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Review

Can exercise training teach us how to treat Alzheimer's disease?

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A B S T R A C T

Alzheimer's disease (AD) is the most common cause of dementia and there is currently no cure. Novel approaches to treat AD and curb the rapidly increasing worldwide prevalence and costs of dementia are needed. Physical inactivity is a significant modifiable risk factor for AD, estimated to contribute to 12.7% of AD cases worldwide. Exercise interventions in humans and animals have shown beneficial effects of exercise on brain plasticity and cognitive functions. In animal studies, exercise also improved AD pathology. The mechanisms underlying these effects of exercise seem to be associated mainly with exercise performance or cardiorespiratory fitness. In addition, exercise-induced molecules of peripheral origin seem to play an important role. Since exercise affects the whole body, there likely is no single therapeutic target that could mimic all the benefits of exercise. However, systemic strategies may be a viable means to convey broad therapeutic effects in AD patients. Here, we review the potential of physical activity and exercise training in AD prevention and treatment, shining light on recently discovered underlying mechanisms and concluding with a view on future development of exercise-free treatment strategies for AD.

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease that accounts for 60–80% of all dementia cases (Association, 2019). As the primary risk factor for AD (or dementia of any cause) is increasing age, and given human life expectancy keeps increasing, the proportion of people with dementia will increase dramatically without development of efficient interventions (Winblad et al., 2016). Poignantly, the number of people living with dementia is estimated to reach 152 million in 2050 tripling from the current 50 million (Patterson, 2018). As dementia patients often require around-the-clock care, this clearly projects a huge increase also in the number of people indirectly affected. Critically, the global cost of dementia has been estimated to double by 2030 to the annual cost estimate of 2 trillion US dollars (Patterson, 2018), with up to 85% of costs being related to family and social care (Livingston et al., 2017).

What neuropathologically distinguishes AD from other causes of dementia, are the accumulation and deposition of amyloid-β (Aβ) into extracellular plaques and hyperphosphorylated tau protein into intracellular neurofibrillary tangles in the brain (Long and Holtzman, 2019). Importantly, such pathology may progress gradually for decades before the symptoms of dementia become noticeable (Dubois et al., 2016; Jack et al., 2013). There is currently no cure for AD and the development of medical drugs to treat AD has turned out problematic, with a failure rate

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of 99.6% (Cummings et al., 2014). Until the approval of the anti-amyloid antibody aducanumab (marketed as Aduhelm) for use in treatment of AD by the U.S. Food and Drug Administration on June 7th 2021 (Cavazzoni, 2021), the drugs in use have only been able to temporarily alleviate some symptoms of the disease (Dong et al., 2019). Aduhelm was approved under the accelerated approval pathway due to its ability to reduce amyloid plaques in the brain (Sevigny et al., 2016), but its clinical benefit is still required to be confirmed for continued approval (Cavazzoni, 2021). Independent of the faith of aducanumab in AD therapeutics, any interventions capable of delaying the clinical onset of AD dementia could give an individual a longer, and/or a healthier life, and significantly reduce the related costs of caretaking (Livingston et al., 2017).

Lifestyle changes targeting the risk factors of the disease before or during the preclinical stage of AD may have the potential to delay cognitive decline and the onset of dementia, also in individuals at high genetic risk (Lourida et al., 2019; Rosenberg et al., 2018; Ngandu et al., 2015). In this regard, it is notable that aged individuals may show preserved cognition to the end of their lives although post-mortem brain examinations exhibit substantial AD pathology (Bennett et al., 2006), suggesting that typical AD brain pathology alone does not necessitate cognitive impairment and eventual dementia. Hence, actions to reduce risk factors for AD may protect from dementia not only through reduced pathology, but also through increased resilience towards such pathology (Livingston et al., 2017).

Although age and genetic predisposition are currently unmodifiable, there is consistent evidence for other potentially modifiable risk factors. Approximately one-third of AD cases could be associated to at least one of the following seven risk factors: low educational level, smoking, depression, diabetes, hypertension, obesity, or physical inactivity (Norton et al., 2014). As the last six of these risk factors are also cardiovascular disease risk factors, maintaining good cardiovascular health may help prevent AD (Norton et al., 2014; Pase et al., 2016). Further, because greater levels of physical activity (PA) and exercise training associate with better cardiorespiratory fitness (CRF) and inversely correlate with cardiovascular disease risk factors (Garber et al., 2011; Lin et al., 2015), exercise seems a tenable means for reducing the prevalence of AD. In fact, physical inactivity was estimated to contribute to 12.7% of worldwide AD cases (Norton et al., 2014). In Europe, the USA, and the UK this estimate is almost doubled (Norton et al., 2014). It is, however, of note that these estimates do not consider overlap with the other risk factors mentioned above (Norton et al., 2014). In comparison, the latest estimates for dementia of any cause suggest 9.6% of dementia cases related to physical inactivity in later life (at the age above 65 years), but when adjusted for clustering of different risk factors, the estimated fraction of cases attributable exclusively to physical inactivity is 1.6% (Livingston et al., 2020).

Since physical inactivity is a key risk factor for AD, we review here the potential of PA and exercise training in AD prevention and treatment, compiling and discussing the landmark studies in the field. We bring together evidence from mice to humans, concentrating on potential underlying mechanisms and how the growing knowledge of exercise effects on the brain may help in the development of novel treatment strategies for AD. Each section here is ended with a brief sum-up and perspectives.

2. Methods

The majority of the literature used for this review was selected based on a systematic search for articles related to each topic addressed throughout the review. We searched PubMed for original articles and reviews, with a set of inclusion and exclusion criteria outlined in detail in the Supplementary material. A total of 1408 abstracts were screened, from which we narrowed to 381 full text reads. Of those, 210 were included in the review. Otherwise, the papers included in the review were either identified from the references of other included studies or were previously familiar to the authors.

2.1. Link between PA, cognitive function, and AD development

2.1.1. Physical activity

PA encompasses any activity involving movement of the body through the work of skeletal muscles and an increase in energy expenditure above resting values (Caspersen et al., 1985). In contrast, exercise is defined as a more structured and planned type of PA, aiming to maintain or improve physical fitness (Caspersen et al., 1985).

Observational studies suggest PA to be associated with a reduced risk of cognitive decline. A meta-analysis of 15 prospective studies including a total of 33816 cognitively healthy subjects (age 35 to over 85 years) found that when compared to reporting no PA at baseline, low-to-moderate levels of PA associated with a 35% reduced risk of cognitive decline during subsequent 1–12 years, whereas a high level of PA associated with a 38% reduced risk (Sofi et al., 2011). However, when the analysis was restricted to the six studies with a follow-up duration of at least 5 years, the respective reductions in risk of cognitive decline were 26% and 33% (Sofi et al., 2011). A more recent meta-analysis of 18 prospective studies with follow-up duration of 1–21 years and a total of 38343 middle-aged to older subjects found a similar effect: moderate level of PA associated with a 26% and high level of PA associated with a 33% reduced risk of cognitive decline when compared to no PA group (Guure et al., 2017). Some retrospective and prospective studies have also reported positive associations between self-reported childhood or teenage PA levels and measures of cognitive function later in middle age or older age (Reas et al., 2019; Middleton et al., 2010; Hakala et al., 2019; Dregan and Gulliford, 2013).

Concentrating specifically on leisure-time PA and therefore being more descriptive of exercise training, a recent systematic review of 14 longitudinal and 9 cross-sectional studies concluded that there is an association between adulthood leisure-time PA of at least moderate intensity and better global cognitive function, executive function, and memory in late adulthood, whereas low-intensity PA may have limited effect on cognition (Engeroff et al., 2018). Results from a recent meta-analysis on individual-based data showed further support to suggest the association being dependent on the intensity of PA (Lipnicki et al., 2019). In the analysis including longitudinal data of 11897 individuals (mean age 73.1 years) from 9 population-based cohorts, performing vigorous-intensity PA at least once a week was found associated with better cognitive function at follow-up (mean 3.1 years) when compared with minimal PA, whereas moderate-intensity PA was not (Lipnicki et al., 2019). These findings together suggest PA level and intensity to be negatively associated with cognitive decline over time.

Considerable evidence similarly suggests PA to protect against dementia due to AD. The earliest meta-analysis to study the association between PA and risk of AD included five studies with a total of 13771 participants 30–70 years old at baseline and follow-up times ranging from 3 to 30 years. This analysis found regular PA associated with a 45% lower risk of AD compared to being physically inactive or performing only a low level of PA (Hamer and Chida, 2009). Subsequent meta-analyses have reported somewhat similar results. A larger analysis including 21 cohorts with a total of 32158 participants (mean baseline age ranging from 44.7 to over 90 years) and follow-up times from 12 months to 28 years found high and moderate levels of PA to reduce the risk of AD by 38% and 29%, respectively, when compared to low or no PA engagement (Guure et al., 2017). Likewise, meta-analyses including only studies with subjects older than 65 or 70 years at baseline found 35–39% lower risk of AD in physically active individuals compared with those who reported only low PA level or no habitual PA at all (Beckett et al., 2015; Santos-Lozano et al., 2016).

Providing some clarification into the volume of PA needed for reduced risk of AD, a further analysis suggested that reaching the internationally recommended PA level of at least 150 min of moderate-to vigorous-intensity PA per week (Garber et al., 2011) was associated

with a similar 40% reduced risk of AD in older adults that were 70–80 years old at baseline (Santos-Lozano et al., 2016). Another recent analysis on reports of leisure-time PA from subjects over 65 years old revealed a linear dose-response relationship between leisure-time PA and AD within a weekly leisure-time PA range of 0–45 metabolic equivalent task (MET: 1 MET defined as 3.5 ml/kg/min VO_2, equivalent to sitting at rest) -hours, where each additional 10 MET-hours per week leisure-time PA decreased the risk of AD by approximately 13% (Xu et al., 2017). Considering the common definitions to moderate- (energy expenditure between 3 and 6 METs) and vigorous-intensity PA (over 6 METs), 10 MET-hours per week equals approximately 100–200 min of moderate- to vigorous-intensity PA per week and hence the recommended weekly PA according to the international guidelines (Garber et al., 2011).

While the results from these meta-analyses suggest being physically active at midlife (45–65 years) and/or at older age is associated with reduced risk of AD, the follow-up times of most individual studies have been relatively short and the influence of earlier life PA or life-long PA on the risk of AD has been less studied. A recent study in 1345 older adults with a mean age of 75.1 years found that subjects who reported persistently high leisure-time PA levels from early life (the age of 12–25 years) had a 72% lower risk of AD when compared with those whose PA levels were persistently low (Ogino et al., 2019). In addition, increasing PA level from low in early life to high in late life was found associated with a 40% reduced risk of AD (Ogino et al., 2019). Although conclusions on causal effect cannot be drawn based on this evidence, these findings together indicate that higher levels of PA are associated with reduced risk of AD. The findings also imply that the effects of PA may be accumulative such that being highly physically active throughout life may confer the greatest protective effect, although the risk of AD may be significantly decreased also by becoming more physically active later in life.

The reduced risk of dementia due to AD in more physically active individuals may largely be explained by the effects of PA on improving cardiovascular and metabolic health, and not only direct effects on the brain and AD pathogenesis. A recent meta-analysis where individual-level data from a total of 404840 individuals (mean age at baseline 45.5 years) from 19 studies were used to investigate the evidence for a long-term association between PA and risk of dementia provides some support to this view (Kivimäki et al., 2019). First of all, PA was found associated with reduced risk of diabetes, coronary heart disease, and stroke in dose-response manner, independent if the analyses were restricted to follow-up time of less or over 10 years. Notably, similar analyses revealed disappearing association for PA and AD or any-cause dementia with long follow-up duration: when taking into account only the first 10 years of follow up from baseline, physical inactivity was found associated with 36% increased risk of AD and 40% increased risk of dementia of any cause, but, when limiting the analyses to those individuals with no diagnosis of dementia within the first 10 years of follow up, there was no indication of an association between physical inactivity and AD or dementia of any cause. These results suggest that reduced PA due to preclinical AD (or any dementia) might have confounded results in studies with shorter follow-up times, and that the direct effect of PA on pathogenetic mechanisms in AD or dementia of any cause might be small. Still, physical inactivity was found associated with a 30% increased risk of dementia beyond 10-year follow-up time specifically within those individuals with an incident cardiometabolic disease after baseline (Kivimäki et al., 2019). Therefore, these results suggest PA might be a specifically significant means for AD and dementia prevention in those individuals with cardiometabolic disease, further implying that the beneficial effects of PA on cardiovascular and metabolic health might explain much of the risk-reducing effect.

2.2. Cardiorespiratory fitness

Most prospective studies have only used subjective self-reporting for the evaluation of PA, which may cause measurement bias. Depending on the measure or scale used to evaluate PA, self-reporting can also make it difficult to compare the results between studies. Thus, studies using an objective measure of PA are less prone to measurement bias and the results of such studies may also be more comparable with each other. To this end, measuring the physical trait CRF can provide additional utility. CRF reflects the maximal capacity of the combination of cardiovascular and respiratory systems to provide oxygen to working muscles, as well as the muscles' capacity to receive and utilize the oxygen (Taylor et al., 1955; Wagner, 2000). It is primarily assessed as maximal or peak oxygen uptake (VO_2 max or VO_2 peak) in a progressive exercise test under controlled laboratory conditions. Although CRF declines with age and due to reduced PA (Jackson et al., 2009), it can be improved through exercise training (Garber et al., 2011). CRF can therefore reflect previous PA behavior and be used as an independent, controlled, objective measure to predict health risk. Low CRF is associated with an increased incidence of cardiovascular disease and all-cause mortality (Harber et al., 2017; Kodama et al., 2009; Myers et al., 2002), whereas improving CRF can decrease the risk of both cardiovascular disease and mortality (Blair et al., 1995; Shah et al., 2016). As several risk factors are common for cardiovascular disease and AD, it may not be surprising that evidence showing similar associations between CRF and risk of AD or any dementia has started to build up (Tari et al., 2019; Defina et al., 2013; Kurl et al., 2018; Hörder et al., 2018).

A study in 6104 older adults found higher CRF, estimated based on performance in a graded treadmill exercise test, associated with reduced risk of clinical diagnosis of cognitive impairment, AD, or any dementia within a mean follow-up time of 10.3 years. Having a CRF estimate of less than 6 METs was associated with a 4.42-fold greater risk relative to an estimate of more than 12 METs, and a 1-MET increase in CRF was associated with approximately 8% reduction in the risk of cognitive impairment (Müller et al., 2017). Other studies have also found higher CRF associated with a slower decline in cognitive functions over time (Barnes et al., 2003; Wendell et al., 2014; Pentikäinen et al., 2019). Importantly, similar associations have also been reported in individuals at risk of AD due to genetic predisposition or diagnosed mild cognitive impairment. In 110 late-middle-aged (mean age 64.2 years) individuals who were considered to be at heightened risk of AD due to parental history of AD, higher baseline CRF associated with a reduced decline in cognitive functions over 3–5 years (mean follow up time 3.26 years) (Dougherty et al., 2021).

