnier et al. (2006) study, trials were distinguished based on whether aerobic capacity was significantly improved (e.g. >14% improvement in peak VO_2). In contrast to previous reviews, older individuals with known (e.g. AD or MCI) or suspected cognitive impairment were excluded (e.g. depression), although other clinical populations were included in the analyses (e.g. COPD). The largest changes in cognitive function were observed in motor function and auditory attention, whereas moderate improvements were observed in cognitive speed and visual attention. However, the majority of comparisons yielded non-significant results and the authors concluded that there is insufficient evidence to show that improvements in cognitive function can be attributed to physical exercise.

We conducted a meta-analytic synthesis of all RCTs examining the effects of aerobic exercise on cognitive performance in non-demented adults, some of whom were at risk for dementia (i.e. MCI) (Smith, Blumenthal, Babyak et al., 2010; Smith, Blumenthal, Hoffman et al., 2010). We found that aerobic exercise interventions were associated with modest improvements in attention/processing speed, executive function, and memory. In addition, trials among individuals with MCI demonstrated greater improvement in memory performance relative to healthier samples, suggesting that the beneficial effects of exercise on various cognitive functions may be most evident in participants with pre-existing cognitive impairment.

5.4. Aerobic exercise impact on neuroimaging indices

In addition to the effects of exercise on cognitive function, several recent studies have examined its impact on neuroimaging markers. Neuroimaging markers have been used to assess both structural measures of brain health, such as brain volume and white matter hyperintensity volume, as well as functional measures, including blood oxygen dependent response (BOLD) during cognitive tasks. Observational studies have suggested that higher levels of fitness may be associated with preserved brain health, as indicated by greater brain volume (Burns et al., 2008; Weinstein et al., 2012), lower white matter lesion volume (Burns et al., 2008), greater volume within the prefrontal cortex (Weinstein et al., 2012), caudate nucleus (Verstynen et al., 2012), and hippocampal formation (Erickson et al., 2011; Erickson, Weinstein, & Lopez, 2012; Pereira et al., 2007), and greater blood flow velocity (Lucas et al., 2012). These studies suggest that the effects of aerobic exercise may be particularly strongly associated with volumetric changes in subregions of the hippocampus (Fabel & Kempermann, 2008; Pereira et al., 2007). In one of the earliest studies to examine this relationship in humans, Pereira et al. (2007) examined this relationship in a small sample of young adults (mean age 33 years). The authors first validated the use of MRI

measurements of cerebral blood volume as an imaging correlate of neurogenesis in mice. The authors then used this imaging technique to examine the impact of a 12-week aerobic exercise intervention. The authors found that aerobic exercise increased MRI markers of neurogenesis in the dentate gyrus, a subregion of the hippocampus. This research supports broader findings of hippocampal volume enlargement as a result of exercise; for example, Erickson et al. (2011) found that a 12-month exercise training program in a sample of 120 older adults increased hippocampal volume by 2%, which was estimated to reverse 1–2 years of normal age-related atrophy. Importantly, improved hippocampal volume was associated with behaviorally relevant improvement in spatial memory.

Although peri-hippocampal regions exhibit the greatest changes following aerobic exercise, several smaller studies suggest that other brain regions and networks are positively affected by exercise as well. Colcombe et al. (2004) have demonstrated that aerobic exercise improves brain activation in the anterior cingulate cortex, a subcortical brain region with frontal lobe connections that is important for executive function, during a complex cognitive task. Similarly, a 4-month aerobic exercise intervention found increased frontal cerebral perfusion and higher functional brain connectivity following aerobic activity, specifically between the hippocampus and anterior cingulate cortex (Colcombe et al., 2004). Another study found that a 12-month trial of aerobic training increased functional efficiency and connectivity in what is commonly described as the default mode network (DMN) (Voss et al., 2010).

