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Title

Multiple Effects of Physical Activity on Molecular and Cognitive Signs of Brain Aging: Can Exercise Slow Neurodegeneration and Delay Alzheimer's Disease?

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Abstract

Western countries are experiencing aging populations and increased longevity; thus the incidence of dementia and Alzheimer's disease (AD) in these countries is projected to soar. In the absence of a therapeutic drug, non-pharmacological preventative approaches are being investigated. One of these approaches is regular participation in physical activity or exercise. This paper reviews studies that have explored the relationship between physical activity and cognitive function, cognitive decline, AD/dementia risk and AD-associated biomarkers and processes. There is now strong evidence that links regular physical activity or exercise to higher cognitive function, decreased cognitive decline and reduced risk of AD or dementia. Nevertheless, these associations require further investigation, more specifically with interventional studies that include long follow-up periods. In particular, relatively little is known about the underlying mechanism(s) of the associations between physical activity and AD neuropathology; clearly this is an area in need of further research, particularly in human populations. While benefits of physical activity or exercise are clearly recognised, there is a need to clarify how much physical activity provides the greatest benefit and also whether people of different genotypes require tailored exercise regimes.

Introduction

A healthy lifestyle is well known to protect against the development of numerous medical disorders.[1-3] Higher incidences of all cause mortality, cardiovascular disease, hypertension, osteoporosis, diabetes, and depression have been observed in physically inactive compared with physically active populations.[4] It now appears that greater levels of physical activity or exercise have positive influences on conditions apart from the traditionally examined diseases (i.e. cardiovascular disease and diabetes). Numerous large prospective cohort studies have indicated that physical activity or exercise may enhance cognitive function and delay the onset of Alzheimer's disease (AD) and other dementias.[5-9] Studies of animal models of AD have also provided compelling evidence for a preventative role of physical activity in AD.[10, 11]

Without a foreseeable cure for AD, potential preventative strategies are being investigated in earnest. To validate these strategies, the underlying molecular mechanism(s) must be recognised, understood, and targeted in therapeutic trials. This review summarises a large body of literature, focussing on the effect of physical activity and exercise on factors associated with healthy brain aging. Specifically, we examine the relationships between physical activity or exercise and cognition, the risk of dementia and AD, as well as contributing neuropathological factors. Finally, we attempt to highlight potential future directions in this field, in light of the information presented.

Can physical activity/exercise enhance cognitive function and protect against dementia?

Evidence from epidemiological Studies

In 1978, Spirduso and Clifford[12] observed better performances in reaction time tasks (both simple and choice reaction time measures) in older men regularly participating in racket sports or running, compared with their sedentary counterparts. These observations were the basis of the first published data to indicate an association between physical activity and cognitive function. Since this publication, numerous studies (Table 1) have shown associations between higher levels of physical activity and lower levels of cognitive decline and/or enhanced cognitive functioning in various domains such as verbal memory,[13] executive functioning,[6, 14] attention,[6] and, global scores of cognitive function.[5, 13, 15] Furthermore, an important point was brought up in a cross-sectional study by Angevaren and colleagues.[16] The authors proposed that intense physical activity, rather than total activity, was associated with better performance in numerous cognitive domains, including speed, memory and mental flexibility. This study indicated that there may be an intensity threshold beyond which cognitive benefits become more pronounced. The concept that the level of physical activity moderates the level of cognitive response is quite logical; however, this theory has yet to be thoroughly investigated in randomized controlled trials. Clearly, if significant cognitive benefits require a threshold level of exercise or physical activity, then this level needs to be established. An activity threshold would have important implications in the designing of exercise programs or lifestyle changes for older adults. In apparent contradiction to this theory of a threshold exercise level, a recent study of 1324 subjects used an exercise questionnaire to evaluate levels of physical exercise, and it was found that moderate (but not light or vigorous) exercise at mid-life or late-life was associated with a

reduced risk of mild cognitive impairment (MCI, a term used for individuals with objective memory impairment that is not severe enough to be classed as dementia).[17]

To date, the majority of studies investigating the effect of physical activity on cognition and cognitive decline have utilised subjective physical activity questionnaires or surveys,[5, 7, 13] tools that are notorious for their limited validity and reliability.[18] One reason for limited reliability is that people's memory of exercise and activities carried out 5-10 years ago is not likely to be that accurate. Another reason is that the perceived levels of physical exertion required for almost all activities has been negatively associated with self-rated fitness levels, in both men and women.[19] To address this issue, the utilisation of objective measures of physical activity, such as accelerometers (used for the measurement of body movement) and measures of aerobic fitness, are becoming more frequent. Barnes et al.[6] measured physical activity using Actigraph accelerometers, to help determine the relationship between total daytime movement and cognitive function in older women. Their cross-sectional findings indicate that individuals in the highest quartile of daytime movement performed better on the Trail making test (Part B) and the Mini Mental State Examination (MMSE) than those in the lowest quartile. In a separate prospective study,[20] cardio-respiratory fitness was assessed in a cohort of 349 people using a standard treadmill exercise test protocol which included peak oxygen consumption (peak VO_2), treadmill exercise duration, and oxygen uptake efficiency slope. The cohort also had their cognitive function evaluated and any cognitive decline was assessed at a follow-up re-evaluation 6 years later. The tertile of participants with the lowest baseline cardio-respiratory fitness performed the worst on all cognitive tests conducted six years later, and also exhibited the greatest decline on the MMSE. Interestingly, within this study the difference in cognitive function across fitness levels was not corroborated by self-report measures of physical activity. For a different objective measure of activity, another

study assumed "activity energy expenditure" to be 90% of total energy expenditure (which was assessed over two weeks using doubly labelled water) minus resting metabolic rate (measured using indirect calorimetry). In the 197 men and women tested, a reassessment 2-5 years after baseline showed a significant dose response between energy expenditure and the later incidence of cognitive impairment.[21]

A decline in cognitive function is one of the hallmark symptoms of AD and dementia. While both epidemiological and interventional studies have examined the influence of physical activity or exercise on cognition, a decline in cognition does not necessarily result in dementia and/or AD. For this reason, several prospective cohort studies have examined the influence of (mostly self-reported) physical activity or exercise directly on the risk of dementia and/or AD (Table 2). One such study by Larson et al.[22], utilising data from The Adult Changes in Thought (ACT) Study, examined the effect of regular exercise on the risk of dementia and/or AD. The results from this study showed that individuals exercising three or more times a week were less likely to develop dementia at follow-up, compared with individuals exercising less than three times a week. Similarly, Scarmeas et al. [23] observed an association between high levels of physical activity and incident AD. Those in the "much" physical activity group and "some" physical activity group were less likely to develop AD, compared with those that reported no participation in any physical activities. These results suggest that even low-moderate levels of physical activity may aid in reducing risk of AD, when compared with leading a sedentary lifestyle. In the first study of its kind, Buchman et al.,[24] examined the association between total daily physical activity, measured by accelerometers, and the incidence of AD and cognitive decline. Higher levels of total daily physical activity were associated with decreased risk of AD. This recent study is the first to link objectively measured physical activity levels with lower AD risk.