Several cohort studies have shown that a higher midlife CRF is associated with a lower risk of developing AD or other types of dementia (Defina et al., 2013; Kurl et al., 2018; Hörder et al., 2018). In a generally healthy cohort of 19458 middle-aged (mean age 49.8 years) individuals followed for an average follow-up of 24 years, the risk of dementia was 36% lower in those within the highest quintile of estimated CRF, as compared to those in the lowest CRF quintile (Defina et al., 2013). Other studies including either middle-aged men (Kurl et al., 2018) or women (Hörder et al., 2018) similarly found high CRF to be inversely related to the incidence of dementia, suggesting that high CRF predicts a lower risk of dementia both in middle-aged men and women. This is notable as sex differences are seen in AD prevalence, where women represent a clear majority of AD patients (Association, 2021). For example, a large population-based study with data from 7901 individuals found that after reaching the age of 45 years, women had almost two times greater risk (approximately 20%) of developing dementia due to AD during the rest of their lifetime when compared to men (Chêne et al., 2015). However, it is also noteworthy that this difference was identified to partly reflect a higher frequency of cardiovascular deaths among men before the age of 65 years (Chêne et al., 2015).

Associations between changes in CRF and the risk of dementia specifically due to AD have not been studied, but current evidence suggests associations with dementia of any cause. In a population-based study with 3559 individuals, changes in self-perceived physical fitness of middle-aged individuals were found associated with the risk of dementia

within the next three decades (Kulmala et al., 2014). The risk was found higher in those whose perceived physical fitness was low at midlife, while those with a decline in physical fitness had a further increased risk of dementia (Kulmala et al., 2014). A recent prospective cohort study by Tari et al. using data from the large population-based Nord-Trøndelag Health Study (HUNT) provided further evidence of a relationship between CRF change and the risk of any-cause dementia (Tari et al., 2019). The analyses in this study showed improving CRF or maintaining it at a higher level relative to the least fit quintile of individuals within the same age group, associated with significantly reduced risk of dementia and dementia-related mortality when compared with having persistently low CRF over time. In a subcohort of 320 adults followed for a median time of 7.6 years, subjects who had improved their estimated CRF from baseline over time were found to have reduced their risk of dementia by 48%, with each 1-MET (3.5 ml/kg/min VO2) increase in CRF reducing the risk by 16%. After a median follow-up time of 19.6 years, improvement of CRF was also associated with 28% reduced risk of dementia-related mortality in a large cohort of 30375 adults, each 1-MET improvement reducing the risk by 10%. Importantly, increase in CRF was associated with 2.2 years delayed onset of dementia and 2.7 years longer life. Maintaining high CRF was also associated with a reduced risk of dementia and dementia mortality in this sample (Tari et al., 2019). In summary, even though conclusions on causality cannot be made based on existing studies, accumulating evidence suggests that improving CRF or maintaining it at a high age-relative level could protect against cognitive decline and the development of dementia later in life.

2.3. Exercise may enhance cognitive reserve

Alongside its beneficial effects on several risk factors for AD, exercise training can promote structural and functional changes in the brain (as described in Section 3) that might enhance the brain's capacity and resilience to tolerate more damage before the manifestation of cognitive impairment (Pedrinolla et al., 2017). The so-called brain reserve and cognitive reserve are partly overlapping concepts proposed to explain substantial individual differences in the relationship between the degree of brain damage or AD pathology and cognitive performance (Stern et al., 2019). The brain reserve refers more to the structural properties of the brain, such as the number of neurons and synaptic connections, whereas the cognitive reserve describes more of a functional ability of the brain to adapt and compensate for damage (Stern et al., 2019). Therefore, enhanced brain and/or cognitive reserve with PA could help explain why the risk of AD seems to be reduced in people who are physically active or have high CRF. Considerable evidence from observational and experimental studies provides indirect support to such a view. In line with the observational data showing PA associated with reduced cognitive decline over time, several experimental studies have also shown exercise training to be beneficial for cognition.

A recent meta-analysis of 36 RCTs including physical exercise intervention in adults above 50 years old, found a significant positive effect of exercise on cognitive functions independent of the participants' baseline cognitive status (Northey et al., 2018). However, the intensity of exercise may play a significant role in mediating the positive effects of exercise on cognition, as only high- and moderate-intensity exercise training were found to exert significant effects on cognition (Northey et al., 2018). Findings from a recent RCT with previously sedentary older adults performing either high-intensity interval training, moderate-intensity continuous training, or stretching 3 times a week for 12 weeks also support the relevance of exercise intensity and improved CRF for cognitive benefit (Kovacevic et al., 2019). In this study, the high-intensity group demonstrated significantly greater memory performance improvements than the other groups, and overall, greater improvements in CRF were associated with greater improvements in memory test performance across all groups. Still, it is worth noting that the memory function of the participants was only tested once within 48 h after finishing the intervention, which leaves open the possibility for only an acute beneficial effect of high-intensity exercise on performance in the used test (Kovacevic et al., 2019). In another RCT, 101 adults aged 65 or older were randomized either into one of three intervention groups performing 75, 150, or 225 min of moderate-intensity aerobic exercise per week for 26 weeks, or into a control group advised to remain their current (low) PA level (Vidoni et al., 2015). CRF was improved in all the exercise intervention groups compared to their baseline, and unlike the control group, exercise groups also improved performance in simple attention and visuospatial processing tests (Vidoni et al., 2015). Notably, the magnitude of change in CRF after the training intervention was strongly correlated with performance in cognitive tasks. In fact, this association was more significant than that found between the total volume of exercise and performance in cognitive tasks (Vidoni et al., 2015). These findings suggest that changes in CRF may be an important predictor of how a patient's cognitive function progress after exercise training programs. Similarly, in a smaller cohort enriched for family history of AD and the APOE ε4 allele (genetic predisposition to AD), improvements in executive function following progressive exercise training for 26 weeks were found to correlate with increases in CRF (Gaitán et al., 2019).

Together with the evidence from observational studies, these findings among healthy older adults suggest that PA has beneficial effects on cognitive functions such as memory, attention, and overall executive functions, which may at least partly explain the association between higher levels of PA and reduced risk of developing dementia through the enhanced brain and/or cognitive reserves in more physically active individuals. However, another question is whether exercise benefits cognitive function also in patients who are already diagnosed with AD.

2.4. Exercise and cognitive functions in AD

Longitudinal studies in early-stage AD patients have found greater volume of PA and higher CRF at baseline associated with slower clinical progression rate over the following one to three years (Minn et al., 2018; Vidoni et al., 2012). Meta-analyses of RCTs with exercise interventions in AD patients have also concluded that aerobic exercise may improve cognitive functions or slow cognitive decline in AD patients (Groot et al., 2016; Du et al., 2018b; Jia et al., 2019). A meta-analysis of 18 RCTs with exercise interventions found a similar beneficial effect of exercise on cognitive functions in patients with AD as in any-cause dementia (Groot et al., 2016). Notably, interventions including aerobic exercise, or both aerobic and non-aerobic exercise were found to enhance cognitive functions, whereas interventions with only non-aerobic exercise showed no benefit on cognition (Groot et al., 2016). Another meta-analysis of 7 RCTs with exercise interventions including at least an aerobic component and global cognitive function measured specifically using a Mini-Mental State Examination (MMSE) also concluded a positive effect of exercise on cognition in AD patients (Du et al., 2018b). Likewise, a recent meta-analysis of 13 RCTs with a total of 673 AD patients also reported improved MMSE scores in patients performing moderate or high-to-moderate intensity PA or exercise (Jia et al., 2019). Collectively, the meta-analyses support the view that aerobic exercise can exert beneficial effects on cognitive functions also in AD patients. Still, the studies included in these analyses mostly included a small number of participants, and varying inclusion criteria for subjects in these studies complicates comparison between studies. Considering the long pre-clinical phase in AD development and the lack of definite clinical diagnostic tools for the disease, the patients included in these studies may represent highly varying stages of the disease. It may be that if the disease already has progressed too far (to clinical phase), the profound pathological changes in the brain could hamper gaining cognitive benefit from exercise.

In a recent study including not only patients with AD ($n = 60$) but also those diagnosed with mild cognitive impairment due to AD ($n = 27$), six months of exercise training and cognitive training were

found similarly beneficial methods at preventing a decline in global cognitive function (MMSE) in both patient groups whereas respective control groups receiving normal pharmacological treatment showed significant declines in MMSE scores (−11.8% in mild cognitive impairment and −16.2% in AD patients) (Fonte et al., 2019). Another measure of global cognitive function (ADAS-Cog: Cognitive subscale test of the Alzheimer's Disease Assessment Scale) specifically measured in AD patients also showed a significant decline in cognitive function for the control group but improvement for the exercise training and cognitive training groups. Exercise training also prevented unfavourable changes in various measures of cardiovascular health and in a 6-minute walk test performance that was used to assess changes in the patients' fitness. Remarkably, the beneficial effects of exercise training on cognitive functions in mild cognitive impairment patients extended to follow-up measurements three months after the completion of the intervention, while AD patients showed a decline in global cognitive function over this period (Fonte et al., 2019). These results suggest that regular exercise training can have wide beneficial cognitive and cardiovascular health effects both in preclinical and established AD, and suggest that persistent exercise training might be particularly important for the maintenance of cognitive functions in patients clinically diagnosed with AD.

It is noteworthy that some larger RCTs did not find significant effects of exercise interventions on cognitive functions in AD patients (Hoffmann et al., 2016; Öhman et al., 2016; Yu et al., 2021). One of the largest studies to date included 210 AD patients allocated into three groups: two groups performing supervised exercise for approximately 1 h twice a week for one year, either alone at home (n = 70) or together with others in an adult daycare center (n = 70), and a control group receiving standard care (n = 70) (Öhman et al., 2016). Home-based exercise training and group-based exercise training were highly versatile including aerobic, strength, endurance, balance, and dual-task training. Although a slight improvement in executive function was found for the home-based exercise group, verbal fluency and global cognitive function (MMSE) deteriorated similarly in all groups (Öhman et al., 2016). Since evidence for beneficial cognitive effects from exercise comes mainly from studies concentrating on aerobic exercise, one cannot rule out that the proportion/volume of aerobic exercise in this study was too low to result in such effects. In another study including a total of 200 patients with mild AD, the patients performed either supervised moderate-to-high intensity exercise three times a week for four months or received standard care (Hoffmann et al., 2016). While there was no significant difference between the two groups in global cognitive function (MMSE), a comparison between the control group and exercisers with at least 80% compliance to the protocol (n = 66) revealed significant effects of exercise on neuropsychiatric symptoms and performance in a test of attention and mental speed (Hoffmann et al., 2016). Subsequent analyses further revealed that within the 49 patients whose CRF was objectively measured, changes in CRF positively correlated with these changes (Sobol et al., 2018). In the largest RCT to include an exercise intervention in dementia patients to date approximately 80% of the total 494 individuals with mild to moderate dementia included in the study were diagnosed with AD (Lamb et al., 2018). The patients were randomized to either perform aerobic and strength exercise training (n = 329) or to receive usual treatment (n = 165) for one year. For the first 4 months, exercise training consisted of one hour of unsupervised exercise and two 60- to 90-minute-long supervised exercise sessions per week. Thereafter the patients in the exercise intervention arm were instructed to exercise at home with a target of reaching a total of 150 min of exercise per week. After six weeks of exercise training, the exercise group showed improved six-minute walk test performance, suggesting these exercises were effective in improving patients' fitness at least at the very beginning of the intervention. Global cognitive function was assessed using ADAS-Cog at 6 months and 12 months, and where both groups of patients showed declines in cognitive function at both time points, impairment at 12 months was found more profound in the patients following the exercise intervention. Subgroup analyses showed similar unexpected results also for patients diagnosed with AD (Lamb et al., 2018). Because exercise was supervised only for the first 4 months and fitness tested only at baseline and six weeks in, it is possible that the nature of the unsupervised at-home exercise might have deviated significantly from the supervised and any potential beneficial (short-term) effects from earlier exercise might have faded before the first assessment of cognitive function.

This evidence with AD patients corroborates the previous conclusion on healthy older adults and suggests that challenging the cardiorespiratory and skeletal muscle systems through aerobic exercise training may confer some beneficial effects on cognitive functions, and a change in CRF might be an important mediator of these effects. This view is also supported by a recent study where CRF and performance in six-minute walk test were found positively correlated with global cognitive function (MMSE) in patients diagnosed with mild cognitive impairment or dementia due to AD (Pedrinolla et al., 2019). Fortunately, with high enough volume and intensity of exercise, CRF can be improved in most people (Garber et al., 2011; Ross et al., 2015), also in AD patients (Sobol et al., 2018). As aerobic exercise training leads to several positive effects on cardiovascular health, such as improved endothelial function (Campbell et al., 2019), reduced vascular stiffness (Shibata et al., 2018), and reduced blood pressure (Whelton et al., 2002; Cornelissen and Smart, 2013), it is reasonable that high CRF may also be positively linked to favourable cardiovascular health and attenuated cardiovascular risk factors (Lin et al., 2015; Defina et al., 2013). Indeed, similar to the associations found for CRF, a better midlife cardiovascular health profile is associated with slower cognitive decline (Samieri et al., 2018; Olaya et al., 2019; González et al., 2018), and a lower risk of AD (Pase et al., 2016). Thus, even though exercise and vascular health management may also independently provide neuroprotective effects (Rabin et al., 2019), the beneficial effects of PA and exercise on cognition and risk for AD may be partly mediated by improved cardiovascular health. Importantly, recent studies have shown beneficial effects of exercise training on various aspects of cardiovascular health and function also in AD patients (Fonte et al., 2019; Pedrinolla et al., 2020), and the accompanying effects of exercise on patients' locomotion, mobility, and ability to perform activities of daily living may have important implications for their quality of life and disease burden (Enette et al., 2020; Vidoni et al., 2019; Pedrinolla et al., 2018).

The associative evidence between PA levels and mental health is robust and convincing. This knowledge from observational studies propelled further investigations in interventional trials, to verify the effects of exercise in mental disorders in general and in AD patients. Although these studies were important, there is a long way to go. Most clinical trials involved small cohorts, so the limited statistical power and unstandardized methodology complicate a comparison among studies, which results in weak conclusions. At this moment, the state of the knowledge indicates that exercise training improves cognitive function in healthy older adults, while evidence in AD patients has not been strongly conclusive, with some notes of improvements in cognitive tests appearing to be more evident in patients experiencing greater improvements in CRF. It also remains unclear whether more pronounced results may be achieved with optimal exercise protocols. This calls for large studies comparing exercise modalities, intensity, and volume in AD patients. Overall, what does it mean for AD patients? It means that exercise appears to be useful for treatment in the early stages of AD and prevention of dementia in general, but it remains difficult to provide specific exercise recommendations for AD prevention and/or therapy. Therefore, more extensive clinical trials are expected with great anticipation by the medical community.

3. Potential neuroprotective mechanisms

Several mechanisms through which exercise may enhance the brain and cognitive reserves, i.e., promote brain plasticity and cognitive function, as well as protect the brain from AD-related pathology are

discussed more in detail in the following sections and summarized in Fig. 1.