5.5. Exercise interventions and mental health outcomes

Although the focus of the present literature review is the relationship between physical activity, exercise, and cognition, it should also be noted that a wealth of data has shown that exercising improves mental health outcomes within multiple psychosocial domains. Perhaps the strongest literature base exists for the impact of exercise on depression (Mead et al., 2009; Stathopoulou, Power, Berry, & Smits, 2006). The beneficial effects of exercise have been examined in both healthy and clinical populations, and have been the subject of several meta-analytic reviews (Lawlor & Hopker, 2001; Mead et al., 2009). As previously noted (Lawlor & Hopker, 2001), existing studies have varied substantially in terms of methodological rigor, size, type of control group, length of follow-up, and even the type of exercise modality. However, there are relatively few, high-quality studies utilizing high-quality methodologies in which treatment allocation is concealed, intention to treat analyses are used, and assessment of depression is conducted by a trained psychologist instead of being based on self-report.

Systematic and met-analytic reviews have generally reported positive effects of exercise on depressive symptoms among randomized trials (Mead et al., 2009; Rethorst, Wipfli, & Landers, 2009; Silveira et al., 2013; Stathopoulou et al., 2006), with some exceptions (Lawlor & Hopker, 2001). A Cochrane review in which randomized controlled trials of exercise in adults were compared to a standard treatment, no treatment, or a placebo control, results suggested a large, clinically meaningful improvement associated with exercise in comparison with controls. However, when the analyses were further limited to those trials using intention to treat analyses and blinded outcome assessment, the effect was modestly

attenuated, and showed only a moderate benefit associated with exercise. In addition, when analyses were conducted among the five trials that collected long-term follow-up data, the effects of treatment were again slightly attenuated for a moderate clinical improvement. Among high-quality interventions, results have tended to show that exercise improves depressive symptoms to a comparable extent as standard pharmacological treatment in both otherwise healthy and cardiac patients with major depressive disorder (Blumenthal et al., 2007, 1999; Blumenthal, Sherwood et al., 2012), although at least one study comparing aerobic exercise to a stretching and toning control group failed to report significant differences (Krogh, Videbech, Thomsen, Gluud, & Nordentoft, 2012)

Existing meta-analyses have also reported that several methodological factors may influence the strength of improvement with exercise, including the type of comparison group, the age of the sample, and the severity of depressive symptoms. In addition to reporting the overall results of exercise compared with controls, the Cochrane review found that improvements in depressive symptoms following exercise were comparable to those seen with cognitive therapy and pharmacological treatment. In addition, a more recent meta-analysis found beneficial effects of exercise on depression outcomes and that these findings were stronger among samples comprised of older adults and milder depressive symptoms (Silveira et al., 2013).

Although the majority of existing evidence has focused on the impact of exercise on depressive symptoms, multiple studies have also examined the impact of exercise interventions on anxiety symptoms. It was recently shown in a meta-analysis of randomized trials that exercise interventions among individuals with anxiety and comorbid chronic illnesses, including cardiovascular disease, fibromyalgia, multiple sclerosis, and others, that exercise treatment was associated with improvements in anxiety symptoms (mean ES change = 0.29 [95% CI: 0.23–0.36]) (Herring, O'Connor, & Dishman, 2010). Another meta-analytic study among patients with anxiety disorders, including panic attacks, social phobia, and generalized anxiety, found that exercise improved anxious symptoms but not to the extent as the improvement seen with pharmacological treatment (Jayakody, Gunadasa, & Hosker, 2013).

5.6. Characteristics of exercise prescription

Although numerous randomized trials have examined the impact of aerobic exercise on cognitive function, few studies have examined specific components of the exercise prescription that may affect changes in neurocognitive performance. As noted earlier, at least one cross-sectional study has suggested that *intensity* of physical activity participation, in contrast to the duration or frequency of exercise, may be an important determinant of neurocognitive enhancement (Angevaren et al., 2007). In contrast, longitudinal studies have generally found that greater duration (Weuve et al., 2004) and frequency (Andel et al., 2008) of exercise are important predictors of better cognitive function. For example, a longitudinal of women participating in the Nurses' Health Study reported that greater levels of time spent engaged in physical activity were associated with lower likelihood of cognitive decline during a two-year follow-up (Weuve et al., 2004).