The association between physical activity and decreased AD risk, while supported by a large body of literature (Table 2), is not without conjecture. Wilson et al.[25] utilised data from the Chicago Health and Aging Project to evaluate the relationship between physical activity and AD risk. No association was observed between physical activity levels and risk of developing AD at follow-up (although participation in cognitively stimulating activities was found to be negatively associated with risk of AD). Furthermore, results from the Religious Orders Study[26] revealed that participants in the lowest quartile of physical activity were at no greater risk of developing AD over a 4.5 year follow-up, than those in the other three (higher) quartiles of physical activity. Although the data from these studies are important, the limitations of these studies need to be recognized and discussed. Both studies used relatively small sample sizes ($n < 1000$) and short follow-up periods (~4-5 years), when compared with the studies that have shown an association ($n = 1449 - 4615$, follow-up periods of 4-21 years; see Table 2). In addition, the Religious Orders Study collected data from a very specific demographic, which may not reflect that of the general population. These conflicting results highlight the need for randomized intervention trials with long follow-up periods.

Evidence from randomised Clinical Intervention Studies

Observational epidemiological studies have provided insight into the relationship between physical activity and cognition. Nevertheless, the inability to control confounding variables (i.e. diet, medications, general health and lifetime health habits) does not allow a true cause and effect relationship to be established. Interventional data to date is limited, yet promising (Table 3).[14, 15, 27-31] The first high impact clinical intervention trial examining the association between physical activity and cognitive function was published by Kramer et al.[29] in 1999. One hundred and twenty four individuals were randomised to an aerobic (walking) group or

an anaerobic (stretching/toning) group, and exercises were carried out for six months. Individuals participating in the walking intervention had improved scores on an executive function task (task switching) compared with the stretching/toning group. Similar results were observed in a study by Baker et al.[27], in which 33 older adults with MCI were randomly allocated to either a high intensity aerobic exercise group or a stretching control group. Both groups completed four days a week of 45 to 60 minutes of activity per session. After six months of aerobic exercise, female participants demonstrated improved performance on executive function tasks, however no association between aerobic exercise and improvement in the executive function tasks was observed in the male participants. This study reported an interesting finding in terms of a possible gender bias in physical activity benefit, which will be further explored later in this review.

The LIFE-P study,[28] designed as a pilot study to assess the feasibility of an exercise intervention trial, examined the influence of a 12-month exercise intervention on variables such as cognitive and physical function. Fifty healthy participants were allocated to the exercise intervention group, which involved strength, balance, flexibility, and aerobic training over a period of six months; followed by a further six months of at-home activities. Additionally, fifty-two individuals were allocated to a control group consisting of weekly healthy living information sessions, for the first 26 weeks, followed by monthly meetings thereafter. No significant differences in cognitive changes were observed between the two groups following the 12 month intervention. It is possible that the intensity of the aerobic intervention (walking) was not sufficient to induce significant cognitive differences between the groups. Nevertheless, even with the relatively small numbers in this study, a positive association was observed between improved physical function and better cognitive functioning, regardless of intervention group.

In the largest intervention study of its kind to date, Lautenschlager et al.[15] examined the influence of a 24-week exercise intervention program consisting of 150 minutes of moderate intensity exercise three days per week (in addition to normal pre-study activity levels) on cognitive decline over 18 months. In this study, 170 individuals aged 50 years and over, with subjective memory complaints (n = 68) and/or mild cognitive impairment (n = 102) were randomised to an exercise intervention group, or usual care control group. After completing a home-based intervention program of moderate-intensity activity for the additional 150 minutes per week (compared to pre-study activity levels), the intervention group improved by 1.3 points on the Alzheimer Disease Assessment Scale (ADAS-COG), compared with the usual care group. At the 18-month follow-up, the observed improvement in cognitive function was still apparent in the exercise group, whereas no improvement was observed in the control group. This was a landmark study demonstrating that moderate-intensity exercise may attenuate cognitive decline in individuals with subjective memory complaints and objective memory impairments.

The above randomised intervention trials investigated the effects of aerobic exercise on cognitive function and/or cognitive decline. However, a meta-analysis has highlighted the possibility that combined aerobic and strength training interventions may give a greater degree of cognitive function improvement, compared with aerobic fitness alone.[32] This theory was the rationale for the completion of a resistance training only intervention, to ascertain the benefits of strength training, separate from aerobic exercise. Cassilhas and colleagues[30] assessed the impact of a six month resistance training program, using two different intensities (the moderate intensity group working to 50% of their repetition maximum and the high intensity group to 80%), on cognitive functioning in a group of 62 men and women. Both the

moderate and high groups of strength training had equal improvements in a range of cognitive tasks, when compared with the control group. Liu-Ambrose and colleagues[31] expanded on these findings by investigating the effect of a 12 month resistance training intervention on cognitive functioning. In this study, the experimental group was split by frequency, with one group performing the training once weekly and the other group undertaking training, twice weekly. Both of the training groups had significantly improved performance on a task assessing executive function, in comparison to the control group. These two studies report improved cognitive functioning in response to strength training, even in relatively small doses. However, a more recent study of community-dwelling older women by Liu-Ambrose et al. has found that twice-weekly (but not once weekly) resistance training for 12 months can positively impact functional plasticity of response inhibition processes in two regions of the cortex.[33] Furthermore twice-weekly resistance training in individuals with probable mild-cognitive impairment was associated with improved performance on an attention task and the enhancing of regional patterns of brain plasticity in three regions of the cortex.[34]

Further intervention studies with separate aerobic and strength training experimental groups, as well as a combined group, are required to evaluate which form or combination of exercise is the most beneficial for cognitive health.