3.1. Enhanced cerebral blood flow

Proper brain metabolism and function are dependent on adequate cerebral blood flow (Kisler et al., 2017). To meet the changing energy requirements, cerebral blood flow in a healthy brain is finely regulated by local changes in neural activity, a relationship termed neurovascular coupling (Kisler et al., 2017). In contrast, cerebrovascular dysregulation and hypoperfusion, potentially driven by Aβ pathology and vascular inflammation (Nortley et al., 2019; Cruz Hernández et al., 2019; Lu et al., 2020), may arise early in AD and precede brain atrophy and cognitive decline (Iturria-Medina et al., 2016; Ruitenberg et al., 2005). Indeed, in older adults of similar age and with similar PA levels, cortical blood flow was found to progressively diminish from the highest perfusion measured in the healthy brain to those in mild cognitive impairment, mild AD, moderate AD, and severe AD (Venturelli et al., 2018). Of note is that measures of systemic vascular function and nitric oxide bioavailability showed similar progressive decline across this AD-related cognitive impairment spectrum (Venturelli et al., 2018). Remarkably, cerebral hypoperfusion may also predict faster cognitive decline in AD (Hanyu et al., 2010). As demonstrated by animal studies, cerebral hypoperfusion and hence limited tissue oxygenation, nutrient delivery and metabolite clearance may accentuate cognitive impairment through a plethora of detrimental changes, including accelerated Aβ and tau accumulation (Nortley et al., 2019; Lu et al., 2020; Park et al., 2019), mitochondrial dysfunction (Parodi-Rullan et al., 2019), increased formation of reactive oxygen species and oxidative damage (Parodi-Rullan et al., 2019), blood-brain barrier breakdown (Shang et al., 2016), all finally culminating in neurodegeneration (Shang et al., 2016).

Importantly, better cardiovascular health is associated with a superior caliber and density of cerebral blood vessels, as well as a higher cerebral blood flow in young adults (≤ 40-year-old) (Williamson et al., 2018). Consistent with those findings, a recent study with 20 years of longitudinal follow-up found higher midlife cardiovascular risk score associated with lower cerebral blood flow later in life, although such association was weakened later in life (Suri et al., 2019). Critically, exercise training may improve cerebrovascular regulation and enhance cerebral blood flow through improved cardiovascular health or reduced vascular risk factors (Williamson et al., 2018; Suri et al., 2019), enhanced formation of new vasculature (Maass et al., 2016), and enhanced cerebral arterial elasticity (Tan et al., 2017a) and cerebrovascular endothelial function (Green et al., 2004; Hong et al., 2020). For instance, regular aerobic exercise increases the bioavailability of nitric oxide, a major mediator of vasodilation (Green et al., 2004). This occurs through enhanced levels of endothelial nitric oxide synthase, hence potentially improving endothelial function and regulation of blood flow also within the brain (Green et al., 2004; Hong et al., 2020). Recent studies in healthy middle-aged to older adults and in patients with amnestic mild cognitive impairment reported 6 months and one year of aerobic exercise training, respectively, effective on improving CRF also beneficial on cerebral blood flow and cognitive functions, and further found that the beneficial effects of exercise on cerebrovascular regulation and cerebral blood flow may be associated with changes in cognitive functions (Guadagni et al., 2020; Thomas et al., 2020; Tomoto et al., 2021). However, in symptomatic AD, the effects of exercise training on cerebral blood flow might be diminished. Although exercise training has been shown beneficial on peripheral vascular function also in patients with mild to moderate AD (Pedrinolla et al., 2020), and 16 weeks of moderate-to-high intensity aerobic exercise three times a week improved CRF in patients with mild AD, no effect of this exercise was found on cerebral blood flow (van der Kleij et al., 2018). The lack of effect may be due to shorter intervention, but these findings might also reflect attenuated response in AD and therefore further suggest the importance of earlier preclinical actions for improving CRF and cardiovascular health to reduce the risk for cognitive impairment and AD in later age.

3.2. Preservation of brain tissue

Brain atrophy occurs with normal aging but accelerated regional atrophy is characteristic to neurodegenerative diseases such as AD (Pini et al., 2016). The medial temporal lobe memory system is subject to progressive atrophy from the early stages of the disease (Kobro-Flatmoen et al., 2021), which correlates with the progression of

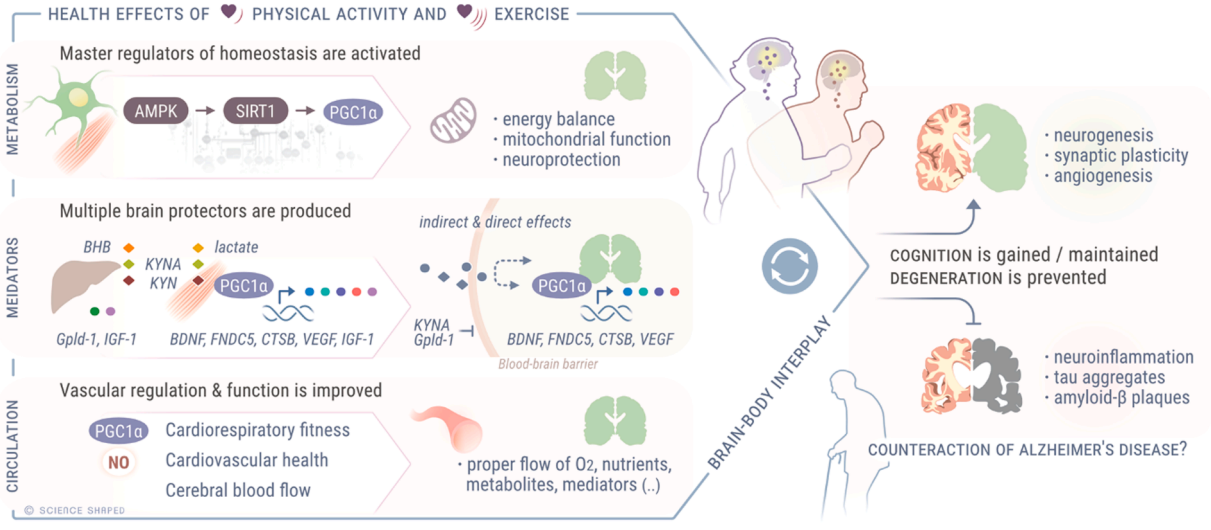

Fig. 1. The image summarizes the proposed mechanisms underlying the benefits of exercise in the brain. The AMPK-SIRT1-PGC1α axis is activated by exercise and is a key regulator of bioenergetic in the neuronal microenvironment. Physical activity also boosts the synthesis and secretion of various biomolecules by other organs, ultimately reaching the brain to exert positive effects, as detailed in the review. Those molecules may demonstrate synergic effects and be capable of potentiating the actions of one another. The increased bioavailability of nitric oxide, as well as PGC1α activity in skeletal muscle, stimulate angiogenesis and promote vascular health throughout the body, consequently improving blood flow and optimizing the supply of oxygen and nutrients to the brain. Overall, exercise promotes an interplay between the brain and other organs, eventually culminating in enhanced brain plasticity and reduced neuroinflammation, which could reduce the risk of Alzheimer's disease.

cognitive decline (Dawe et al., 2020; Jack et al., 2000). PA and aerobic exercise training may mitigate brain atrophy related to aging and AD development, thus delaying cognitive decline and the onset of dementia. Several longitudinal studies have shown higher baseline PA and CRF associated with greater brain volumes after mean follow-up times of 4.5–21 years (Dougherty et al., 2021; Rabin et al., 2019; Erickson et al., 2010; Rovio et al., 2010; Braskie et al., 2014; Zhu et al., 2015; Spartano et al., 2016; Tan et al., 2017b; Zotcheva et al., 2019). Intervention studies with 6–12 months of aerobic exercise training have also supported causal effect and reported associations between changes in CRF and various brain volume measures both in healthy older adults and in AD patients (Colcombe et al., 2006; Erickson et al., 2011; Reiter et al., 2015; Morris et al., 2017). A five-year intervention study in healthy older adults, however, did not find changes in CRF associated with brain volume changes, but instead, found higher baseline CRF associated with greater cortical volume at all 1, 3, and 5-year measurements (Pani et al., 2021).

Sitting atop the medial temporal lobe memory system, the hippocampus plays a key role in declarative memory (Burgess et al., 2002) and, along with its main source of input, the entorhinal cortex, the hippocampus suffers accelerated atrophy even in preclinical stages of AD (Jack et al., 2000, 1998). Three months of aerobic exercise training was found to improve CRF and increase hippocampal volume and perfusion in healthy older adults, and these changes correlated positively with changes in recognition memory (Maass et al., 2015). Similarly, CRF changes associated with changes in hippocampal volume and memory in early-stage AD patients following six months of aerobic exercise training (Morris et al., 2017). These results suggest that the beneficial effects of exercise on cognitive functions may be linked to changes in hippocampal perfusion and structure. A meta-analysis of 14 human studies including a total of 737 individuals with varying cognitive status found that aerobic exercise had a significant positive effect on hippocampal volume, specifically the left hemisphere, but the effect of exercise on total hippocampal volume was not found to be statistically significant for the total sample (Firth et al., 2018). In contrast, a more recent meta-analysis including 22 studies of which all but one included at least an aerobic exercise component in the exercise intervention, found a significant effect of exercise on total hippocampal volume, but not specifically on either hemisphere (Wilckens et al., 2021). Caveats of the existing studies are that they have been, so far, relatively short-lasting and comprised very different exercise programs in varying populations, and thus, more studies are needed to make more compelling conclusions on the effect of exercise, and more specifically the exercise frequency and intensity, on human hippocampal volume (Firth et al., 2018; Wilckens et al., 2021). Interestingly, results from a five-year exercise intervention study in older adults showed greater hippocampal atrophy in a high-intensity interval training group when compared to a control group that showed high adherence to national PA guidelines reaching at least 30 min of daily PA (Pani et al., 2021). Although the annual atrophy rates (1.1% for the high-intensity and 0.8% for the control group) were well within normal ranges, these results suggest the exercise parameters may significantly modulate the effects of exercise on the hippocampus and should be further investigated.

Collectively, reduced cerebral atrophy may partly explain the reduced risk of AD dementia in physically active and high-fitness individuals compared to those who are more sedentary and have lower CRF. As also suggested by the evidence of cerebrovascular dysregulation and hypoperfusion preceding brain atrophy (Iturria-Medina et al., 2016), the beneficial effects of exercise on cardiovascular health may at least partly mediate the protective effect on brain volume (Pase et al., 2018; Lane et al., 2019). Two recent studies not only showed cross-sectional associations between higher vascular risk factor scores and lower brain volumes but also that longitudinally, higher vascular risk scores earlier in life showed the greatest associations with later brain volumes (Pase et al., 2018; Lane et al., 2019). Overall, these lines of evidence suggest that exercise training and its beneficial effects on the cardiovascular system may help preserve brain tissue and even enhance the volume of the important hippocampus by ensuring proper regulation of cerebral blood flow and hence delivery of essential oxygen, nutrients, and other neurotrophic factors to the brain. In the next section, we take a step further into detail to the forms of brain plasticity promoted by exercise in the hippocampus.

3.3. Promoted brain plasticity

3.3.1. Hippocampal plasticity in rodents

It is well established that adult hippocampal neurogenesis, i.e., formation of new neurons, occurs in the rodent brain, where it declines with aging (Kuhn et al., 1996; Kempermann et al., 1998). A recent study demonstrated a reversal of age-related decline in hippocampal functions by genetically stimulated neurogenesis (Berdugo-Vega et al., 2020). Specifically, an acute increase in neurogenesis restored declines in allocentric navigation and spatial memory in old mice, whereas chronic increase preserved contextual learning throughout life, suggesting the relevance of neurogenesis for maintained or improved hippocampal function and cognition (Berdugo-Vega et al., 2020). Also, ablating neurogenesis in AD mice at an early stage of the AD-like pathogenesis exacerbated neuronal loss and cognitive impairment in later stages of the disease, further suggesting its importance in the maintenance of the existing neuronal population (Choi et al., 2018). Together these findings suggest that early interventions able to counteract the age- or disease-related decline in neurogenesis may also be beneficial with regards to preserving cognitive functions.

Remarkably, aerobic exercise has been widely shown as a potent stimulator of neurogenesis in the dentate gyrus, which may account for at least part of the associated improvements in cognition reported in rodents (van Praag et al., 1999, 2005; Vivar et al., 2016), including rodent AD models (Choi et al., 2018; Adlard et al., 2005). It was first shown in mice that voluntary wheel running enhances the number of new-born cells in the dentate gyrus and improves learning and memory (van Praag et al., 1999a; van Praag et al., 1999b). Later studies have further demonstrated that exercise not only promotes the formation of new neurons but also their morphological maturation and integration into neuronal circuitry (Vivar et al., 2016; van Praag et al., 2002; Sah et al., 2017). Furthermore, the newly generated neurons may transiently show enhanced excitability and lower threshold for induction of long-term potentiation, or the strengthening of synapses, which is thought to underlie learning and memory (Farmer et al., 2004; Schmidt-Hieber et al., 2004; Bliss and Lomo, 1973). Exercise also promotes cerebral angiogenesis (van Praag et al., 2005; Swain et al., 2003; Morland et al., 2017; Lopez-Lopez et al., 2004), the formation of new vasculature, which seems closely linked and supportive to neurogenesis, potentially to meet the needs for trophic factors (Palmer et al., 2000; Shen et al., 2019).

In addition to promoting neurogenesis, exercise-induced plasticity of pre-existing neurons may also contribute to the improvements in cognitive performance. This plasticity is known to involve increases in dendritic length and complexity, as well as in dendritic spine density, all of which have been reported in neurons of the hippocampal circuitry (Serra et al., 2019; Eadie et al., 2005; Redila and Christie, 2006; Stranahan et al., 2007). These alterations may be long-lasting and persist independent of subsequent PA at least after early life exercise (Serra et al., 2019). In addition to enhanced structural plasticity, exercise also enhances hippocampal long-term potentiation with accompanying improvements in learning and memory, both in wild-type rodents and in transgenic rodent models of AD (van Praag et al., 1999; Farmer et al., 2004; Zhao et al., 2015). Overall, not only can exercise induce an increase in hippocampal neuronal number but also trigger modifications in neuronal networks and synaptic plasticity that all contribute to improved cognitive functions.

3.3.2. Hippocampal plasticity in humans

Generation of new neurons in the hippocampal dentate gyrus in humans was first demonstrated in 1998 (Eriksson et al., 1998), and recent studies have provided further evidence to suggest this hippocampal neurogenesis persists throughout a human lifetime (Boldrini et al., 2018; Moreno-Jiménez et al., 2019). Of note, a significantly lower number of immature neurons were found in the post-mortem brain of AD patients than in healthy controls independent of age, and the number of cells was further decreased with later stages of AD, thus suggesting a progressive decline in neurogenesis with AD (Moreno-Jiménez et al., 2019). Another study similarly reported persistent neurogenesis at very old age in the brain of subjects with mild cognitive impairment or AD but additionally found a higher level of neurogenesis associated with better cognitive status (Tobin et al., 2019). In line with the evidence from animal studies mentioned above, these findings imply that the degree of neurogenesis may play an important role in human cognitive function.