Interestingly, the majority of existing studies has failed to find a relationship between training characteristics and neurocognitive outcomes, with several notable exceptions (Erickson et al., 2011; Smith, Blumenthal, Babyak et al., 2010; Smith, Blumenthal, Hoffman et al., 2010). In their meta-regression analyses, Etnier et al. (2006) examined the 'Cardiovascular Fitness Hypothesis', which posits that greater aerobic fitness is associated with greater neurocognitive abilities. Interestingly, they did not find an association between improved aerobic fitness and cognitive function in observational studies and found a *negative* association in pre–post comparison studies, suggesting that larger aerobic gains were related to lesser improvements in aerobic fitness. Our meta-analysis similarly did not find an association between either intensity or duration of interventions and improvements in cognitive function (Smith, Blumenthal, Babyak et al., 2010; Smith, Blumenthal, Hoffman et al., 2010). Similarly, although Angevaren et al. (2008) found an overall positive impact of exercise on cognitive function in their meta-analytic review, the authors also noted that from their findings it was inconclusive as to whether improvements in cognitive function due to exercise are the result of improvements in cardiovascular fitness.

In contrast to these meta-analytic studies, several recent interventions have found that greater fitness improvements are predictive of improvements in cognitive function and neuroimaging markers of brain health (Erickson et al., 2011). For example, improvements in fitness following one year of exercise training have been associated with increased hippocampal volume among sedentary, older adults (Erickson et al., 2011). In addition to these findings, in the few RCTs that have conducted assessments at multiple time points, both memory performance from neurocognitive testing (Lautenschlager et al., 2008) and improvements in brain imaging markers (Erickson et al., 2011) have tended to show dose–response improvements, with small improvements following several months of treatment that continue to improve with sustained intervention.

Only one study has examined different intensities of aerobic activity on cognitive function, to our knowledge. In this small study of elderly adults with mild cognitive impairment, participants in the intervention groups exercised at either 60% or 40% of heart rate reserve (Varela, Ayan, Cancela, & Martin, 2012). Compared to an untrained control group who participated in recreational activities, no group differences were found on Mini-Mental State Examination scores or the Timed Up and Go test.

Taken together, it remains unclear whether improvements in cardiovascular fitness are predictive of improved cognitive function. There is preliminary evidence that improvements in fitness may be associated with better cognitive and neuroimaging outcomes among older adults with or without memory deficits (Erickson et al., 2011; Lautenschlager et al., 2008). However, meta-analyses combining results from multiple trials have failed to report a consistent relationship between improved fitness and cognitive function (Angevaren et al., 2008; Etnier et al., 2006). It is possible that the relationship between fitness and cognitive outcomes is more pronounced in older adults, where the presence of cognitive impairments provides greater power to detect associations between fitness and cognition. However, it is likely that the lack of a consistent fitness and cognition relationship is partially due to the fact that exercise may improve cognition through several different mechanisms, as reviewed below.

6. Mechanisms of action

6.1. Neurogenesis

Beginning with animal models examining the impact of brain derived neurotrophic factor (BDNF) on the brain (Cotman & Berchtold, 2002; Cotman & Engesser-Cesar, 2002; van Praag, Kempermann, & Gage, 1999), experimental studies over the past two decades have confirmed that physical activity is associated with a modest increase in neurogenesis (Uda, Ishido, Kami, & Masuhara, 2006). Although only a handful of studies has examined the impact of exercise on neurogenesis among humans, the results consistently suggested that exercise increases brain volume in the memory centers of the brain. As noted earlier, the impact of exercise on neurogenesis has been demonstrated in both young (Pereira et al., 2007) and older adults (Erickson et al., 2011). As noted above, it has previously been shown that regularly exercising for as little as 3 months improves cerebral blood flow to the dentate gyrus among younger adults. Increased volume within the dentate gyrus was also demonstrated following 6 months of aerobic exercise among sedentary, older adults, and additional increases were shown when participants were assessed at the completion of the full 12-month intervention, suggesting a dose–response relationship (Erickson et al., 2011). Interestingly, neurogenesis has also been implicated in mediating the effects of some antidepressant treatments (Sahay & Hen, 2007), although it remains unclear whether improvements in depressive symptoms result in improved cognitive function (Duman, 2005). Further evidence for the impact of exercise on neuronal function may be found from studies examining the relationship between fitness and *N*-acetylaspartate (NAA) levels. NAA is a central nervous system metabolite found predominantly in the cell bodies of neurons and previous studies have found that higher aerobic fitness appears to offset age-related declines in NAA in the right prefrontal cortex among older adults without cognitive impairment (Erickson et al., 2012).