Evidence from meta-analyses and systematic reviews

Data from a large number of observational and randomised clinical trials indicate that physical activity is beneficial for brain health. A summary of recent systematic reviews and meta-analyses is provided here.

The first meta-analysis of its kind was published by Colcombe and Kramer in 2003.[32] The aim of the review was to examine the effect of aerobic fitness training on cognitive functioning, in non-demented older adults. Fitness training was found to increase cognitive performance by an average 0.5 of a standard deviation. However, this effect appeared to be process specific, as the greatest benefit was observed in tasks assessing executive functioning, controlled processing and visuospatial functioning.

Paterson and Warburton[35] conducted a systematic review to assess the relationship between physical activity and a number of indicators of functional independence. Sixty six studies were included, 34 of which had a cognitive functioning outcome (19, 988 participants). The authors reported that a positive association between physical activity and cognitive function was found in 71% of the investigated studies. The proportion of positive outcomes was higher in prospective "follow-up" cohort studies (78%), when compared with exercise interventions (58%), which may indicate that long-term or mid-life physical activity may confer the greatest benefits in terms of cognitive health. This review also emphasized that the cognitive assessment tools and the methods for measuring levels of physical activity and exercise were inconsistent across studies, and this must be considered when interpreting results from reviews such as these.

Sofi and colleagues[36] conducted a meta-analysis to assess the relationship between physical activity and exercise and the risk of cognitive decline. Fifteen prospective cohort studies were selected (drawn from 12 cohorts), with a combined number of 33, 816 previously non-demented individuals, of which 3210 experienced cognitive decline. After follow-up periods ranging from 1 to 12 years, a significant protective effect of physical activity or exercise was reported. High levels of exercise induced the greatest protective effects with a hazard ratio of

0.62 (95% CI, 0.54-0.70; $p < 0.00001$). Similarly, low to moderate levels of exercise conferred significant benefit, compared to a sedentary lifestyle, with a hazard ratio of 0.65 (95% CI, 0.57-0.75; $p < 0.00001$).

Finally, another meta-analysis[37] compiled evidence from epidemiological studies of physical activity and neurodegenerative disease risk. Sixteen studies were included, which together were comprised of 163, 797 non-demented participants at baseline, with 3219 cases of neurodegenerative disease at follow-up. On average, the relative risk of dementia in the highest physical activity groups (the definition of this highest category varied between studies) compared with the lowest or control groups was calculated to be 0.72 (95% CI, 0.60, 0.86; $p < 0.001$) and the relative risk of AD was found to be 0.55 (95% CI, 0.36-0.84, $p = 0.006$) .

Collectively, these systematic reviews provide strong support for the notion that physical activity reduces the risk of cognitive decline leading to AD and dementia.

Is the association between physical activity and brain health gender dependent?

Gender differences in the physiological responses to exercise[38] may have relevance to cognitive health. A number of mixed gender studies have found a more pronounced response to physical activity in females, in terms of enhanced cognitive functioning, reduced cognitive decline or AD risk. Furthermore, a meta-analysis has reported that in general, physical activity interventions demonstrated greater effects of physical activity on cognition in studies with a higher proportion of females, compared with studies that had more males.[32] Nevertheless a number of male-only and female-only studies have reported beneficial effects of greater levels of physical activity.

In the female only cohort of the Nurses' Health Study[13], women that walked at least 1.5 hours per week performed better on a range of cognitive tasks (measured by a global score that combined six cognitive tasks), when compared with those walking less than 40 minutes per week. Furthermore, after the cohort was stratified into quintiles based on energy expenditure, those in the second through fifth quintile of energy expenditure performed significantly better than those in the first quintile. Similarly, in a prospective study of cognitively unimpaired women by Yaffe et al.[7], demonstrated an association between walking levels and cognitive decline over 5 to 8 years. Women in the quartile that undertook the greatest amount of walking were 37% less likely to experience cognitive decline than those in the quartile which undertook the least walking.

As mentioned above, a number of men-only cohorts have also reported associations between physical activity and reduced cognitive decline. In the Zutphen Elderly Study,[39] men participating in less than one hour a day of physical activity were found to be two times more likely to experience cognitive decline, compared with those participating in more than one hour a day of physical activity (physical activity such as gardening and cycling). These findings are supported by a prospective study by van Gelder et al.,[40] who reported a significant negative relationship between cognitive decline over ten years, and both the duration and frequency of physical activity. In terms of dementia risk in men, Abbott et al.[41] found in a prospective cohort of over 2000 participants, those who had reported walking the least (less than a quarter of a mile a day) had a 1.8-fold increased risk of developing dementia 1-6 years later (relative hazard, 1.77; CI, 1.04-3.01), compared with men who had been walking more than 2 miles a day. In the same study, a 1.7 fold increased risk of dementia was

observed in men who had been walking 0.25 to 1 mile per day compared with those who had been walking more than two miles (relative hazard, 1.71; 95% CI, 1.02-2.86).

In mixed gender studies, gender differences in benefits to brain health have been recognised. For example, in the large prospective Canadian Study of Health and Aging cohort which consisted of 4615 men and women, Laurin et al.[9] examined the association between physical activity levels (calculated by intensity and frequency of exercise) and the risk of developing dementia and AD. A reduced risk of AD was observed in women partaking in either moderate or high levels of activity, which was not reflected in the more active males in this cohort. Similarly Ho et al.[42] reported an association between physical inactivity and incident cognitive impairment. However, when the cohort was stratified based on gender, the association was observed in women only.