Whether exercise training stimulates hippocampal plasticity with implications to cognition in humans like that in rodents is largely unknown. There is, however, indirect evidence to suggest effects of exercise on hippocampal adult neurogenesis and angiogenesis also in humans. It was shown that 3 months of aerobic exercise not only improved CRF, but also increased the cerebral blood volume specifically in the dentate gyrus in humans 21–45 years of age (Pereira et al., 2007). The individual changes in the CRF and dentate gyrus volume were also correlated. In mice, similar exercise-induced increases in dentate gyrus blood volume correlated with enhanced neurogenesis (Pereira et al., 2007). The region-specific increase in the blood volume may reflect exercise-induced angiogenesis in the dentate gyrus to meet the increased need for nutrients (Palmer et al., 2000; Pereira et al., 2007). Thus, the observed increase in human dentate gyrus blood volume after exercise training might have also been accompanied by promoted neurogenesis in the adult human brain (Pereira et al., 2007). It is therefore possible that the findings of increased hippocampal volumes from aerobic exercise training in humans reflect promoted hippocampal neurogenesis and angiogenesis (Maass et al., 2016; Erickson et al., 2010; Horgusluoglu-Moloch et al., 2019).

Thus, PA and exercise may be able to partially compensate for age- and AD-related neurodegeneration and protect the brain from cognitive impairment through stimulatory effects on neurogenesis, angiogenesis, and synaptic plasticity. Promotion of these key mechanisms of brain plasticity and the structural and functional changes they entail may help enable brain and cognitive reserve and hence provide more resilience to AD pathology and delay the onset of dementia. However, there are also potential direct effects of exercise on AD pathology that likely play a part in the protection of the brain against AD.

3.4. Prevented AD pathology

As was already mentioned in the introduction, the first pathological changes in AD may occur decades before clinical symptoms (Dubois et al., 2016; Jack et al., 2013). Specifically, the intracellular accumulation of soluble oligomeric forms of Aβ, preceding the formation of the hallmark extracellular Aβ plaques, has been proposed as a key early event in the disease progression (Long and Holtzman, 2019; Hardy and Higgins, 1992). A recent study mapping alterations in neocortical proteins from non-AD to preclinical AD further found that initial changes associate with endocytosis and the secretory pathway, suggesting subtle alterations at synaptic contacts as a key early change, possibly brought on by oligomeric forms of Aβ (Li et al., 2021). Microtubule-associated tau-protein abnormalities resulting in the aggregation of hyperphosphorylated tau to form the neurofibrillary tangles also begins many years before clinical onset (Henstridge et al., 2019; Hanseeuw et al., 2019). Other pathological events in early, preclinical AD include neuroinflammation (Heppner et al., 2015), impaired glucose metabolism (An et al., 2018), and loss of mitochondrial function and dynamics (Swerdlow, 2018). The gradual progression of AD pathology, including increased oligomeric forms of Aβ (Näslund et al., 2000; McLean et al., 1999), tau pathology (Hanseeuw et al., 2019; Aschenbrenner et al., 2018), and to a lesser extent extracellular Aβ plaques (Nelson et al., 2012) correlates with the severity of cognitive impairment resulting from synaptic and neuronal dysfunction and loss. In the following sections we provide evidence on how exercise impacts the above-mentioned AD pathologies.

3.4.1. Amyloid pathology

Studies in rodent AD models have found aerobic exercise training to reduce both the levels of soluble Aβ (He et al., 2017; Alkadhi and Dao, 2018; Moore et al., 2016; Khodadadi et al., 2018; Xia et al., 2019b; Zhang et al., 2019) and Aβ plaque load (Choi et al., 2018; Adlard et al., 2005; Khodadadi et al., 2018; Xia et al., 2019b; Zhang et al., 2018; Liu et al., 2013) when compared to remaining sedentary. Several mechanisms by which exercise may alleviate amyloid pathology have also been proposed, including downregulation of β- and γ-secretases which are the enzymes responsible for the formation of Aβ through sequential proteolytic processing of amyloid precursor protein, but also enhanced central and peripheral clearance of Aβ (He et al., 2017; Alkadhi and Dao, 2018; Moore et al., 2016; Khodadadi et al., 2018; Xia et al., 2019b; Zhang et al., 2019, 2018).

Findings from observational studies in humans investigating the association between PA and amyloid pathology are contradictory (Brown et al., 2019), but several studies have suggested slower amyloid accumulation with greater engagement in PA (Rabin et al., 2019; Liang et al., 2010; Brown et al., 2013; Okonkwo et al., 2014; Law et al., 2018). Human interventional studies have not found that exercise alleviates amyloid pathology. The only two existing studies in AD patients both reported no effect of 16-week long moderate-to-high intensity exercise intervention on cerebrospinal fluid (CSF) Aβ levels (Steen Jensen et al., 2016) or cortical Aβ (Frederiksen et al., 2019). It is possible that the duration of the interventions may not have been long enough to show a modifying effect of exercise on Aβ. Also, exercise may have greater effects on amyloid pathology in the earlier stages of the disease. Indeed, in a transgenic mouse model of AD showing progressive Aβ deposition from the age of 4 months, a 5-month exercise intervention resulted in reduced soluble Aβ levels in both 8- and 17-month-old mice compared to age-matched sedentary counterparts, whereas amyloid plaque load was only reduced in the younger mice (Zhao et al., 2015). However, recent studies with amnestic mild cognitive impairment patients and cognitively unimpaired older adults with either elevated or subthreshold brain amyloid levels found no effects of one-year aerobic exercise training on brain Aβ (Tarumi et al., 2019; Vidoni et al., 2021). Overall, despite the promising findings from interventional studies in rodent models of AD suggesting exercise to reduce the accumulation of Aβ in the brain, current evidence from studies in humans is not sufficient to conclude such beneficial effect of exercise on amyloid pathology in the human brain yet.

3.4.2. Tau pathology

Tau hyperphosphorylation, which precedes the formation of neurofibrillary tangles, has been reported to reduce with exercise in transgenic AD mice (Liu et al., 2013), as well as in several models of tauopathies (Brown et al., 2019). Studies in cognitively healthy humans have shown higher levels of self-reported PA associated with lower tau levels (Brown et al., 2018), and greater accelerometer-measured levels of moderate-intensity PA associated with lower CSF ratios of total tau and phosphorylated tau to Aβ42 (Law et al., 2018). These findings may be of high importance, as the accumulation of neurofibrillary tangles correlates with the severity of dementia in terms of neuron loss, synaptic loss, and the degree of cognitive impairment (Nelson et al., 2012; Arriagada et al., 1992; Brier et al., 2016; Ingelsson et al., 2004), and reducing hyperphosphorylated tau may alleviate neuronal dysfunction and behavioural abnormalities (Roberson et al., 2007). Still, the overall

evidence for a potential causal effect of exercise on tau pathology is limited.

3.4.3. Neuroinflammation

Recent evidence suggests neuroinflammation, or a chronic immune response of the brain, to have a key role in AD pathogenesis. This is largely mediated by microglia and astrocytes, which are known to have important homeostasis-maintaining functions in a healthy brain, whereas in AD, the actual roles of these cells may range from neuroprotective to neurotoxic depending on the stage of the disease (Shi and Holtzman, 2018; Arranz and De Strooper, 2019). These processes are complex and our understanding of them remains limited. For example, one line of research suggests microglia may initially phagocytose Aβ peptides protecting the brain from plaque deposition (Keren-Shaul et al., 2017). Microglial functions may thereafter vary from promoting Aβ formation to degrading the forming plaques (Shi and Holtzman, 2018). Other, recent findings suggest microglia may coax plaques into their classical, dense-cored shape, and that this is a protective measure serving to minimize the impact of Aβ on neurons (Huang et al., 2021). Following later accumulation of tau pathology and neuronal insult, microglia may promote tau pathology and recruit reactive astrocytes to secrete neurotoxic factors to further drive neurodegeneration (Shi and Holtzman, 2018; Arranz and De Strooper, 2019).

Systemic inflammation may cause neuroinflammation and aberrant microglial and astrocytic activation to drive neurodegeneration through chronic generation of proinflammatory mediators and neurotoxic factors (Shi and Holtzman, 2018; Arranz and De Strooper, 2019). Indeed, markers of systemic inflammation, such as C-reactive protein levels, have been shown to predict longitudinal changes in regional brain volume and cortical thickness (Corlier et al., 2018), as well as in cognitive functions (Beydoun et al., 2018; Walker et al., 2019). Thus, evidence of exercise training and CRF as modulators of systemic inflammation may partly explain the protective role of exercise and higher CRF against neurodegeneration and cognitive decline (Fedewa et al., 2017; Dorneles et al., 2019). Correspondingly, several studies in rodent AD models have shown exercise to reduce the levels of inflammatory mediators and markers of neuronal death (Do et al., 2018; Lu et al., 2017), potentially due to improved mitochondrial function and modulation of microglial activation (Lu et al., 2017).

3.4.4. Brain metabolism

Mitochondria are organelles central in energy metabolism and show both structural and functional impairment in AD. Inflammation may impair mitochondrial function, whereas mitochondrial dysfunction may in turn exacerbate inflammation, thus creating a vicious cycle that may drive neurodegeneration (van Horssen et al., 2019). Also, accumulation of Aβ and phosphorylated tau have been distinctly demonstrated as possible triggers for mitochondrial dysfunction and impaired mitophagy, the autophagy of mitochondria, which generally activates as a response to mitochondrial damage or dysfunction in order to protect the rest of the cell from damage (Manczak et al., 2018; Kandimalla et al., 2018; Reddy et al., 2018; Fang et al., 2019). Impaired mitochondrial quality control causes accumulation of dysfunctional mitochondria and may result in intracellular calcium imbalance, increased oxidative damage, and accelerated Aβ and tau pathologies, causing synaptic dysfunction and neuronal death, consequently impairing cognitive functions (Chakravorty et al., 2019). Thus, strategies promoting mitochondrial integrity and their quality control mechanisms could possibly counteract neurodegeneration and cognitive impairment due to AD.

Growing evidence suggests that the positive effects of exercise on cognition may be at least partly mediated by enhanced mitochondrial function. For instance, a recent study found that gene expression patterns associated with late-life PA levels opposed those associated with aging and AD in mitochondrial energy production and synaptic function (Berchtold et al., 2019), hence suggesting that PA may counteract the effects of aging and AD on hippocampal mitochondrial and synaptic functions. Supporting this view, recent studies in AD mice have reported exercise-induced upregulation of hippocampal markers of mitochondrial biogenesis, dynamics, and mitophagy, suggesting enhanced mitochondrial quality control (Yan et al., 2019; Li et al., 2019; Zhao et al., 2020b; Kim et al., 2019). Further, improved hippocampal mitochondrial respiratory function and attenuated reactive oxygen species generation and oxidative damage were also found (Li et al., 2019), and all these studies reported accompanying improved cognitive performance (Yan et al., 2019; Li et al., 2019; Zhao et al., 2020b; Kim et al., 2019).

Overall, cerebral glucose metabolism is impaired in AD. Specifically the frontal and temporal regions in AD-subjects' brains show impaired neuronal uptake and utilization of glucose (An et al., 2018; Croteau et al., 2018), which may reflect not only mitochondrial dysfunction (Swerdlow, 2018), but also reduced cerebral blood flow (Kisler et al., 2017), impaired insulin signalling (Steen et al., 2005), and reduced glycolytic enzymes (An et al., 2018). Exercise training is well-known to improve blood glucose control and peripheral insulin sensitivity in humans (Lin et al., 2015), and recent studies in high-fat diet fed rodents also suggest exercise training to ameliorate impaired cerebral insulin signalling, with concomitant effects on neuronal plasticity and cognitive function (Park et al., 2019a; Wang et al., 2019b). In addition, exercise training may counteract the reduced cerebral glucose uptake in AD by increasing the expression of insulin-independent glucose transporter proteins that allow glucose uptake in neurons and glial cells (Pang et al., 2019).

In summary, exercise provides clear benefits for the vascular and cellular systems that sustain adequate brain function. While the neuroprotective effects of exercise have been observed in humans, more detailed knowledge on the neuroprotective mechanisms has relied on preclinical animal models. Exercise training increases the production of neurotrophic factors (discussed in further detail in the next section) that facilitate neurotransmission in the hippocampus and cortical areas. It also has the capacity to delay the age-related decline in neurogenesis. Increased physical activity also benefits brain vasculature, sustaining the integrity of the blood-brain barrier and increasing proteolytic degradation of Aβ species. Overall, the neuroprotective effects of exercise converge to sustain brain health into old age. In our perspective, understanding the mechanisms underlying such neuroprotective benefits is crucial, since they seem to be the key to answering the question of whether exercise can teach us how to treat mental disorders and AD. Therapeutic activation of mechanisms leading to improved brain plasticity, and reduced inflammation and neurotoxicity holds an incredible potential to revolutionize AD treatment, and exercise serves as a platform for discovering effective molecular mediators. In this context, the next section dives deeper into these mechanisms, discussing promising biomolecules whose production and/or availability are stimulated by exercise, delivering significant benefits to brain health.

4. Molecular regulators and mediators of exercise effects

The repeated energetic challenge brought by exercise training induces cellular adaptations in several tissues that improve cellular metabolic capacity. These adaptations are largely mediated by the activation of 5' adenosine monophosphate-activated protein kinase (AMPK), the major regulator of cellular energy homeostasis, and its downstream effectors that can alter the expression of genes related to energy metabolism (Cantó et al., 2009). AMPK generally activates in response to increased energy consumption, or the increased intracellular AMP/ATP-ratio, to promote ATP generating pathways and inhibit ATP consuming pathways (Cantó et al., 2009). These effects can be achieved through direct phosphorylation of various targets and indirect modulation of gene expression through transcriptional regulators such as NAD+ dependent type III deacetylase sirtuin 1 (SIRT1) (Cantó et al., 2009).

One downstream effector of AMPK and SIRT1 is the transcriptional coactivator peroxisome proliferator-activated receptor gamma

coactivator 1-α (PGC-1α), which acts as a key regulator of mitochondrial biogenesis and respiratory function within various tissues, including brain and skeletal muscle (Steiner et al., 2011). In the hippocampus, the effects of PGC-1α include modulation of synaptogenesis (Cheng et al., 2012), and, via mitochondrial SIRT3, protection of neurons from oxidative stress and damage (Cheng et al., 2016). Reduced hippocampal expression of PGC-1α is evident in the brains of AD patients and may contribute to the impaired mitochondrial functions and synaptic and neuronal loss in AD (Sheng et al., 2012). It is therefore notable that enhanced PGC-1α expression from exercise training may counteract these defects (Zhao et al., 2020a). Interestingly, PGC-1α not only mediates the adaptations of skeletal muscle to exercise training involving increased mitochondrial number and oxidative capacity that can improve maximal oxygen uptake (Calvo et al., 2008), but, it also regulates the expression of several skeletal muscle-derived circulating molecules with neurotrophic effects in the brain (Agudelo et al., 2014; Wrann et al., 2013).