6.2. Growth factor modification

Exercise may also improve cognitive function by modifying growth factors (Cotman & Berchtold, 2002; Cotman, Berchtold, & Christie, 2007). Numerous animal studies have demonstrated that aerobic exercise is associated with increased production of BDNF (Erickson et al., 2011), vascular endothelial growth factor (VEGF) (During & Cao, 2006), and insulin-like growth factor (IGF) (Foster, Rosenblatt, & Kuljis, 2011; Lista & Sorrentino, 2010). Human studies have reported similar findings, demonstrating that aerobic exercise improves growth factor expression, although these improvements may be somewhat transient (Knaepen, Goekint, Heyman, & Meeusen, 2010). Nevertheless, recent studies in humans have demonstrated that enhancement of growth factors is associated with increased brain volume within the dentate gyrus, a subregion of the hippocampus. Erickson et al. (2011) found that moderate physical activity was associated with increased BDNF expression and that BDNF levels were associated with modest volume increases in the dentate gyrus following one year of modest exercise among previously sedentary adults. Importantly, increased dentate gyrus volume was associated with performance on a test of visual memory in this study, suggesting that these improvements in brain volume may have been related to clinically-relevant changes in cognitive function. Growth factor modulation, particularly BDNF, has also been implicated as a potential mediator of the neuroplastic

changes found to underlie improvements in depressive symptoms, suggesting that this growth factor may play an important role in both improvements in depressive symptoms and cognitive function (Castren & Rantamaki, 2010).

6.3. Impact on cerebrovascular risk factors

Exercise may impact cognitive function through several different mechanisms. It is well established that individuals with fewer or more well-controlled cerebrovascular risk factors are associated with reduced incidence of cognitive impairment in prospective studies (Unverzagt et al., 2011). Epidemiological studies have shown strong evidence that strokes, lacunar infarcts, and carotid atherosclerosis can lead to cognitive impairment and increase the risk for dementia (Breteler, 2000; Hachinski et al., 1975; Hayden et al., 2006; Luchsinger et al., 2005; Tatemichi, Sacktor, & Mayeux, 1994; Vermeer et al., 2003), and some dementia risk profiles now include vascular risk factors (Kivipelto et al., 2006). Moreover, neuropathological studies indicate that the pathological changes associated with dementia frequently co-occur with vascular pathology, suggesting that vascular disease plays an important role in the pathogenesis of dementia (Tomlinson, Blessed, & Roth, 1970). Elevated cerebrovascular risk factors appear to be associated with poorer brain function even among older adults without manifest cardiovascular disease. For example, longitudinal studies have demonstrated that chronically elevated BP is associated not only with greater frequency of white matter hyperintensities, but also reductions in regional perfusion loss within the frontal lobes (Beason-Held, Moghekar, Zonderman, Kraut, & Resnick, 2007). Abnormalities in glucose metabolism are also associated with dementia (Arvanitakis, Wilson, Bienias, Evans, & Bennett, 2004; Cukierman, Gerstein, & Williamson, 2005; Hayden et al., 2005; Launer et al., 2000; Steen et al., 2005; Watson & Craft, 2003; Whitmer, Sidney, Selby, Johnston, & Yaffe, 2005) and elevated levels of inflammatory markers such as C-reactive protein are associated with more rapid cognitive decline (Yaffe et al., 2003) and impairment (Okereke, Hankinson, Hu, & Grodstein, 2005), particularly in the presence of the metabolic syndrome (Yaffe et al., 2004).

Despite the existing evidence demonstrating that elevated blood pressure is associated with neurocognitive impairment, it remains unclear whether reducing blood pressure is associated with reduced risk of cognitive dysfunction. Among older hypertensive patients, there have been several, large-scale, randomized controlled trials examining the impact of antihypertensive medications on dementia, including the SYST-EUR, PROGRESS, HOPE, MRC, SHEP, SCOPE, and HYVET-COG (Duron & Hanon, 2010). These studies have generally reported small reductions in the development of dementia, although at least one meta-analysis has linked the protective effects of antihypertensives to larger reductions in blood pressure (Birkenhager & Staessen, 2006).