Collectively, these studies suggest that the positive effect of physical activity/exercise on cognition and AD risk is more pronounced in females; however it is clear that men still do receive a benefit in terms of brain health. There are a number of potential hypotheses to explain this association being more pronounced in women. For example, some cohorts may comprise women that are more at risk of developing cognitive impairment than their male counterparts. For example, in the study by Ho et al.[42], where it was reported only females benefited from physical activity in terms of decreased risk of cognitive impairment, the females in this study were less educated and reported poorer health than the men at baseline; and at follow up the women were 2.7 times more likely to have experienced cognitive decline. However, these demographic differences do not occur in all cohorts, and a physiological response to exercise is a more likely explanation for this gender bias. A number of studies have suggested that the sex hormones (testosterone and oestrogen) have

neuroprotective properties (see review Pike, 2009[43]). Females experience a marked drop in reproductive hormones at menopause, whereas men experience a more gradual decrease in sex hormones in andropause. It is understood that physical activity raises the levels of such sex hormones, particularly testosterone, and it is possible that women receive the greater benefit from physical activity, as their basal hormone levels are lower in the first place. This is the basis of a potential mechanism for the more pronounced cognitive function benefits seen in females following increased physical activity or exercise. Future intervention studies should consider the measurement of these hormones at baseline and post-intervention, to assess exercise-induced hormonal changes in relation to cognitive function changes.

Influence of physical activity on AD-associated biomarker levels and brain processes

While epidemiological and interventional studies have provided compelling evidence for a positive association between greater physical activity and a decline in AD risk and enhanced cognitive function, it is important to identify the mechanisms through which these associations occur (Figure 1).

Reducing Amyloid-β levels

The hallmark characteristic of AD is the formation of Amyloid-β (Aβ) plaques in the cerebral cortex and hippocampus. If physical activity can reduce cognitive decline and/or reduce the risk of AD, then it would be reasonable to hypothesise that physical activity reduces deposition of Aβ plaques. In support of this theory, Adlard et al.[10] observed significantly lower Aβ plaque levels in the frontal cortex and hippocampus of AD transgenic mice (TgCRND8; predisposed to excess Aβ production) after five months of voluntary treadmill exercise. Another study reported significantly lower levels of $A\beta_{1-42}$ peptides in the brains of transgenic mice after a 16 week exercise intervention, compared with sedentary mice.[11] Studies have also looked at humans for a similar association between physical activity and Aβ plaque levels in the cerebral cortex. For example, Liang et al.[44] investigated the association between physical activity and amyloid brain load, as measured by [^{11}C] Pittsburgh Compound B (PiB) Positron Emission Tomography (PET) imaging. They demonstrated that individuals with elevated PiB binding (i.e. higher levels of amyloid in the brain) had significantly lower reported levels of exercise. The study of physical activity effects on Aβ also included the measurement of Aβ levels in cerebrospinal fluid (CSF). In the 69 cognitively healthy older adults, a non-significant trend toward lower levels of CSF $A\beta_{1-42}$ was observed in high exercising individuals.[44] In another study, when comparing the effect of a six month high intensity aerobic exercise regime versus a stretching-only exercise regime

(33 adults with MCI, aged 55-85 years), mean plasma levels of $A\beta_{1-42}$ were 24% lower in the aerobic exercise group after 6 months, compared with the stretching group that showed a marginal decrease of 6%, however this result did not reach statistical significance.[27] A similar finding was reported after a six month aerobic exercise intervention in individuals with poor glucose tolerance, with a decrease of $A\beta_{1-42}$ in the aerobic exercise group ($p = 0.07$).[45] To add to these previous findings, our group[46] has just reported a significant association between higher levels of habitual physical activity (assessed using the International Physical Activity Questionnaire) and reduced plasma $A\beta_{1-42/1-40}$ in a cohort of 546 cognitively healthy individuals (aged 60-95, although this was only seen in the non-carriers of the Apolipoprotein E (APOE) ε4 carriers). Furthermore, reduced brain amyloid levels, as assessed by PiB PET scanning, were also observed in APOE ε4 carriers reporting higher levels of physical activity.

Exercise may reduce brain atrophy and induce functional network changes

Magnetic resonance imaging (MRI) can be used to measure the volume of the brain quantitatively, and thus has been a useful tool in examining the relationship between physical activity and brain atrophy. Bugg et al.[47] investigated the relationship between exercise and brain atrophy in 52 older adults (aged 55-79). It was observed that higher levels of exercise were associated with larger frontal lobe volume ($p = 0.001$). Aerobic fitness can be used as an objective indicator of physical activity participation, and has been associated with higher hippocampal, frontal lobe, parietal lobe and temporal cortex volumes.[48-52] Colcombe and colleagues reported that both reduced brain tissue loss[48] and increased brain volume[50] are associated with higher levels of aerobic fitness and exercise. In another study of brain areas commonly affected by atrophy in aging (such as the prefrontal, superior parietal and temporal cortices), higher levels of aerobic fitness (as measured by an estimated VO_2 score) were found to be associated with lower levels of atrophy.[48] Furthermore, in a study of 59

cognitively healthy but sedentary volunteers aged 60-79 years, a significant increase in grey and white matter volume of the prefrontal and temporal cortices was observed after a six month aerobic training intervention trial.[50] In a cross-sectional study of 165 older adults aged 59-81 years, higher levels of fitness (VO_2 peak) were associated with larger left and right hippocampi.[49] Furthermore the follow-up to this study found that a one-year aerobic exercise training program increased hippocampal volume by 2%, compared to the control subjects who experienced the expected age-related decline of 1-2%.[52] Importantly, the increase in volume was specific for the anterior hippocampus, an area including the dentate gyrus (where cell proliferation occurs) as well as the subiculum and CA1 subfields. It must be noted that studies in this field have primarily focussed on cognitively healthy individuals. Such studies should be aimed at individuals with the greatest risk of AD or dementia (i.e. diagnosis of MCI), to assess whether physical activity can attenuate neuropathology associated neuronal loss.

Functional networks within the brain have been identified, and advancing age has been associated with dysfunctions in a number of these networks. Studies of AD and cognitive decline have focussed on network patterns that are susceptible to age-related disruptions; including the Default Mode Network (DMN) and Frontal Executive Network (FEN).[53, 54] Using functional magnetic resonance imaging (fMRI), functional connectivity analyses can characterise the nature of interactions among brain regions, and the relationship between exercise on these networks has been investigated. Voss et al.[55] reported that a one year walking program enhanced the functional connectivity between the frontal, temporal and posterior cortices within the DMN and FEN. Interestingly, a control group (who engaged in non-aerobic stretching and toning exercises) also showed increased functional connectivity in the DMN, which could possibly be attributed to experience-dependent brain plasticity. This

intriguing area of research should be continued and expanded, possibly with the inclusion of a 'non-contact' control group in physical activity intervention trials. Another recent fMRI study looked at cardiovascular fitness, brain activation and spatial learning in healthy middle-aged people. This study reported improved cardiovascular fitness impacts on brain regions involved in spatial learning: cardiovascular fitness correlated positively with changes in brain activation in the medial frontal gyrus and the cuneus.[56] There are few publications in this field to date, as this field of work is relatively new, thus it is clearly an area in need of further investigation.