Overall, exercise induces secretion of several biomolecules from various tissues and organs into the circulation that may partly mediate the beneficial effects of exercise on the brain to provide protection against cognitive impairment and AD (Tari et al., 2019). Indeed, healthy brains show considerable uptake of plasma proteins (Yang et al., 2020), and several blood-borne proteins and metabolites that are upregulated by exercise have been suggested able to enter the brain and exert effects on hippocampal plasticity and AD pathology. Below we summarize these factors that have been suggested to mediate the effects of exercise on the brain more in detail.

4.1. BDNF

Brain-derived neurotrophic factor (BDNF) is a neurotrophin important in brain development, function, and plasticity, and it seems to play a key role in mediating the effects of exercise on cognition (Nilsson et al., 2020; Vaynman et al., 2004). Exercise promotes BDNF expression directly in the brain (Ding et al., 2011), where cerebrovascular endothelial cells seem to be a major source of BDNF alongside neurons (Monnier et al., 2017), but it can also induce its secretion from skeletal muscle (Fulgenzi et al., 2020), potentially through the activation of PGC-1α (Peng et al., 2017). To what extent the muscle-derived BDNF may contribute to brain levels is unclear. Nevertheless, BDNF signalling in the hippocampus is dependent on the activation of a tropomyosin kinase B (TrkB) receptor, which in turn triggers several intracellular signalling pathways (Ding et al., 2011), that can ultimately promote neurogenesis and synaptic plasticity, and hence mediate the exercise-related improvements in cognitive performance (Choi et al., 2018; Farmer et al., 2004; Vaynman et al., 2004).

Exercise-induced upregulation of BDNF may also contribute to suggested beneficial effects of exercise on AD pathology. BDNF was found to increase the non-amyloidogenic processing of amyloid precursor protein and hence reduce the levels of Aβ peptides produced in vitro (Nigam et al., 2017). In contrast, deficient BDNF expression and signalling in vivo enhances pro-inflammatory mediators, while also leading to more amyloidogenic processing of amyloid precursor protein and aberrant processing of tau, resulting in exacerbated Aβ production and neurodegeneration, ultimately manifesting as impaired cognition (Wang et al., 2019c Xiang et al., 2019). Accordingly, post-mortem examination studies of human brains indicate lower BDNF levels in the hippocampus and temporal and parietal cortices of AD patients when compared with those in healthy individuals (Du et al., 2018a). Furthermore, CSF and blood levels of BDNF may also be significantly lower in AD patients compared with cognitively unimpaired controls, at least in the later stages of the disease (Du et al., 2018a Ng et al., 2019). It is therefore noteworthy that aerobic exercise seems to acutely upregulate peripheral BDNF expression not only in healthy adults regardless of age (Dinoff et al., 2017), but also in mild cognitive impairment and AD patients (Coelho et al., 2014; Devenney et al., 2019). A recent study also demonstrated the functional relevance of the exercise-induced upregulation of BDNF in humans by showing that the acute changes in plasma BDNF may mediate the outcome of following cognitive training in healthy older adults (Nilsson et al., 2020). Still, it is important to note that the ability of BDNF to cross the blood-brain barrier seems limited (Nagahara and Tuszynski, 2011), and any potential beneficial effects of peripheral BDNF on the brain and cognitive functions may be indirect. For example, BDNF released from skeletal muscle may also regulate insulin secretion in the pancreas and hence be an important regulator of exercise-induced changes in glucose metabolism (Fulgenzi et al., 2020).

The effects of chronic exercise training on blood BDNF levels in humans are equivocal; increase, no change, or decrease have all been reported (Dinoff et al., 2016; Marinus et al., 2019). In addition, while some cross-sectional studies have found peripheral BDNF levels positively associated with human hippocampal volume and performance in memory tests (Erickson et al., 2010; Mizoguchi et al., 2020), others reported BDNF levels not associated with cognitive performance (Driscoll et al., 2012). In a recent study in late middle-aged adults at risk for AD, a 26-week aerobic exercise intervention resulted in decreased plasma BDNF levels and no association with cognition (Gaitán et al., 2021). In this study, a metabolomic analysis revealed that multiple metabolites (~30%) correlated with changes in BDNF. In particular, lipid metabolites (ceramides, sphingo-, and phospholipids) that have been found to be elevated in blood in AD patients (Trushina and Mielke, 2014), were reduced by the exercise intervention and associated closely with plasma BDNF levels (Gaitán et al., 2021). These results suggest that the chronic effects of exercise on peripheral BDNF levels may be regulated by metabolic changes and the level of BDNF in blood may not be directly linked to cognitive performance. Overall, evidence suggests BDNF to be an important mediator of exercise effects on cognitive functions, but the effects may be predominantly dependent on increased BDNF level in the hippocampus that might not be directly associated with the acute increases in peripheral BDNF with exercise.

4.2. FNDC5/Irisin

Exercise-induced formation and release of the polypeptide irisin from skeletal muscle into the circulation may also serve as an important mediator of brain function (Wrann et al., 2013; Boström et al., 2012). Regulated by PGC-1α, irisin is cleaved from its transmembrane precursor protein fibronectin type III domain-containing protein 5 (FNDC5) before its release into the blood (Boström et al., 2012), which may eventually promote hippocampal BDNF expression (Choi et al., 2018; Wrann et al., 2013). Aerobic exercise training increases plasma levels of irisin both in mice and in humans (Boström et al., 2012), and although exercise training may also upregulate the PGC-1α/FNDC5/BDNF-pathway directly in the hippocampus (Wrann et al., 2013), circulating irisin can also cross the blood-brain barrier to elevate cerebral irisin levels (Islam et al., 2021). Suggesting namely the increase in hippocampal irisin levels to play an essential role in mediating exercise effects on cognitive function, hippocampal infusion of irisin was found to improve cognitive function in FNDC5 knockout mice which otherwise showed impaired cognitive function and no cognitive effects of exercise (Islam et al., 2021).

Of note, cerebral FNDC5/irisin expression is reduced both in AD mouse models and in AD patients (Islam et al., 2021; Lourenco et al., 2019), and elevating plasma levels of irisin was recently shown to improve cognitive function in mouse models of AD (Islam et al., 2021). Blocking either peripheral or cerebral FNDC5/irisin also impeded beneficial effects of exercise in AD mice (Lourenco et al., 2019), further demonstrating a key role of FNDC5/irisin mediating synaptic plasticity and memory. Interestingly, in vitro studies have also suggested FNDC5 may interact with amyloid precursor protein to alter its processing and reduce Aβ formation (Noda et al., 2018) and that irisin may prevent Aβ-oligomers from binding to neurons (Lourenco et al., 2019). Furthermore, in AD mouse models, FNDC5/irisin overexpression

reduced soluble, but not insoluble, Aβ42 in the hippocampus (Lourenco et al., 2019), and FNDC5 knockout resulted in higher levels of soluble Aβ40 in the cortex (Islam et al., 2021). It is worth noting that it is still not known whether, or to what extent, these effects observed in vivo are directly mediated by irisin or FNDC5. Reduced size of astrocytes and microglia and downregulation of glia-specific genes in AD mice with peripheral overexpression of irisin suggests irisin might also modulate neuroinflammation (Islam et al., 2021). Importantly, CSF levels of irisin were found to positively correlate with the CSF levels of BDNF and Aβ42, as well as MMSE scores both in cognitively unimpaired humans and AD patients, suggesting irisin is associated with reduced amyloid pathology and improved cognitive functions in humans too (Lourenco et al., 2020).

4.3. IGF-1 & VEGF

The closely related processes of angiogenesis and neurogenesis are commonly regulated by insulin-like growth factor-1 (IGF-1) and vascular endothelial growth factor (VEGF) (Morland et al., 2017; Fabel et al., 2003; Rich et al., 2017; Jin et al., 2002). Both IGF-1 and VEGF contribute to the growth of new vessels in the brain, where IGF-1 upregulates VEGF expression (Lopez-Lopez et al., 2004). VEGF is also produced in skeletal muscle under the regulation of PGC-1α (Boström et al., 2012), and has been demonstrated to regulate hippocampal cerebral blood flow and be essential for exercise-induced neurogenesis (Fabel et al., 2003; Rich et al., 2017). Similarly, inhibiting peripheral IGF-1 entry into the brain was shown to abolish the effects of exercise on hippocampal neurogenesis (Trejo et al., 2001), and blocking the hippocampal IGF-1 receptor diminished exercise-induced improvements in memory (Ding et al., 2006). IGF-1 may exert its effects on hippocampal plasticity partly through activation of BDNF signalling, since intracarotid administration of IGF-1 increased BDNF expression (Carro et al., 2000), while inhibition of hippocampal IGF-1 signalling reduced it (Ding et al., 2006).

4.4. Cathepsin B

Exercise also increases plasma levels of cathepsin B, a protein expressed in skeletal muscle under the regulation by PGC-1α (Moon et al., 2016). Cathepsin B can cross the blood-brain barrier, but its effects on the brain may also be more direct, as exercise also increased cathepsin B gene expression directly in the hippocampus (Moon et al., 2016). Nevertheless, plasma levels of cathepsin B were found to increase in healthy young humans following four months of exercise training, and to positively correlate with changes in fitness and memory (Moon et al., 2016). A recent study in older adults at risk for AD due to family history and genetic factors similarly found cathepsin B levels in plasma to be increased following a 26-week aerobic exercise intervention and the changes in cathepsin B positively associated with changes in cognitive function (Gaitán et al., 2021). It has been shown in vitro that AMPK activation triggers cathepsin B secretion and administration of cathepsin B in hippocampal progenitor cells promotes BDNF expression (Moon et al., 2016). Ablation of cathepsin B expression in mice, in turn, impedes the effects of exercise on neurogenesis and cognitive function (Moon et al., 2016). It is therefore notable that, seemingly in line with reduced BDNF expression in AD brains, cathepsin B levels were recently found to be reduced in the brains of AD patients and transgenic AD mouse models when compared to the brains of healthy age-matched humans and wild-type mice (Long et al., 2020). Interestingly, whereas cathepsin B levels in peripheral blood mononuclear cells have also been reported lower in humans with severe-stage AD when compared with healthy controls, the opposite was reported for plasma levels (Morena et al., 2017). Together these findings suggest cathepsin B as another important factor that mediates the effects of exercise on the brain and whose expression seems to be dysregulated in AD.

4.5. Kynurenine/Kynurenic acid

Tryptophan is an essential amino acid that acts as a precursor for the neurotransmitter serotonin. However, the major catabolic pathway of tryptophan is the kynurenine pathway, where tryptophan is first converted to kynurenine. Kynurenine can then be converted to either kynurenic acid or to 3-hydroxykynurenine, which is followed by several downstream metabolites before the preferred end-product energy cofactor NAD+ that acts as an important cofactor in energy metabolism (Savitz, 2020). While kynurenic acid is thought to be neuroprotective, 3-hydroxykynurenine, both alone and through its downstream metabolite quinolinic acid, is associated with neurotoxic functions in the brain (Savitz, 2020). Altered expression or activity of the enzymes regulating the kynurenine pathway, and the subsequent changes in the levels of the intermediate metabolites, are thought to be implicated in various mental disorders and neurodegenerative diseases (Savitz, 2020). Systemic inflammation is thought to promote peripheral production of kynurenine and its transportation into the brain, where the accumulation of kynurenine may eventually have implications to neuroinflammation and degeneration (Agudelo et al., 2014; Savitz, 2020). Further linking enhanced peripheral tryptophan catabolism through the kynurenine pathway to AD pathology, the plasma ratio of kynurenine to tryptophan positively correlated with plasma biomarkers of neurodegeneration and brain Aβ load in older adults presenting preclinical AD (Chatterjee et al., 2019), and CSF ratio of 3-hydroxykynurenine to kynurenine correlated with tau biomarkers in clinical AD (Jacobs et al., 2019). In addition, plasma kynurenine, quinolinic acid, and kynurenine to tryptophan ratio are all increased in individuals with Down syndrome (Powers et al., 2019), who are highly susceptible to early AD pathology build-up (Snyder et al., 2020). Alterations in tryptophan catabolism may hence be involved in AD pathogenesis and provide a potential therapeutic target.

Exercise training may provide neuroprotection by reducing the accumulation of kynurenine in the brain (Agudelo et al., 2014). This is based on the promoted expression of kynurenine aminotransferases in peripheral immune cells and skeletal muscle in humans following acute or chronic endurance exercise (Joisten et al., 2020; Schlittler et al., 2016). Kynurenine aminotransferases catalyse the irreversible conversion of kynurenine to kynurenic acid, and their peripheral activity may hence reduce the kynurenine available for transport into the brain (Agudelo et al., 2014). Interestingly, the expression of kynurenine aminotransferases in skeletal muscle is regulated by the activation of PGC-1α (Agudelo et al., 2014), and the function of these enzymes was also found to mediate skeletal muscle oxidative capacity and exercise performance in mice (Agudelo et al., 2019). In addition, the increased levels of kynurenic acid in blood following exercise (Schlittler et al., 2016) enhances adipose tissue energy metabolism and insulin sensitivity, by activating GPR35 (G protein-coupled receptor 35), a cell membrane receptor that initiates intracellular signalling cascades in adipocytes ultimately leading to increased lipid metabolism (Agudelo et al., 2018).

4.6. Gpld-1

A recent study in mice suggests a liver-derived enzyme glycosylphosphatidylinositol-specific phospholipase D1 (Gpld-1) to play a significant role mediating the exercise effects on the brain (Horowitz et al., 2020). Plasma levels of Gpld-1 were found positively correlated with cognitive functions in mice and both exercise-trained mice and physically active older adults had higher plasma Gpld-1 levels compared to the respective sedentary groups (Horowitz et al., 2020). Furthermore, merely inducing Gpld-1 overexpression in the liver was found sufficient to enhance hippocampal BDNF expression, promote neurogenesis and enhance cognitive function in sedentary mice (Horowitz et al., 2020). However, as Gpld-1 was not found to enter the brain, it likely conveys its effects via other factors able to cross the blood-brain barrier (Horowitz

et al., 2020).

4.7. Ketone bodies

Exercise results in increased energy consumption and altered metabolism. Prolonged exercise depletes the body's glycogen stores and as the blood glucose levels become low, fatty acid-derived ketones produced by the liver become a major source of energy, also in the brain. Accordingly, exercise increases the expression of monocarboxylate transporters that mediate the uptake of ketone bodies (and lactate) in the brain (Takimoto and Hamada, 2014). Interestingly, while cerebral glucose uptake is impaired in mild cognitive impairment and AD, ketone uptake is not (Croteau et al., 2018), and similar to exercise, ketogenic therapies show potential of improving cognitive functions in mild cognitive impairment and AD patients (Grammatikopoulou et al., 2020). This may not only be due to enhanced brain energy metabolism, but also other neurotrophic support. Exercise-induced increases in hippocampal levels of the ketone body β-hydroxybutyrate (BHB) may also serve as a means that upregulates BDNF expression (Sleiman et al., 2016). BHB was found to enhance BDNF expression and synaptic function independent of PGC-1α and FNDC5, further experiments suggesting an epigenetic regulation mechanism (Sleiman et al., 2016). Therefore, the intermittent reductions in glucose availability and increases in ketone production in the liver and uptake in the brain may be one means by which exercise training stimulates brain plasticity and improves cognitive function.