Two studies have examined the impact of exercise on BP reductions and concomitant changes in neurocognitive functioning. As noted above, a study at Duke (Pierce et al., 1993) showed that exercise training was associated with improved fitness among hypertensive patients but did not improve cognitive functioning. In a recently published randomized trial, we have demonstrated that a combined aerobic exercise and dietary modification intervention was associated with improvements in executive function, memory, and

psychomotor speed (Smith, Blumenthal, Babyak et al., 2010; Smith, Blumenthal, Hoffman et al., 2010). Interestingly, improvements in peak VO_2 and weight loss were associated with improvements in neurocognitive functioning, whereas changes in BP were not. Although no study has explored whether the benefits of exercise on cognitive function are mediated by improved CVD risk factors, this is one of the primary goals of the ongoing ENLIGHTEN trial (Blumenthal, Sherwood et al., 2012; Blumenthal, Smith et al., 2012). In addition, several ongoing randomized trials plan to examine the impact of physical activity on neuroimaging markers of cerebrovascular function in the near future (Cyarto et al., 2012; Tyndall et al., 2013).

In addition to the potential impact of exercise on cerebrovascular risk factors, several observational studies suggest that exercise may improve cognitive function through its direct effects on cerebrovascular perfusion (Davenport, Hogan, Eskes, Longman, & Poulin, 2012; Lucas et al., 2012). Cross-sectional studies have shown that higher blood flow velocity is associated with better cognitive performance (Lucas et al., 2012) and improved cerebrovascular reserve is a logical mechanism explaining the impact of improved fitness on cognitive function. Cerebrovascular reserve is the ability of the cerebral blood vessels to respond to oxygen demand, such as during hypercapnia. Although no experimental work has examined the impact of exercise on this cerebrovascular mechanism, prior work has shown that cerebrovascular conductance is better among physically active women compared to their sedentary counterparts (Brown et al., 2010) and at least one quasi-randomized study in heart failure patients failed to find a relationship between cerebrovascular reactivity and changes in cognition (Tanne et al., 2005), although this relationship has not been examined experimentally within healthy adults, to our knowledge.

7. Conclusions and future directions

In conclusion, there is growing evidence that aerobic exercise may improve cognitive function and overall brain health in a number of different populations. Existing evidence suggests that even modest levels of physical activity may be associated with improved cognitive function within randomized trials, as well as lower rates of dementia and cognitive impairment among longitudinal studies. In addition, numerous studies have demonstrated that aerobic exercise is associated with improvements in depressive and anxious symptoms among both healthy and clinical populations. Several plausible biologic mechanisms have been suggested, including direct influence on neuronal growth, improved growth factor modulation, and reduction of cerebrovascular risk factors. Future studies should examine the impact of exercise on cognitive function in other clinical populations, including individuals with neurological illness, as well as examining potential mediators that may underlie both mental health and cognitive outcomes. Future studies would also benefit from examination of additional mechanisms that have been implicated in observational studies, such as increased cerebral perfusion and reduced neuroinflammation (Barrientos, 2011), which have yet to be examined in the context of RCTs. More RCTs with longer follow-up time periods are needed to examine the impact of exercise on cognitive function in an effort to reduce the risk of cognitive impairment in adults vulnerable to develop dementia in later life. In addition, future studies should more rigorously examine other lifestyle factors that influence

cognitive function, including dietary factors (Scarmeas et al., 2009) and cognitive activities (Barnes et al., 2013; Valenzuela & Sachdev, 2009).

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Table 1

Meta-analyses examining the relationship between physical activity, exercise, and cognitive function.