It has been argued that preservation of brain tissue, in response to physical activity, may not be due to neural integrity, but in fact is predominantly mediated by improved vascularisation of the brain regions in question. To test this hypothesis, Erickson et al.[57] measured the association between aerobic fitness and levels of N-acetylaspartate (NAA) in the brain. NAA is a nervous system specific metabolite detected only in neurons, which can be measured using magnetic resonance spectroscopy.[58] The authors hypothesised that if in fact vascularisation was the only mediator in the relationship between physical activity and increased brain volume then there would be no difference in NAA levels between people with high and low aerobic fitness. Results from their study showed that higher aerobic fitness was associated with an attenuation of expected age-related decreases in NAA levels, suggesting that the effect of aerobic fitness on brain function is not limited to enhanced vascularisation.

Exercise may increase levels of Growth Factors and Neurotransmitters

The relationship observed between physical activity and AD risk may be mediated via growth factors, in particular brain-derived neurotrophic factor (BDNF) and insulin-like growth factor I (IGF-I). Physical activity has been shown to induce BDNF production,[27, 59-62] and BDNF is

known to be associated with the growth and survival of neurons.[63] BDNF is also found in lower than normal levels in the AD brain.[64-66] Adlard et al.[59] examined the effect of wheel running on BDNF levels in rat models, and observed a positive dose response between such physical activity and cerebral BDNF levels. Furthermore, in the presence of oestrogen, physical activity was able to increase levels of hippocampal BDNF mRNA in female rats.[67] However, when the rats were oestrogen deprived, physical activity was unable to induce the same effect, and levels of BDNF mRNA did not increase. In humans, BDNF has only been measured in blood fractions, such as plasma, serum and platelets. Baker et al.[27] observed decreased BDNF in exercising individuals after an intervention trial. Further to this, in a group of regularly exercising individuals, an inverse association between both estimated VO_2 max and long-term sporting participation and serum BDNF was observed.[68] There remains some controversy as to whether lower or higher levels of BDNF levels in the periphery are protective. It has been suggested that lower levels of BDNF in people with higher fitness levels may reflect more effective BDNF clearance in the periphery of these individuals (see review by Knaepen and colleagues[69]), furthermore the form of BDNF being investigated (i.e. pro-BDNF vs total BDNF) may also be a determining factor in terms of the effect of BDNF on AD risk. The significance of circulating BDNF levels is not fully understood, and further research is required to properly evaluate the effect of physical activity on this growth factor, both in the brain and the periphery.

A reduction in IGF-I expression and signalling has been associated with AD neuropathology, and it has been suggested this growth factor may protect against AD.[70] In support of this, physical activity has been shown to regulate levels of serum IGF-I and induce the uptake of the circulating growth factor into the brain.[71, 72] Thus, IGF-I may play a mechanistic role in the relationship between physical activity and AD pathology. Although we do not understand

fully how increases in blood IGF-I can reduce AD, it has been shown that IGF-I is vital for mediating physical activity-induced angiogenesis and neurogenesis. In particular, a peripheral infusion of IGF-I has been shown to increase hippocampal neurogenesis levels[73], whilst the blocking of IGF-I has been observed to inhibit exercise-associated neurogenesis[74]. There is also evidence to suggest a synergistic relationship between IGF-I signalling and BDNF signalling.[75, 76] For example, the blocking of IGF-I prevents the induction of hippocampal BDNF in response to exercise[75]. Furthermore, IGF-I increases levels of the BDNF receptor (TrkB), which in turn increases levels of BDNF signalling.[76]

Levels of many neurotransmitters are known to be significantly lower in AD, particularly acetylcholine, such that many current pharmaceutical treatments for AD are aimed at raising acetylcholine levels. As another example, up to 70% of norepinephrine-projecting cells are lost in AD. In mice, norepinephrine stimulates microglia to suppress the Aβ-induced production of cytokines and stimulates microglial phagocytosis of Aβ, suggesting this loss might have a role in causing AD.[77] Dopamine has also been shown to be involved in AD, and to be linked to acetylcholine neurotransmission, for example, dopamine has been shown to restore deficient short latency afferent inhibition normally found in AD.[78]

A number of animal studies have indicated that exercise induces several neurotransmitters, including serotonin, acetylcholine, dopamine, epinephrine and norepinephrine.[79, 80] Winter et al.[60] have also reported that peripheral levels of catecholamines (dopamine, epinephrine and norepinephrine) increase in human subjects immediately after exercise. The increases in dopamine and epinephrine levels were found to be associated with better intermediate (dopamine) and long-term (epinephrine) retention on a vocabulary task. In addition to this, exercise has been shown to increase the activity of receptor neurotransmitter subtypes; which

can then change cortical activity.[81] These studies suggest another possible mechanistic link between physical activity/exercise and enhanced cognitive functioning and reduced dementia risk.

Other potential mechanisms

There are several other physical activity-induced changes that can occur in the brain that may result in significant cognitive benefits; in particular, neurogenesis, angiogenesis, increased cerebral blood flow and enhanced synaptic plasticity. Van Praag et al.[82] reported that voluntary wheel running in mice results in twice the amount of surviving newborn cells in the adult dentate gyrus, suggesting that aerobic exercise alone is sufficient to significantly increase neurogenesis levels. In addition, two independent studies[83, 84] observed increased levels of hippocampal synaptic plasticity in mice that completed a voluntary wheel running regimen. In humans, exercise has been shown to improve long-term outcomes in stroke patients, and animal studies indicate this may be attributed to the positive effects of exercise on angiogenesis and cerebral blood flow.[85, 86] Physical activity is known to up-regulate endothelial nitric oxide synthase (eNOS), and the improvements in cerebral blood flow and greater levels of angiogenesis are likely to occur via eNOS-dependent mechanisms.[85, 86]