4.8. Lactate

Lactate is an important energy substrate and signalling molecule in the brain, where it is mainly produced by glial cells (Magistretti and Allaman, 2018). The lactate-mediated interplay between astrocytes and neurons, where lactate produced by astrocytes is taken up and used by neurons, is thought to be essential for synaptic plasticity and memory modulation (Magistretti and Allaman, 2018). In addition to the endogenous lactate, the brain can also utilize the systemic lactate that is produced by the skeletal muscle under intense exercise.

Like ketone bodies, the muscle-derived lactate can cross the blood-brain barrier via monocarboxylate transporters whose expression increases with exercise (Hu et al., 2021; Park et al., 2021). The increase in lactate with high-intensity exercise has been suggested to enhance hippocampal mitochondrial biogenesis and function (Hu et al., 2021; Park et al., 2021) and to promote cerebral VEGF levels and BDNF signalling in mice, with concomitant increases in hippocampal angiogenesis and neurogenesis (Morland et al., 2017; El Hayek et al., 2019). Specifically, increases in cerebral VEGF levels and angiogenesis were found to occur via activation of lactate receptor hydroxycarboxylic acid receptor 1 in endothelial cells as a response to increased blood lactate levels from high-intensity interval training (Morland et al., 2017). BDNF expression, in turn, was found to be promoted by increased blood lactate levels via the PGC-1α/FNDC5/BDNF-pathway in a SIRT1-dependent manner (El Hayek et al., 2019). In support of these findings, another recent study found daily intraperitoneal administration of lactate to promote hippocampal neurogenesis in mice, and inhibition of its transport into neurons to abolish this effect (Lev-Vachnish et al., 2019). In contrast, another recent study found that disrupted clearance of lactate into the blood and subsequent accumulation of lactate impaired hippocampal neurogenesis and cognitive function (Wang et al., 2019a), suggesting that fine regulation of lactate homeostasis is critical for neurogenesis and cognition.

Some studies further imply a similar central mediating effect of lactate in humans. A recent study in young male subjects found that increased blood lactate levels measured after a single sprint-interval exercise correlated with serum BDNF, IGF-1, and VEGF concentrations, and the BDNF concentrations also correlated with post-exercise executive function test performance (Kujach et al., 2019). Also, infusion of lactate intravenously at a resting state in humans has been shown to increase blood BDNF levels (Schiffer et al., 2011). However, whether an increase in blood lactate also upregulates the levels of these factors and the related signalling pathways associated with angiogenesis and neurogenesis in the human brain remains largely unknown. Still, these findings may together indicate that the intensity of exercise, and the consequent change in blood lactate level, may be an important factor determining the effects of exercise on the brain. Therefore, it may be that at least some of the variation in the results of interventional studies investigating the effects of exercise on cognition could be due to differences in exercise intensity, which could change the level of lactate in the blood in turn.

In summary, exercise increases the expression of several biomolecules in the brain, skeletal muscle, and liver that have been linked to enhanced hippocampal plasticity and cognitive functions. Specifically, the exercise-induced increases in the expression of BDNF, IGF-1, and VEGF directly in the brain, as well as the increases in circulating skeletal muscle-derived biomolecules irisin and cathepsin B seem to be supportive to cognitive functions through varying effects on neurogenesis, angiogenesis and/or synaptic plasticity. Exercise-induced increases in the liver-derived enzyme Gpld1 and the metabolites β-hydroxybutyrate and lactate are other potential mediators of the beneficial effects of exercise on the brain. Furthermore, reduced availability of kynurenine in the blood may be one means through which exercise protects the brain from neurodegeneration (see Fig. 2 for a summary of the effects).

Although the molecules discussed here hold potential for future therapeutic applications, the knowledge on mechanisms responsible for the beneficial effects of exercise in the brain barely scratches the surface. It would be naïve to suppose that all benefits promoted by exercise could be explained by so few molecular mediators. Important questions remain about new targets and other sources of molecular mediators such as gut microbiota. Mimicking and/or increasing the positive effects of exercise on the brain through manipulation of new drug targets would be a major step towards enhancing mental health. In our view, future studies should focus on unbiased, high throughput technologies ("omics" screenings) for dissecting novel molecules related to the effects of exercise in the brain, in addition to exhaustive validations through manipulation of those molecules using in vivo models of AD. Establishment of a large consortium might be required to take on such a huge undertaking, and we would strongly support and participate in initiatives in this direction.

5. Mimicking exercise for AD therapeutics

Although current knowledge suggests exercise as a promising means to improve or maintain cognition and reduce the risk of AD, the characteristic declined expression of some key factors linked to brain plasticity, such as irisin, may attenuate the effects of exercise in AD patients. In addition, structural and functional changes in the blood-brain barrier, such as loss of pericytes and altered endothelial function and protein transport mechanisms, together with associated reduced total uptake of circulating proteins (Yang et al., 2020; Chen et al., 2020) may also play a role here. It is also important to note that the increasing physical deterioration and functional disability with aging and progressing AD or comorbidities may severely hinder the ability to exercise. Thus, even if exercise might confer some therapeutic effects (e.g., slower disease progression) in AD patients, its limited feasibility highlights the need for alternative therapeutic approaches. Pharmacologically mimicking the systemic effects of exercise could be one means.

Stimulation of neurotrophic factors and hippocampal neurogenesis may be an essential combination mediating the effect of exercise on cognitive functions. Adding newborn neurons was found sufficient to improve cognitive function in AD mice only when combined with additional stimuli from either direct exercise or elevated BDNF (Choi et al., 2018). Where merely stimulating hippocampal neurogenesis

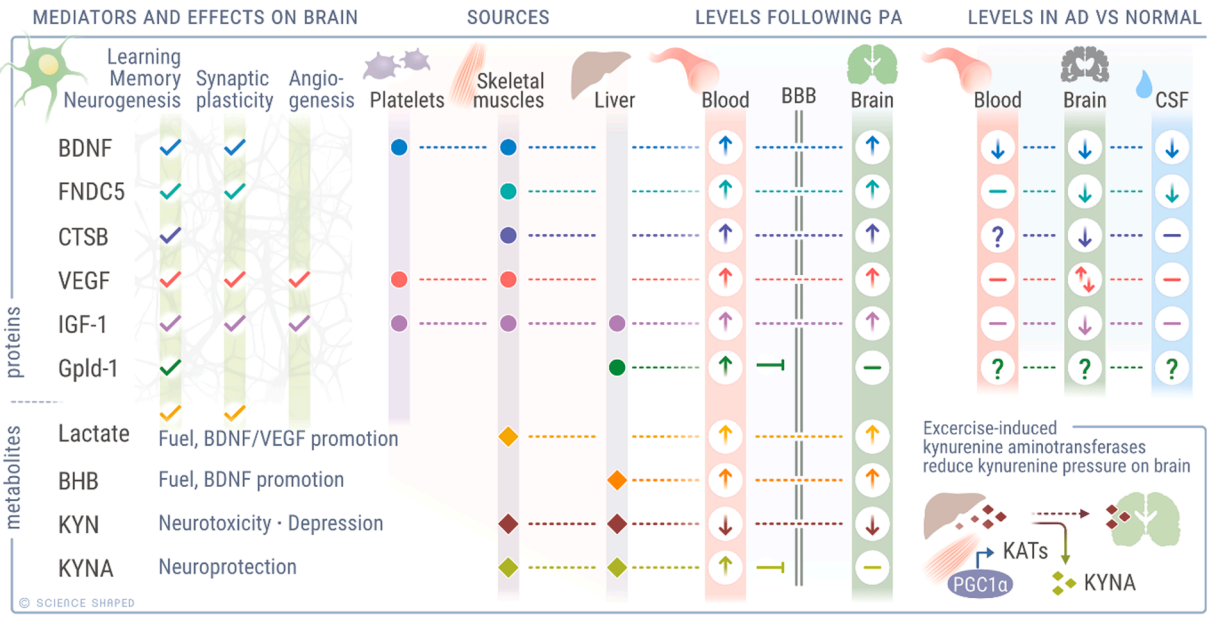

Fig. 2. A summary of molecular regulators and mediators underlying the benefits of exercise on the brain. Physical activity stimulates the synthesis of multiple biomolecules in skeletal muscles, liver, and platelets. BDNF, Irisin, Cathepsin B, VEGF, IGF-1, Lactate, and BHB are also able to cross the blood-brain barrier (BBB) and, consequently, display increased abundance in the brain of exercised vs. non-exercised animals. Conversely, physical activity boosts Kynurenine (which is maleficent to brain function) conversion to Kynurenic acid, thereby reducing Kynurenine plasma concentrations and its negative actions in the brain. Some of the molecules modulated by exercise are also found in abnormal abundance in blood, brain, or cerebrospinal fluid (CSF) of AD patients when compared to individuals without neurological complications. Moreover, these molecules have been implicated in cellular processes that are crucial for optimal brain function, such as neurogenesis, angiogenesis, and synaptic plasticity. (a) Many of these molecules (BDNF, Irisin, Cathepsin B, VEGF, IGF-1, Gpld-1, Kynurenic acid, Lactate, and BHB) were shown to be released by source organs into the systemic circulation and were found in increased concentrations in blood after physical activity. (b) Each molecule is presented with a different color in the image, illustrating their potential effect in the brain, peripheral source, and relative concentration after physical activity and in AD (arrows). (For interpretation of the references to colour in this figure, the reader is referred to the web version of this article.)

through the administration of compounds that enhance proliferation and survival of neural progenitor cells was found to have very limited effects on cognitive function in AD mice, combining this treatment with the administration of AMPK agonist 5-aminoimidazole-4-carboxamide ribonucleotide to pharmacologically increase BDNF expression (Guerrieri and van Praag, 2015) successfully mimicked the beneficial effects of exercise on cognitive performance observed in this mouse model (Choi et al., 2018). Still, in contrast to exercising, this combination did not ameliorate Aβ pathology, suggesting other exercise-induced factors or mechanisms involved in reduced Aβ burden (Choi et al., 2018). Moreover, prolonged administration of this compound may result in detrimental effects such as an upregulation of neuroinflammation (Guerrieri and van Praag, 2015). Similar procedures may not be directly translatable to human subjects, but overall, combined stimulation of neurogenesis and systemic neurotrophic support may be able to improve cognitive functions.

Considering the central role of the PGC-1α transcription coactivator mediating not only the metabolic adaptations to exercise but also the expression of neurotrophic factors associated with hippocampal plasticity, it seems a potential target for exercise-mimicking therapeutics. Chronic overexpression of skeletal muscle-specific PGC-1α has been shown sufficient to significantly improve endurance exercise performance and VO_2 peak in mice (Calvo et al., 2008). However, it was found insufficient to prevent the decline in hippocampal neurogenesis with aging, regardless of enhanced skeletal muscle gene expression of VEGF, FNDC5, and cathepsin B (Karlsson et al., 2019). It was similarly not sufficient to stimulate hippocampal neurogenesis in young or middle-aged passive mice, or to show additive effect on neurogenesis in running mice (Karlsson et al., 2020). Together these studies suggest that skeletal muscle PGC-1α may not present a viable target for chronically promoting hippocampal plasticity even though it could promote the expression of some systemic factors associated with such effects. Still, an open question is whether a more intermittent activation of the skeletal muscle PGC-1α could have beneficial effects on the brain.

Additional evidence suggests that skeletal muscle might altogether not be a sufficient target for promoting hippocampal neurogenesis or cognitive function. A recent study in mice demonstrated that although systematic electrical stimulation of hind limb muscles of mice under anaesthesia was sufficient to increase blood lactate levels and promote hippocampal generation of astrocytes, it did not promote neurogenesis or produce any cognitive changes (Gardner et al., 2020). Overall, these findings may suggest that although the contracting skeletal muscle secrete several factors with potential beneficial effects in the brain, these muscle-derived factors alone may not be enough to induce neurogenesis or changes in cognitive function, but an interplay with (secreted factors from) other tissues may be required for such effects.

However, it is also possible that the lack of promoted hippocampal neurogenesis following chronic overexpression of skeletal muscle-specific PGC-1α could be due to the skeletal muscle-derived factors not reaching the brain at a sufficient quantity, as the cerebral levels of these factors were not investigated (Karlsson et al., 2019). Also, the effects of PGC-1α overexpression or electrical skeletal muscle stimulation in the context of AD could differ from those in normal aging. For example, delivery of the human PGC-1α gene directly in the brain using a viral vector was found to increase hippocampal BDNF, reduce Aβ accumulation, neuroinflammation, and neuronal loss, as well as to improve memory in a mouse model of AD, while not having any effect on the neuronal count or memory function in wild-type mice (Katsouri et al., 2016). Similarly, whereas enhancing the brain FNDC5 expression via intracerebroventricular infection with FNDC5-overexpressing adenovirus was found to ameliorate synaptic function and memory impairment in AD mice, it did not improve synaptic function or cognitive function in wild-type mice (Lourenco et al., 2019). Despite these promising results, such invasive strategies are not directly translatable to humans and, on the other hand, taking into account the body-wide effects of exercise, more systemic approaches might best mimic

exercise and confer the greatest benefit in human patients.

5.1. "Exercised" plasma administration

Studies in mice have demonstrated that blood transfer-induced changes in the systemic environment can alter brain function (Villeda et al., 2014; Katsimpardi et al., 2014; Xia et al., 2019a, Middeldorp et al., 2016; Zhao et al., 2020b). Exposure of old animals to a young systemic environment has been shown to enhance hippocampal synaptic plasticity, angiogenesis, and neurogenesis, resulting in improved cognitive functions (Villeda et al., 2014, 2011; Katsimpardi et al., 2014). Four studies have subsequently investigated the effects of young blood administration in animal models of AD, with findings of improved learning and memory (Xia et al., 2019a; Middeldorp et al., 2016; Zhao et al., 2020), or no significant effects on cognitive functions (Kim et al., 2020). While one of these studies found no effect of young blood treatment on amyloid pathology (Middeldorp et al., 2016), two others did (Xia et al., 2019a; Zhao et al., 2020b), one also reporting evidence of reduced tau pathology (Zhao et al., 2020b). Interestingly, only two of these studies explored the effect of young plasma treatment on hippocampal neurogenesis and neither of them found effect (Zhao et al., 2020b; Kim et al., 2020), although one found better spatial learning and memory in the plasma-treated mice compared to control mice (Zhao et al., 2020b). This discrepancy could be attributed to different effect of treatment on tau pathology as only in the study where plasma treatment was found beneficial for spatial learning and memory, it was also found to reduce the level of tau pathology (Zhao et al., 2020b). In addition, although the AD model used in these two studies was the same triple transgenic mouse model, the overall setting and methods used were different. Of note is that the donor mice were one to two months younger (2–3 months old) and the recipient mice four to five months older (16–17 months old) in the study that reported beneficial effects on cognitive function and tau pathology compared to the study reporting no effect on either. The greater age difference and hence greater difference in the degree of AD pathology and the systemic environment might therefore be another potential reason for the different results.