Author, year	Methodology/Number of studies	Inclusion/Exclusion Criteria	Findings
Etnier et al., 1997	Meta-analysis of observational and interventional studies/134	All studies providing adequate data for effect size calculation, utilizing a cognitive test measure as the outcome variable, and in which data on the exercise training paradigm was provided were included.	Overall effect size of 0.25. Cross-sectional/ correlational studies showed the strongest effect sizes, followed by chronic exercise training, and then acute exercise. The effect of exercise was smaller among more methodologically rigorous studies.
Colcombe & Kramer, 2003	Meta-analysis of published, randomized trials from 1966 to 2001 examining the impact of exercise on cognitive function/18	Studies utilizing random assignment to intervention, supervised exercise, an aerobic exercise intervention, and an average age of participants ≥ 55.	Exercise improved cognitive function for tests of executive function, controlled processing, visuospatial abilities, and speed.
Sibley & Etnier, 2003	Meta-analysis of published observational and interventional studies before January, 2002 examining the relationship between physical activity, exercise, and cognition in children/44	All studies providing adequate data for effect size calculation, utilizing a cognitive test measure as the outcome variable, and in which data on the exercise training paradigm was provided were included.	Overall effect size of 0.32. This association was similar across different study designs and study populations.
Heyn et al., 2004	Meta-analysis of published articles and unpublished manuscripts from 1970 to 2003 of randomized trials evaluating exercise in persons 65 years of age or older with cognitive impairment/30 total (9 for cognitive function)	Studies utilizing an exercise program or form of rehabilitative exercises, physical activity, fitness, or recreational therapy, nonintervention control group, subjects >65 years of age, baseline Mini-Mental Status Examination (MMSE) < 26 or diagnosis of cognitive impairment, minimum of 5 subjects in each group.	Exercise resulted in improvements in strength (ES = 0.75), physical fitness (ES = 0.69), functional performance (ES = 0.59), cognitive performance (ES = 0.57), and behavior (ES = 0.54).
Etnier et al., 2006	Meta-regression published and unpublished studies from 1927 to October 2005, both observational and interventional, examining the relationship between fitness and cognitive function (Cardiovascular Fitness Hypothesis)/8 cross-sectional; 24 post-test; 30 pre–post; 10 correlational	Studies included if they examined the relationship between current fitness level or participation in an exercise program and a measure of cognitive performance, used a chronic exercise paradigm, a cross-sectional design in which cognitive performance was examined in a "fit" and a "less fit" group, or a correlational design in which cognition and fitness were correlated, assessed aerobic fitness using a submaximal or maximal measure of VO_{2max}, or a composite measure of fitness that included a measure of VO_{2max}.	Cross-sectional ES = 0.40; post-test ES = 0.27; pre–post ES = 0.25; correlational ES = 0.29. Although cognitive function improved in pre – post studies (ES = 0.25), aerobic fitness was negatively associated with aerobic fitness.
Angevaren et al., 2008	Meta-analysis of all published randomized controlled trials comparing aerobic physical activity programs with any other intervention or no intervention with participants older than 55 years of age without known cognitive impairment/11	Studies including individuals without known cognitive impairment (including depression), randomly assigned to treatment, and also included a fitness parameter.	The largest effects on cognitive function were found on motor function and auditory attention (effect sizes of 1.17 and 0.50 respectively). Moderate effects were observed for cognitive speed (speed at which information is processed; effect size 0.26) and visual attention (effect size 0.26).
Hamer & Chida, 2009	Meta-analysis of published, prospective studies in which a diagnosis of a neurodegenerative disease was available/ 16 studies. 3219 participants non-demented at baseline	Studies included if they provided a measure of physical activity and a diagnosis of neurodegenerative illness.	The risk ratio of dementia in the highest physical activity category compared with the lowest was 0.72 overall: 0.55 for Alzheimer's, 0.55 and 0.82 for Parkinson's.
Smith, Blumenthal, Babyak et al., 2010; Smith, Blumenthal,	Meta-analysis of published and unpublished randomized trials from 1966 to 2009 examining the impact of aerobic training on cognitive function/29	Studies in which random assignment was used, mean age ≥ 18 years of age and non-demented, duration of treatment ≥1 month, intervention involved aerobic exercise training (e.g. brisk walking, biking, or	Aerobic exercise training was associated with modest improvements in attention and processing speed (g = 0.16), executive function (g = 0.12),