Finally, physical activity is a well-known modifiable protective factor for Type II diabetes[87], and has been strongly associated with insulin sensitivity.[88] For example, time spent watching television has been found to correlate with serum insulin levels, whereas leisure-time physical activity has been found to be inversely associated with insulin levels.[89] This highlights another potential mechanism for the link between AD risk and physical activity, as insulin sensitivity and metabolic disease have been implicated in AD, and are associated with alterations in Aβ processing.[90] It has also been suggested that exercise might reduce chronic

inflammation, which has been shown to be involved in age-associated chronic conditions such as Type II diabetes, Alzheimer's disease, cardiovascular disease and arthritis. Thus increasing physical activity may reduce the risk of Alzheimer's disease by lowering chronic inflammation.[91]

The effect of the Apolipoprotein E ε4 allele

The Apolipoprotein E (APOE, gene) ε4 allele is the strongest genetic risk factor for late onset AD.[92] Apolipoprotein E (apoE, protein) has critical functions in redistributing lipids among central nervous system cells for normal lipid homeostasis, apoE also helps to repair injured neurons and maintain synapto-dendritic connections. Transgenic mouse studies have found that the apoE ε4 protein is associated with higher rates of Aβ aggregation, reduced clearance of Aβ from the brain, impaired learning and memory, increased tau phosphorylation, and increased neuronal vulnerability.[93]

However, quite apart from the effects related directly to Alzheimer's disease, possession of APOE ε4 alleles is also strongly associated with an increased risk of developing atherosclerotic cardiovascular disease (CVD), a condition which itself is a risk factor for Alzheimer's disease. In fact, CVD and Alzheimer's share several risk factors, such as hypertension, lack of exercise, high (saturated) fat diets, high cholesterol levels and diabetes. Any improvement in cardiovascular and cerebrovascular health via increased physical activity would understandably reduce the risk of these conditions.

Various studies have shown that physical activity influences AD risk, brain amyloid deposition, and plasma $A\beta_{(1\text{-}42/1\text{-}40)}$ levels differently depending on APOE genotype. For example, Podewils et al.[8] reported an association between physical activity and reduced AD

risk, which was restricted to carriers of the APOE ε4 allele. Conversely, Obisesan et al.[94] found that physical activity correlates with cognitive status in non-carriers of the APOE ε4 allele, but not in APOE ε4 carriers. In studies of brain Aβ load, it has been found that carriers of the APOE ε4 allele are more susceptible to increased amyloid deposition, if they have a sedentary lifestyle. This relationship between brain amyloid levels and exercise participation was discovered by Head and colleagues[95] who found that brain amyloid burden (quantified by PiB PET) was highest in sedentary people that were APOE ε4 carriers, whereas in exercising individuals, APOE allele status did not appear to influence brain amyloid burden. This association between physical activity and brain amyloid load in APOE ε4 carriers has recently been confirmed by Brown et al.[46] in the highly characterised AIBL study cohort. This study also found that plasma $A\beta_{(1\text{-}42/1\text{-}40)}$ levels were lower in people undertaking higher levels of physical activity, yet this was only significant in non-APOE ε4 subjects. From these studies it would appear that engaging in regular exercise helps all people avoid AD, although mechanisms through which this benefit occurs are influenced differently depending on APOE allele status. These studies highlight the need for further longitudinal studies and randomised intervention trials to characterise the mechanisms for these APOE genotype-associated differences more fully. Such studies would aim to ascertain the optimum levels of activity needed for individuals of each genotype to attain the greatest benefit to cognitive health.

Sedentary lifestyles, physical activity and exercise

Many studies discussed in this review have used the terms physical activity and exercise interchangeably, yet these terms are not equal. Physical activity and exercise can both be defined as body movement produced by skeletal muscle that expends energy. Such energy can be measured and the amount of activity or exercise will correlate positively with physical fitness. However, physical activity can include any daily activity except sleep, whereas

exercise is a subset of physical activity, usually including planned, structured, repetitive activity, partly or solely for the purpose of improving or maintaining some level of physical fitness.[96]

In this review, we have tried to distinguish between general physical activity, and planned exercise interventions. Studies which reviewed the effect of strength training were again indicated within the text. We have included studies that utilised objective measures of physical activity (such as accelerometer data) and aerobic fitness (as measured by $VO2_{max/peak}$). Considering that the outcome of all these studies will hopefully be an outline or regimen of recommended exercises sufficient to reduce the risk of AD and dementia significantly, and/or to maintain cognitive function as best as possible, it would be useful to standardise the types of physical activity in such research. Similarly, the term "sedentary" needs definition, as some papers use this word to mean a sitting or reclining position, whereas others use the term to cover any activity that only requires low energy expenditure.[97]

Due to the many hours people of all ages are spending in front of computer and television screens in our increasingly sedentary lifestyles, the increases in diabetes, cardiovascular disease and obesity are not surprising. There is also an increasing acceptance of the notion that pharmaceutical treatments are a good substitute for exercise, and require much less time and effort. A public health education priority should be to bring about a change in attitude towards exercise and fitness, especially in the exercise-resistant elderly. As such, the implementation of appropriately tailored exercise regimens, or at least lifestyle changes to include several activities that require sufficient energy expenditure, will reduce cognitive health problems and dementia. Furthermore, an increase in physical activity levels in the wider community would reduce cardiovascular disease, diabetes, and a host of other related

conditions, effectively improving the quality of life of the elderly, as well as hopefully reducing public health costs.

Future Directions

With an aging population comes the increasing demand for preventative strategies to delay the onset of dementia and AD. Based on the literature presented in this article, physical activity has the potential to significantly contribute to this goal. Nevertheless, questions still remain as to the most effective exercise programs (i.e. intensity, frequency, duration) that will provide the greatest benefit. Furthermore, considerations of exercise type (i.e. aerobic versus strength training), should be a major focus of future research in order to develop evidence based effective interventions. A comprehensive understanding of biological and physiological mechanisms is essential to support the use of physical activity as a preventative strategy. Animal studies including studies of transgenic animal models have indicated that physical activity may directly reduce levels of AD related biomarkers such as Aβ, and increase IGF-1 and BDNF levels.[10, 11, 59] Further research examining the effect of physical activity on these biomarkers is necessary in large human cohort studies. These biomarkers should be used as outcome variables along with cognitive measures in intervention trials to elucidate the efficacy of physical activity as an AD prevention strategy. Furthermore, the greater use of emerging neuroimaging techniques such as amyloid imaging and NAA quantification in randomised controlled trials will be highly beneficial.