Considering the remarkable capacity of exercise as a trigger for the release of systemic factors with various beneficial effects in the brain, it might not be surprising that administration of blood plasma from exercised donors was recently found beneficial to aged mice (Horowitz et al., 2020). Injecting blood plasma from either exercised adult or exercised aged mice to sedentary aged mice conferred similar beneficial effects on the brain as the complete exercise intervention, including promoted neurogenesis and enhanced cognitive functions (Horowitz et al., 2020). These results provide further evidence for systemically mediated neuroprotective effects of exercise and suggest that exogenously administrated "exercised" plasma can convey the broad beneficial effects of exercise on the aged brain. Whether exercised plasma administration could similarly exert therapeutic effects in the AD brain therefore seems an intriguing study topic that could lead towards novel therapeutic strategies.

Only one study investigating the effects of plasma administration from, not only young, but exercise-trained young donors in an animal model of AD has been published so far. In this recent study (Kim et al., 2020), the effects of plasma administration were explored in a triple transgenic AD model, which expresses both Aβ and some tau pathology. Specifically, plasma administered into 12-month-old AD mice was collected from two groups of young 4-month-old wild-type mice: those that were exercised on a treadmill 5 times a week for 12 weeks preceding plasma collection, and those who were not. As expected, untreated 12-month-old AD mice showed significantly impaired learning and memory, reduced levels of BDNF and other markers of synaptic plasticity, reduced neurogenesis, and increased markers of mitochondrial dysfunction and cell death compared to wild-type mice (Kim et al., 2020). Plasma from exercised, young mice was found to ameliorate spatial learning and memory and long-term memory in the 12-month-old AD mice (Kim et al., 2020). These behavioural improvements were accompanied by significantly increased hippocampal cell proliferation and neurogenesis, increased expression of BDNF and synaptic proteins, improved mitochondrial function, and reduced markers of cell death (Kim et al., 2020). However, plasma administration was not found to affect the hippocampal expression of tau or its phosphorylation (Kim et al., 2020).

Remarkably, administration of plasma from non-exercised young mice did also increase hippocampal BDNF expression, but significantly less than treatment with exercised plasma, and it did not produce statistically significant effects on any other measured variables, including neurogenesis and performance in behavioural tests (Kim et al., 2020). The significantly greater BDNF levels in the plasma from exercised donor mice compared to the plasma from non-exercised donor mice may at least partially explain the differential outcomes in the two treated groups (Kim et al., 2020). Indeed, while hippocampal BDNF expression was significantly greater in both plasma-treated groups compared with the control AD mice, the mice treated with exercised plasma showed significantly greater BDNF expression compared to the mice treated with non-exercised plasma (Kim et al., 2020). Still, it is important to note that the ability of peripheral BDNF to reach the brain is limited (Nagahara and Tuszynski, 2011), and as reviewed above, other exercise-induced circulating factors have also been linked to enhanced hippocampal BDNF expression and neurogenesis. Overall, these results again imply that exercise-induced circulating factors are indeed capable of promoting neuronal proliferation and integrity and improving cognitive functions even in a neurodegenerative AD-like context, and may significantly enhance the potency of beneficial effects from young plasma treatment in AD. The mechanisms through which exercise or exercised plasma convey their beneficial effects still need more investigation.

No human studies have investigated plasma transfer from exercised donors to AD patients yet, but a small RCT testing the safety and feasibility of young plasma administration in AD patients has been performed, concluding this therapeutic strategy as safe and well tolerated (Sha et al., 2019), and hence paving the way for future studies to investigate the therapeutic potential of "exercised" plasma in AD. One trial is set to be started this year by our group (EudraCT #2018–000148–24) and it may provide important knowledge on the effectiveness of this form of treatment strategy in humans.

6. Conclusion

In addition to their well-studied significant effects on lowering the risks of cardiovascular disease and mortality, there is growing evidence that higher levels of PA and CRF are inversely associated with cognitive decline and risk of AD, suggesting exercise training to promote healthy aging. Exercise may confer neuroprotective effects on the brain through promoted plasticity and reduced pathology, and exercise interventions preceding clinical manifestation of AD may provide the best benefit. It is probable that if the neurodegeneration has progressed beyond a certain point, exercise may not be able to alleviate the symptoms or reverse the course. Contradictory findings from studies in AD patients may reflect this, but it is also possible that due to the characteristics of dementia, it may not be possible for all patients to perform exercise of adequate volume to gain the exercise benefit.

CRF may be a key target for improving brain health both in healthy individuals and those with AD. Depending on the limiting factors, improved CRF may reflect improved function of any of the contributing systems, i.e., the cardiovascular, respiratory, and skeletal muscle function. While considerable evidence from observational studies in humans suggests cardiovascular health important for brain health, studies mainly conducted in rodents have also found several potential exercise-induced neuroprotective factors associated with skeletal muscle oxidative capacity. These findings do not exclude each other but may instead be synergistic such that a healthy cardiovascular system provides a sound background for the systemically mediated interplay between

peripheral organs and the brain.

Exercise is known to induce secretion of a wide array of biomolecules from tissues across the body and several of these exercise-induced biomolecules may contribute to the beneficial effects of exercise in the brain. Studies in animals have further demonstrated that exposure of old animals to some of these secreted biomolecules or, more comprehensively, to a young or exercised systemic environment through blood transfer is sufficient to stimulate hippocampal plasticity and improve cognitive functions. Similarly, transferring blood from exercised donors to animals presenting early AD pathology could mimic the neuroprotective effects of exercise. Given this evidence, it may be presumed that blood transferred from healthy, exercised donors could also have exercise-mimicking therapeutic effects in human AD patients.

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Declaration of competing interest

The authors declare no competing interest.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.arr.2022.101559.

References

Adlard, P.A., Perreau, V.M., Pop, V., Cotman, C.W., 2005. Voluntary exercise decreases amyloid load in a transgenic model of Alzheimer's disease. J. Neurosci. 25, 4217–4221. https://doi.org/10.1523/jneurosci.0496-05.2005.

Agudelo, L.Z., Femenía, T., Orhan, F., Porsmyr-Palmertz, M., Goiny, M., Martinez-Redondo, V., Correia, J.C., Izadi, M., Bhat, M., Schuppe-Koistinen, I., Pettersson, A. T., Ferreira, D., Krook, A., Barres, R., Zierath, J.R., Erhardt, S., Lindskog, M., Ruas, J. L., 2014. Skeletal muscle PGC-1α1 modulates kynurenine metabolism and mediates resilience to stress-induced depression. Cell 159, 33–45. https://doi.org/10.1016/j.cell.2014.07.051.

Agudelo, L.Z., Ferreira, D., Cervenka, I., Bryzgalova, G., Dadvar, S., Jannig, P.R., Pettersson-Klein, A.T., Lakshmikanth, T., Sustarsic, E.G., Porsmyr-Palmertz, M., Correia, J.C., Izadi, M., Martínez-Redondo, V., Ueland, P.M., Midttun, Ø., Gerhart-Hines, Z., Brodin, P., Pereira, T., Berggren, P.O., Ruas, J.L., 2018. Kynurenic acid and Gpr35 regulate adipose tissue energy homeostasis and inflammation. Cell Metab. 27 (378–392), e375–392. https://doi.org/10.1016/j.cmet.2018.01.004.

Agudelo, L.Z., Ferreira, D., Dadvar, S., Cervenka, I., Ketscher, L., Izadi, M., Zhengye, L., Furrer, R., Handschin, C., Venckunas, T., Brazaitis, M., Kamandulis, S., Lanner, J.T., Ruas, J.L., 2019. Skeletal muscle PGC-1α1 reroutes kynurenine metabolism to increase energy efficiency and fatigue-resistance. Nat. Commun. 10, 2767. https://doi.org/10.1038/s41467-019-10712-0.

Alkadhi, K.A., Dao, A.T., 2018. Exercise decreases BACE and APP levels in the hippocampus of a rat model of Alzheimer's disease. Mol. Cell Neurosci. 86, 25–29. https://doi.org/10.1016/j.mcn.2017.11.008.

An, Y., Varma, V.R., Varma, S., Casanova, R., Dammer, E., Pletnikova, O., Chia, C.W., Egan, J.M., Ferrucci, L., Troncoso, J., Levey, A.I., Lah, J., Seyfried, N.T., Legido-Quigley, C., O'Brien, R., Thambisetty, M., 2018. Evidence for brain glucose dysregulation in Alzheimer's disease. Alzheimer'S. Dement. J. Alzheimer'S. Assoc. 14, 318–329. https://doi.org/10.1016/j.jalz.2017.09.011.

Arranz, A.M., De Strooper, B., 2019. The role of astroglia in Alzheimer's disease: pathophysiology and clinical implications. Lancet Neurol. 18, 406–414. https://doi.org/10.1016/s1474-4422(18)30490-3.

Arriagada, P.V., Growdon, J.H., Hedley-Whyte, E.T., Hyman, B.T., 1992. Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer's disease. Neurology 42, 631–639. https://doi.org/10.1212/wnl.42.3.631.

Aschenbrenner, A.J., Gordon, B.A., Benzinger, T.L.S., Morris, J.C., Hassenstab, J.J., 2018. Influence of tau PET, amyloid PET, and hippocampal volume on cognition in Alzheimer disease. Neurology 91, e859–e866. https://doi.org/10.1212/wnl.0000000000006075.

Association, A. s, 2019. 2019 Alzheimer's disease facts and figures. Alzheimer'S. Dement. 15, 321–387. https://doi.org/10.1016/j.jalz.2019.01.010.

Association, A. s, 2021. 2021 Alzheimer's disease facts and figures. Alzheimer'S. Dement. J. Alzheimer'S. Assoc. 17, 327–406. https://doi.org/10.1002/alz.12328.

Barnes, D.E., Yaffe, K., Satariano, W.A., Tager, I.B., 2003. A longitudinal study of cardiorespiratory fitness and cognitive function in healthy older adults. J. Am. Geriatr. Soc. 51, 459–465. https://doi.org/10.1046/j.1532-5415.2003.51153.x.

Beckett, M.W., Ardern, C.I., Rotondi, M.A., 2015. A meta-analysis of prospective studies on the role of physical activity and the prevention of Alzheimer's disease in older adults. BMC Geriatr. 15, 9. https://doi.org/10.1186/s12877-015-0007-2.

Bennett, D.A., Schneider, J.A., Arvanitakis, Z., Kelly, J.F., Aggarwal, N.T., Shah, R.C., Wilson, R.S., 2006. Neuropathology of older persons without cognitive impairment from two community-based studies. Neurology 66, 1837–1844. https://doi.org/10.1212/01.wnl.0000219668.47116.e6.

Berchtold, N.C., Prieto, G.A., Phelan, M., Gillen, D.L., Baldi, P., Bennett, D.A., Buchman, A.S., Cotman, C.W., 2019. Hippocampal gene expression patterns linked to late-life physical activity oppose age and AD-related transcriptional decline. Neurobiol. Aging 78, 142–154. https://doi.org/10.1016/j.neurobiolaging.2019.02.012.

Berdugo-Vega, G., Arias-Gil, G., López-Fernández, A., Artegiani, B., Wasielewska, J.M., Lee, C.C., Lippert, M.T., Kempermann, G., Takagaki, K., Calegari, F., 2020. Increasing neurogenesis refines hippocampal activity rejuvenating navigational learning strategies and contextual memory throughout life. Nat. Commun. 11, 135. https://doi.org/10.1038/s41467-019-14026-z.

Beydoun, M.A., Dore, G.A., Canas, J.A., Liang, H., Beydoun, H.A., Evans, M.K., Zonderman, A.B., 2018. Systemic inflammation is associated with longitudinal changes in cognitive performance among urban adults. Front Aging Neurosci. 10, 313. https://doi.org/10.3389/fnagi.2018.00313.

Blair, S.N., Kohl, H.W., Barlow, C.E., Paffenbarger RS, Jr, Gibbons, L.W., Macera, C.A., 1995. Changes in physical fitness and all-cause mortality. A prospective study of healthy and unhealthy men. Jama 273, 1093–1098.

Bliss, T.V., Lomo, T., 1973. Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. J. Physiol. 232, 331–356. https://doi.org/10.1113/jphysiol.1973.sp010273.

Boldrini, M., Fulmore, C.A., Tartt, A.N., Simeon, L.R., Pavlova, I., Poposka, V., Rosoklija, G.B., Stankov, A., Arango, V., Dwork, A.J., Hen, R., Mann, J.J., 2018. Human hippocampal neurogenesis persists throughout aging. Cell stem Cell 22 (589–599), e585–599. https://doi.org/10.1016/j.stem.2018.03.015.

Boström, P., Wu, J., Jedrychowski, M.P., Korde, A., Ye, L., Lo, J.C., Rasbach, K.A., Boström, E.A., Choi, J.H., Long, J.Z., Kajimura, S., Zingaretti, M.C., Vind, B.F., Tu, H., Cinti, S., Højlund, K., Gygi, S.P., Spiegelman, B.M., 2012. A PGC1-alpha-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. Nature 481, 463–468. https://doi.org/10.1038/nature10777.

Braskie, M.N., Boyle, C.P., Rajagopalan, P., Gutman, B.A., Toga, A.W., Raji, C.A., Tracy, R.P., Kuller, L.H., Becker, J.T., Lopez, O.L., Thompson, P.M., 2014. Physical activity, inflammation, and volume of the aging brain. Neuroscience 273, 199–209. https://doi.org/10.1016/j.neuroscience.2014.05.005.

Brier, M.R., Gordon, B., Friedrichsen, K., McCarthy, J., Stern, A., Christensen, J., Owen, C., Aldea, P., Su, Y., Hassenstab, J., Cairns, N.J., Holtzman, D.M., Fagan, A. M., Morris, J.C., Benzinger, T.L., Ances, B.M., 2016. Tau and Abeta imaging, CSF measures, and cognition in Alzheimer's disease. Sci. Transl. Med. 8, 338ra366 doi: 10.1126/scitranslmed.aaf2362.

Brown, B.M., Peiffer, J.J., Taddei, K., Lui, J.K., Laws, S.M., Gupta, V.B., Taddei, T., Ward, V.K., Rodrigues, M.A., Burnham, S., Rainey-Smith, S.R., Villemagne, V.L., Bush, A., Ellis, K.A., Masters, C.L., Ames, D., Macaulay, S.L., Szoeke, C., Rowe, C.C., Martins, R.N., 2013. Physical activity and amyloid-beta plasma and brain levels: results from the Australian imaging, biomarkers and lifestyle study of ageing. Mol. Psychiatry 18, 875–881. https://doi.org/10.1038/mp.2012.107.

Brown, B.M., Rainey-Smith, S.R., Dore, V., Peiffer, J.J., Burnham, S.C., Laws, S.M., Taddei, K., Ames, D., Masters, C.L., Rowe, C.C., Martins, R.N., Villemagne, V.L., 2018. Self-reported physical activity is associated with tau burden measured by positron emission tomography. J. Alzheimer'S. Dis. JAD 63, 1299–1305. https://doi.org/10.3233/jad-170998.