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Hoffman et al., 2010		jogging), and the presence of a control group that did not engage in aerobic exercise.	and memory (g = 0.13). Effects were stronger in trials among individuals with mild cognitive impairment.
McMorris et al., 2011	Meta-analysis of published studies examining the impact of acute exercise on working memory performance/24	Studies were included if they examined healthy individuals, the exercise intervention involved the activation of large muscle groups, repeated measures, within-subject design was used, data were provided showing the intensity of the exercise, the dependent variables were response time and/or accuracy/error, and tests met the criteria for classification as working memory tasks.	Exercise was associated with significantly improved response time (g = −1.41), but had a detrimental impact on accuracy (g = 0.40). It was concluded that acute, intermediate intensity exercise has a strong beneficial effect on speed of response in working memory tasks but a low to moderate, detrimental one on accuracy.
Aarsland et al., 2010	Meta-analysis of published, prospective studies examining the relationship between physical activity and vascular dementia/24 with 1378 patients with VaD and 10,108 controls	Studies were included if case selection included total dementia, VaD or vascular cognitive impairment, a prospective design was utilized, diagnosis of dementia and VaD were based on operational criteria, exercise was measured, a temporal relationship between exercise and dementia could be observed, and reported an odds ratio (OR) or relative risk (RR).	Physical activity was associated with reduced risk of developing VaD: OR 0.62.
Lambourne & Tomporowski, 2010	Meta-regression of impact of acute exercise bouts on arousal published from 1900 to December, 2008/29	Studies were included if they were performed on healthy adults, the exercise intervention elicited the activation of large muscles and cardiovascular responses, used a within-subject design, and published in English.	Cognitive task performance was impaired during exercise (mean ES = −0.14), but improved performance following exercise for tasks involving rapid decisions and automatized behaviors (mean ES = 0.20). Arousal continued to facilitate speeded mental processes and also enhanced memory storage and retrieval, and positive effects were observed following exercise regardless of study protocol.
Sofi et al., 2011	Meta-analysis of published, prospective studies examining the association between physical activity and cognitive decline among non-demented subjects/15 (including 12 cohorts)	Studies were included if they utilized a prospective cohort design, examined the association between physical activity and cognitive function as the primary or secondary outcome, were comprised of non-demented subjects evaluated at baseline, and used clear definitions of methods to assess cognitive performance and cognitive decline.	33,816 non-demented subjects were included with a follow-up of 1–12 years with 3210 individuals exhibiting cognitive decline during the follow-up. Random-effects model showed that subjects who performed a high level of physical activity were 38% less likely to develop cognitive decline during the follow-up (HR = 0.62). Low-to-moderate levels of exercise were also protective exercise also showed a significant protection (35%) against cognitive impairment (HR = 0.65).
Chang et al., 2012	Meta-analysis of published studies examining the impact of acute bouts of exercise on cognitive function/79	Studies included if they examined the effects of acute exercise on cognitive performance (defined as “performed on a single day”) and exercise was defined based upon the American College of Sports Medicine 2010 definition	Overall analyses suggested a small, positive impact of acute exercise on cognition (g = 0.097, n = 1034), and this was consistent across phases of exercise: during exercise (g = 0.101), immediately following exercise (g = 0.108), and after a delay (g = 0.103).
Morgan et al., 2012	Meta-analysis of prospective studies examining the relationship between	Studies were included if they utilized a prospective cohort design, measured the	Physical activity was associated with lower

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	leisure-time and work-related physical activity on dementia/21	association between physical activity and cognitive impairment or dementia, reported a validated, clinically-relevant outcome measure of cognitive impairment or a pre-specified decline in cognitive function from baseline	likelihood of developing cognitive impairment (OR = 0.66) and dementia (OR = 0.78), and these results did not appear to be related to follow-up length.
Hindin & Zelinski, 2012	Meta-analysis of published studies examining extended practice and aerobic exercise interventions/17	Studies included healthy, cognitively unimpaired community-residing adults ≥ 55 years of age, original research reporting extended cognitive domain practice of basic tasks such as N-back or aerobic fitness interventions hypothesizing cognitive improvements, experimental and control groups; multiple-session training; and pre- and post-tests of untrained cognitive tasks.	Aerobic exercise training was associated with improvements in cognitive function (ES = 0.33).

ES = effect size; HR = hazard ratio; OR = odds ratio; VaD = vascular dementia.