Conclusion

Results from the studies presented here suggest that physical activity can help maintain superior cognitive functioning as well as modify the risk of cognitive decline, AD and dementia. The evidence for physical activity being a contributor to healthy brain aging is strong. However, little is known about the underlying mechanism(s) of this association, and clearly this is an area in need of further research, particularly in human populations.

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Table 1. Physical activity and cognitive function: epidemiological studies

Study	Cohort	*N* Age /Gender	Analysis Type	Physical Activity/Fitness Assessment	Outcome and Main Results
Angevaren et al. (2007)[16]	Doetinchem Cohort Study	1927 45-70 ♂♀	Cross-sectional	Physical Activity. Self reported frequency/duration.	Higher intensity of physical activity, not duration, was associated with better processing speed ($p < 0.01$), memory ($p < 0.05$), mental flexibility ($p < 0.05$) and overall cognitive function ($p < 0.01$).
Barnes et al. (2003)[20]	Sonoma, CA Study	349 ≥55 ♂♀	Cross-sectional	Physical Fitness. Cardio-respiratory fitness.	Higher cardio-respiratory fitness was associated with global cognitive function ($p = 0.002$).
Barnes et al. (2008)[6]	Study of Osteoporotic Fractures	2736 80-89 ♀	Longitudinal	Physical Activity. Measured by Actigraphy.	A significant association was found between high levels of daytime movement and better cognitive functioning ($p < 0.001$).
Middleton et al. (2008)[5]	Canadian Study of Health and Aging	8403 ≥65 ♂♀	Longitudinal	Physical Activity. Self reported frequency/intensity.	High exercises (≥ 3 times/week) were more likely to remain stable or improve, in terms of cognitive function (95% CI, 40.6-44.0), when compared with low/non exercisers (<3 times/week).
Schuit et al. (2000)[39]	The Zutphen Elderly Study (Netherlands)	347 65-84 ♂	Longitudinal	Physical Activity. Self reported frequency/duration. Participation	Men with an APOE ε4 allele who participated in less than an of hour physical activity per day had an increased risk of cognitive decline (odds ratio, 3.7; 95% CI, 0.60-0.90).
van Gelder et al. (2004)[40]	Finland, Italy and Netherlands Elderly (FINE) Study	295 ≥70 ♂	Longitudinal	Physical Activity. Self reported frequency/duration/intensity.	An association was found between decreased intensity ($p = 0.002$) and duration ($p = 0.02$) of physical activity and greater odds of cognitive decline.
Weuve et al. (2004)[13]	Nurses Health Study (USA)	18766 70-81 ♀	Longitudinal	Physical activity. Self reported duration/frequency/intensity.	Individuals undertaking 1.5 hours or more of physical activity per week performed better compared with those who undertook less than 40 mins ($p < 0.001$). Those in the highest quintile of energy expenditure had higher cognitive functioning than those in the lowest quintile.
Yaffe et al. (2001)[7]	Study of Osteoporotic Fractures (USA)	5925 ≥65 ♀	Longitudinal	Physical Activity. Self reported walking.	Participants with higher levels of walking and stair-climbing were less likely to experience cognitive decline (odds ratio; 0.66; 95% CI, 0.54-0.82).

Table 2. Physical activity and dementia/AD: prospective cohort studies

Study	Cohort	N/Follow-up	Age /Gender	Method of Physical Activity Assessment	Outcome and Results
Abbott et al. (2004)[41]	Honolulu-Asia Aging Study (USA)	2257 7 years	71-93 ♂	Self reported. Distance walked/day.	Men who reported walking the least were more likely to develop dementia, compared with those who walked the most (relative hazard 1.93; 95% CI, 1.11-3.34).
Buchman et al. (2012)[24]	The Rush Memory and Aging Project (USA)	716 4 years	53-100 ♂♀	Total daily activity measured by actigraphy.	High total daily physical activity was associated with reduced risk of AD (hazard ratio = 0.47; 95% CI 0.27-0.83).
Laurin et al. (2001)[9]	Canadian Study of Health and Aging	4615 5 years	≥ 65 ♂♀	Self reported. Frequency and intensity.	High physical activity levels were associated with reduced risk of AD (odds ratio, 0.50; 95% CI, 0.28-0.90) and dementia (odds ratio, 0.63; 95% CI, 0.40-0.98).
Larson et al. (2006)[22]	Adult Changes in Thought (ACT) Study	1740 6.2 years	≥ 65 ♂♀	Self reported. Frequency	Persons who exercised ≥ 3 times/week were less likely to develop dementia (hazard ratio, 0.68; 95% CI, 0.48-0.96; p = 0.03) and AD (hazard ratio, 0.64; 95% CI, 0.43-0.96; p = 0.031).
Rovio et al. (2005)[98]	Cardiovascular Risk Factors, Aging and Incidence of Dementia (CAIDE) Study	1449 21 years	65-79 ♂♀	Self reported. Frequency.	A minimum of twice weekly leisure-time physical activity at midlife was associated with a decreased risk of dementia (OR, 0.48; 95% CI, 0.25-0.91).
Scarmeas et al. (2009)[23]	Washington Heights-Inwood Columbia Aging Project (WHICAP)	1880 5.4 years	≥ 65 ♂♀	Self reported. Frequency, duration and intensity.	Those doing the most physical activity were less likely to develop AD (HR 0.67, 95% CI: 0.47-0.95), compared with those doing the least.
Wilson et al. (2002)[25]	Chicago Health and Aging Project (USA)	835 4.1 years	≥ 65 ♂♀	Self reported. Frequency and duration.	No association between physical activity and incident AD.
Wilson et al. (2002) [26]	Religious Orders Study	801 4.5 years	≥ 65 ♂♀	Self reported. Frequency.	No association between physical activity and incident AD.

Table 3. Physical activity/exercise and cognitive function: intervention trials

Study	*N* Age /Gender	Physical Activity Intervention	Outcome and Main Results
Baker et al. (2009)[27]	33 55-85 ♂♀	Aerobic Exercise and Stretching Group. Each group carried out activity routines 4 d/wk for 45-60 minutes for 6 months.	Aerobic exercise improved performance on executive function: Trails B (p = 0.04), and in women only (n = 17): Digit Symbol (p = 0.04), Category Fluency (p = 0.01), and Stroop (p = 0.02).
Cassilhas et al. (2007)[30]	62 65-75 ♂	24 weeks of resistance exercise. Experimental moderate group (50% of repetition maximum) and experimental high group (80% or repetition maximum) and control group.	The moderate and high exercise groups performed significantly better on a range of cognitive function tasks, compared with the control group ($p < 0.05$).
Fabre et al. (2002)[14]	32 ≥60 ♂♀	Physical Training Group, Mental Training Group and Combination Mental and Physical Training. Physical activity training involved two one hour aerobic exercise sessions per week.	Those in the physical activity training group were significant improved in memory performance ($p < 0.01$) compared with the control group.
Kramer et al. (1999)[29]	124 60-75 ♂♀	Six month aerobic exercise (walking) and anaerobic (stretching and toning) training.	Those participating in aerobic exercise improved in terms of performance on executive function tasks. No difference observed between two groups in other domains of cognition.
Lautenschlager et al. (2008)[15]	170 ≥50 ♂♀	Participants in the physical activity intervention group were encouraged to undertake three 50-minutes sessions of exercise per week, in addition to pre-study levels. Activity programs were individualised to suit each participant.	At an 18 month follow up, those in the intervention group had experienced an increase of 0.73 points (95% CI, -1.27-0.03) on a cognitive measure, whilst the control group experienced an increase of only 0.04 points (95% CI, -0.46-0.88)
Liu-Ambrose et al. (2010)[31]	155 65-75 ♂♀	Once weekly and twice-weekly resistance training and twice weekly balance and tone training (control group) for twelve months.	Performance on the Stroop task improved by 12.6% and 10.9% in the once weekly and twice weekly resistance training groups respectively, compared with the control group that experienced a decline in 0.5% ($p \leq 0.03$)
Williamson et al. (2009) [28]	102 70-89 ♂♀	One year physical activity intervention consisting of aerobic, strength, balance and flexibility exercises. Primary focus of intervention was walking, at least 150 minutes a week was to be completed.	No differences in cognitive function between the two groups were observed in following the intervention.

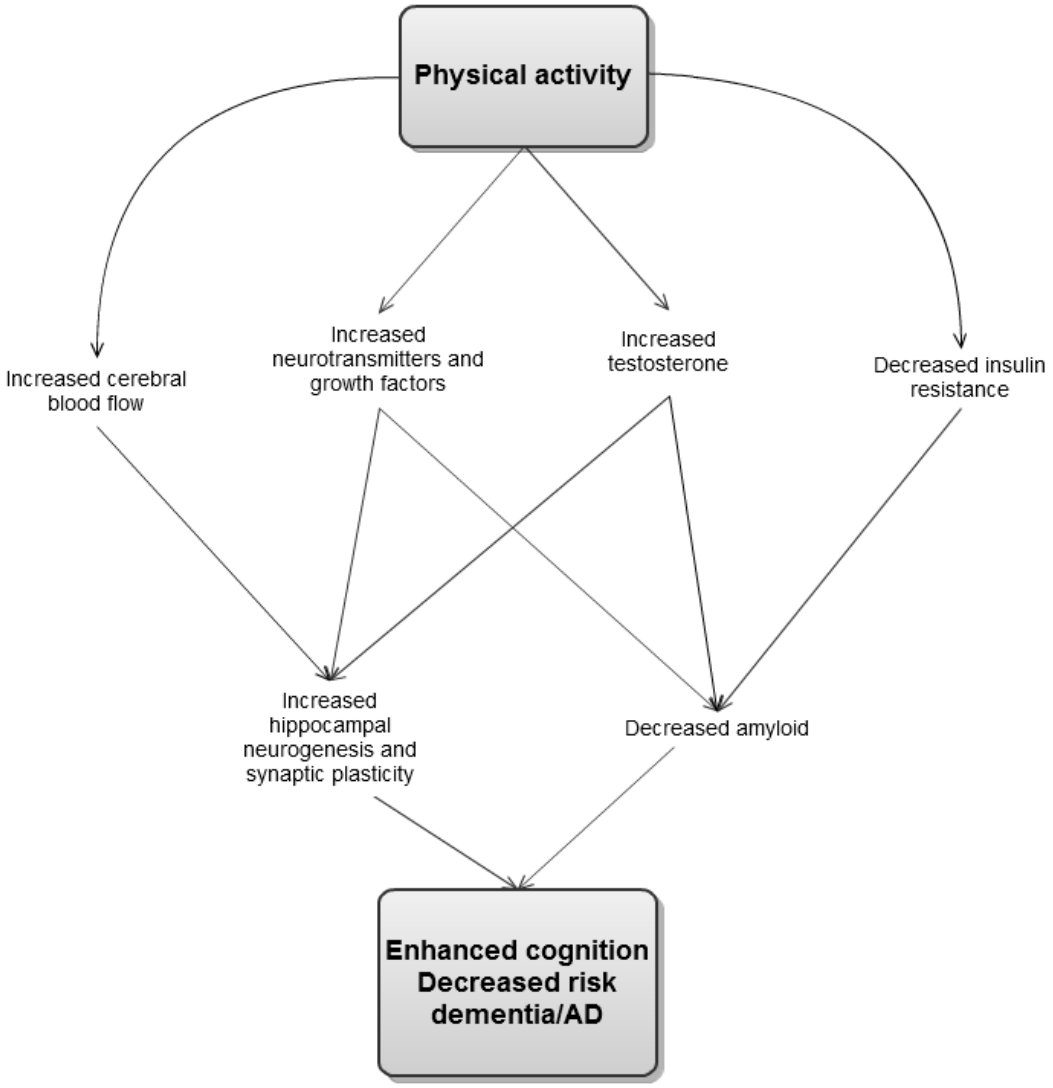

Figure 1. Physical activity induces neurotransmitters and growth factors (i.e. BDNF and IGF-I), increases circulating testosterone levels and decreases insulin resistance. Each of these has been shown to reduce levels of Aβ in the brain, via increased clearance or decreased production of the protein. In addition, the induction of neurotransmitters, growth factors and testosterone leads to enhanced hippocampal neurogenesis and synaptic plasticity. Increased cerebral blood flow in response to greater physical activity may also play a mechanistic role in this association.