Brown, B.M., Peiffer, J., Rainey-Smith, S.R., 2019. Exploring the relationship between physical activity, beta-amyloid and tau: a narrative review. Ageing Res Rev. 50, 9–18. https://doi.org/10.1016/j.arr.2019.01.003.

Burgess, N., Maguire, E.A., O'Keefe, J., 2002. The human hippocampus and spatial and episodic memory. Neuron 35, 625–641. https://doi.org/10.1016/s0896-6273(02)00830-9.

Calvo, J.A., Daniels, T.G., Wang, X., Paul, A., Lin, J., Spiegelman, B.M., Stevenson, S.C., Rangwala, S.M., 2008. Muscle-specific expression of PPARgamma coactivator-1alpha improves exercise performance and increases peak oxygen uptake. J. Appl. Physiol. 104, 1304–1312. https://doi.org/10.1152/japplphysiol.01231.2007.

Campbell, A., Grace, F., Ritchie, L., Beaumont, A., Sculthorpe, N., 2019. Long-term aerobic exercise improves vascular function into old age: a systematic review, meta-analysis and meta regression of observational and interventional studies. Front. Physiol. 10, 31. https://doi.org/10.3389/fphys.2019.00031.

Cantó, C., Gerhart-Hines, Z., Feige, J.N., Lagouge, M., Noriega, L., Milne, J.C., Elliott, P. J., Puigserver, P., Auwerx, J., 2009. AMPK regulates energy expenditure by modulating NAD+ metabolism and SIRT1 activity. Nature 458, 1056–1060. https://doi.org/10.1038/nature07813.

Carro, E., Nuñez, A., Busiguina, S., Torres-Aleman, I., 2000. Circulating insulin-like growth factor I mediates effects of exercise on the brain. J. Neurosci. 20, 2926–2933. https://doi.org/10.1523/jneurosci.20-08-02926.2000.

Caspersen, C.J., Powell, K.E., Christenson, G.M., 1985. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Rep. 100, 126–131.
Cavazzoni, P. FDA's Decision to Approve New Treatment for Alzheimer's Disease, 2021).
Chakravorty, A., Jetto, C.T., Manjithaya, R., 2019. Dysfunctional mitochondria and mitophagy as drivers of Alzheimer's disease pathogenesis. Front Aging Neurosci. 11, 311. https://doi.org/10.3389/fnagi.2019.00311.
Chatterjee, P., Zetterberg, H., Goozee, K., Lim, C.K., Jacobs, K.R., Ashton, N.J., Hye, A., Pedrini, S., Sohrabi, H.R., Shah, T., Asih, P.R., Dave, P., Shen, K., Taddei, K., Lovejoy, D.B., Guillemin, G.J., Blennow, K., Martins, R.N., 2019. Plasma neurofilament light chain and amyloid-β are associated with the kynurenine pathway metabolites in preclinical Alzheimer's disease. J. Neuroinflamm. 16, 186. https://doi.org/10.1186/s12974-019-1567-4.
Chen, M.B., Yang, A.C., Yousef, H., Lee, D., Chen, W., Schaum, N., Lehallier, B., Quake, S. R., Wyss-Coray, T., 2020. Brain endothelial cells are exquisite sensors of age-related circulatory cues. Cell Rep. 30 (4418–4432), e4414–4432.e4. https://doi.org/10.1016/j.celrep.2020.03.012.
Chêne, G., Beiser, A., Au, R., Preis, S.R., Wolf, P.A., Dufouil, C., Seshadri, S., 2015. Gender and incidence of dementia in the Framingham Heart Study from mid-adult life. Alzheimer'S. Dement. J. Alzheimer'S. Assoc. 11, 310–320. https://doi.org/10.1016/j.jalz.2013.10.005.
Cheng, A., Wan, R., Yang, J.L., Kamimura, N., Son, T.G., Ouyang, X., Luo, Y., Okun, E., Mattson, M.P., 2012. Involvement of PGC-1α in the formation and maintenance of neuronal dendritic spines. Nat. Commun. 3, 1250. https://doi.org/10.1038/ncomms2238.
Cheng, A., Yang, Y., Zhou, Y., Maharana, C., Lu, D., Peng, W., Liu, Y., Wan, R., Marosi, K., Misiak, M., Bohr, V.A., Mattson, M.P., 2016. Mitochondrial SIRT3 mediates adaptive responses of neurons to exercise and metabolic and excitatory challenges. Cell Metab. 23, 128–142. https://doi.org/10.1016/j.cmet.2015.10.013.
Choi, S.H., Bylykbashi, E., Chatila, Z.K., Lee, S.W., Pulli, B., Clemenson, G.D., Kim, E., Rompala, A., Oram, M.K., Asselin, C., Aronson, J., Zhang, C., Miller, S.J., Lesinski, A., Chen, J.W., Kim, D.Y., van Praag, H., Spiegelman, B.M., Gage, F.H., Tanzi, R.E., 2018. Combined adult neurogenesis and BDNF mimic exercise effects on cognition in an Alzheimer's mouse model. Science 361. https://doi.org/10.1126/science.aan8821.
Coelho, F.G., Vital, T.M., Stein, A.M., Arantes, F.J., Rueda, A.V., Camarini, R., Teodorov, E., Santos-Galduróz, R.F., 2014. Acute aerobic exercise increases brain-derived neurotrophic factor levels in elderly with Alzheimer's disease. J. Alzheimer'S. Dis. JAD 39, 401–408. https://doi.org/10.3233/jad-131073.
Colcombe, S.J., Erickson, K.I., Scalf, P.E., Kim, J.S., Prakash, R., McAuley, E., Elavsky, S., Marquez, D.X., Hu, L., Kramer, A.F., 2006. Aerobic exercise training increases brain volume in aging humans. J. Gerontol. A Biol. Sci. Med. Sci. 61, 1166–1170. https://doi.org/10.1093/gerona/61.11.1166.
Corlier, F., Hafzalla, G., Faskowitz, J., Kuller, L.H., Becker, J.T., Lopez, O.L., Thompson, P.M., Braskie, M.N., 2018. Systemic inflammation as a predictor of brain aging: contributions of physical activity, metabolic risk, and genetic risk. Neuroimage 172, 118–129. https://doi.org/10.1016/j.neuroimage.2017.12.027.
Cornelissen, V.A., Smart, N.A., 2013. Exercise training for blood pressure: a systematic review and meta-analysis. J. Am. Heart Assoc. 2, e004473 https://doi.org/10.1161/jaha.112.004473.
Croteau, E., Castellano, C.A., Fortier, M., Bocti, C., Fulop, T., Paquet, N., Cunnane, S.C., 2018. A cross-sectional comparison of brain glucose and ketone metabolism in cognitively healthy older adults, mild cognitive impairment and early Alzheimer's disease. Exp. Gerontol. 107, 18–26. https://doi.org/10.1016/j.exger.2017.07.004.
Cruz Hernández, J.C., Bracko, O., Kersbergen, C.J., Muse, V., Haft-Javaherian, M., Berg, M., Park, L., Vinarcsik, L.K., Ivasyk, I., Rivera, D.A., Kang, Y., Cortes-Canteli, M., Peyrounette, M., Doyeux, V., Smith, A., Zhou, J., Otte, G., Beverly, J.D., Davenport, E., Davit, Y., Lin, C.P., Strickland, S., Iadecola, C., Lorthois, S., Nishimura, N., Schaffer, C.B., 2019. Neutrophil adhesion in brain capillaries reduces cortical blood flow and impairs memory function in Alzheimer's disease mouse models. Nat. Neurosci. 22, 413–420. https://doi.org/10.1038/s41593-018-0329-4.
Cummings, J.L., Morstorf, T., Zhong, K., 2014. Alzheimer's disease drug-development pipeline: few candidates, frequent failures. Alzheimer'S. Res. Ther. 6, 37. https://doi.org/10.1186/alzrt269.
Dawe, R.J., Yu, L., Arfanakis, K., Schneider, J.A., Bennett, D.A., Boyle, P.A., 2020. Late-life cognitive decline is associated with hippocampal volume, above and beyond its associations with traditional neuropathologic indices. Alzheimer'S. Dement. J. Alzheimer'S. Assoc. 16, 209–218. https://doi.org/10.1002/alz.12009.
Defina, L.F., Willis, B.L., Radford, N.B., Gao, A., Leonard, D., Haskell, W.L., Weiner, M.F., Berry, J.D., 2013. The association between midlife cardiorespiratory fitness levels and later-life dementia: a cohort study. Ann. Intern. Med. 158, 162–168. https://doi.org/10.7326/0003-4819-158-3-201302050-00005.
Devenney, K.E., Guinan, E.M., Kelly, Á.M., Mota, B.C., Walsh, C., Olde Rikkert, M., Schneider, S., Lawlor, B., 2019. Acute high-intensity aerobic exercise affects brain-derived neurotrophic factor in mild cognitive impairment: a randomised controlled study. BMJ Open Sport Exerc. Med. 5, e000499 https://doi.org/10.1136/bmjsem-2018-000499.
Ding, Q., Vaynman, S., Akhavan, M., Ying, Z., Gomez-Pinilla, F., 2006. Insulin-like growth factor I interfaces with brain-derived neurotrophic factor-mediated synaptic plasticity to modulate aspects of exercise-induced cognitive function. Neuroscience 140, 823–833. https://doi.org/10.1016/j.neuroscience.2006.02.084.
Ding, Q., Ying, Z., Gómez-Pinilla, F., 2011. Exercise influences hippocampal plasticity by modulating brain-derived neurotrophic factor processing. Neuroscience 192, 773–780. https://doi.org/10.1016/j.neuroscience.2011.06.032.
Dinoff, A., Herrmann, N., Swardfager, W., Liu, C.S., Sherman, C., Chan, S., Lanctôt, K.L., 2016. The effect of exercise training on resting concentrations of peripheral brain-derived neurotrophic factor (BDNF): a meta-analysis. PloS One 11, e0163037. https://doi.org/10.1371/journal.pone.0163037.
Dinoff, A., Herrmann, N., Swardfager, W., Lanctôt, K.L., 2017. The effect of acute exercise on blood concentrations of brain-derived neurotrophic factor in healthy adults: a meta-analysis. Eur. J. Neurosci. 46, 1635–1646. https://doi.org/10.1111/ejn.13603.
Do, K., Laing, B.T., Landry, T., Bunner, W., Mersaud, N., Matsubara, T., Li, P., Yuan, Y., Lu, Q., Huang, H., 2018. The effects of exercise on hypothalamic neurodegeneration of Alzheimer's disease mouse model. PloS One 13, e0190205. https://doi.org/10.1371/journal.pone.0190205.
Dong, Y., Li, X., Cheng, J., Hou, L., 2019. Drug development for Alzheimer's disease: microglia induced neuroinflammation as a target? Int. J. Mol. Sci. 20 https://doi.org/10.3390/ijms20030558.
Dorneles, G.P., da Silva, I., Boeira, M.C., Valentini, D., Fonseca, S.G., Dal Lago, P., Peres, A., Romão, P., 2019. Cardiorespiratory fitness modulates the proportions of monocytes and T helper subsets in lean and obese men. Scand. J. Med Sci. Sports 29, 1755–1765. https://doi.org/10.1111/sms.13506.
Dougherty, R.J., Jonaitis, E.M., Gaitán, J.M., Lose, S.R., Mergen, B.M., Johnson, S.C., Okonkwo, O.C., Cook, D.B., 2021. Cardiorespiratory fitness mitigates brain atrophy and cognitive decline in adults at risk for Alzheimer's disease. Alzheimers Dement 13, e12212. https://doi.org/10.1002/dad2.12212.
Dregan, A., Gulliford, M.C., 2013. Leisure-time physical activity over the life course and cognitive functioning in late mid-adult years: a cohort-based investigation. Psychol. Med 43, 2447–2458. https://doi.org/10.1017/s0033291713000305.
Driscoll, I., Martin, B., An, Y., Maudsley, S., Ferrucci, L., Mattson, M.P., Resnick, S.M., 2012. Plasma BDNF is associated with age-related white matter atrophy but not with cognitive function in older, non-demented adults. PloS One 7, e35217. https://doi.org/10.1371/journal.pone.0035217.
Du, Y., Wu, H.T., Qin, X.Y., Cao, C., Liu, Y., Cao, Z.Z., Cheng, Y., 2018a. Postmortem brain, cerebrospinal fluid, and blood neurotrophic factor levels in alzheimer's disease: a systematic review and meta-analysis. J. Mol. Neurosci. 65, 289–300. https://doi.org/10.1007/s12031-018-1100-8.
Du, Z., Li, Y., Li, J., Zhou, C., Li, F., Yang, X., 2018b. Physical activity can improve cognition in patients with Alzheimer's disease: a systematic review and meta-analysis of randomized controlled trials. Clin. Inter. Aging 13, 1593–1603. https://doi.org/10.2147/cia.S169565.
Dubois, B., Hampel, H., Feldman, H.H., Scheltens, P., Aisen, P., Andrieu, S., Bakardjian, H., Benali, H., Bertram, L., Blennow, K., Broich, K., Cavedo, E., Crutch, S., Dartigues, J.F., Duyckaerts, C., Epelbaum, S., Frisoni, G.B., Gauthier, S., Genthon, R., Gouw, A.A., Habert, M.O., Holtzman, D.M., Kivipelto, M., Lista, S., Molinuevo, J.L., O'Bryant, S.E., Rabinovici, G.D., Rowe, C., Salloway, S., Schneider, L.S., Sperling, R., Teichmann, M., Carrillo, M.C., Cummings, J., Jack CR, Jr, Proceedings of the Meeting of the International Working Group (IWG) and the American Alzheimer's Association on "The Preclinical State of AD"; July,; Washington DC, U., 2016. Preclinical Alzheimer's disease: definition, natural history, and diagnostic criteria. Alzheimer'S. Dement. J. Alzheimer'S. Assoc. 12, 292–323. https://doi.org/10.1016/j.jalz.2016.02.002.
Eadie, B.D., Redila, V.A., Christie, B.R., 2005. Voluntary exercise alters the cytoarchitecture of the adult dentate gyrus by increasing cellular proliferation, dendritic complexity, and spine density. J. Comp. Neurol. 486, 39–47. https://doi.org/10.1002/cne.20493.
El Hayek, L., Khalifeh, M., Zibara, V., Abi Assaad, R., Emmanuel, N., Karnib, N., El-Ghandour, R., Nasrallah, P., Bilen, M., Ibrahim, P., Younes, J., Abou Haidar, E., Barmo, N., Jabre, V., Stephan, J.S., Sleiman, S.F., 2019. Lactate mediates the effects of exercise on learning and memory through sirt1-dependent activation of hippocampal brain-derived neurotrophic factor (BDNF). J. Neurosci. 39, 2369–2382. https://doi.org/10.1523/jneurosci.1661-18.2019.
Enette, L., Vogel, T., Merle, S., Valard-Guiguet, A.G., Ozier-Lafontaine, N., Neviere, R., Leuly-Joncart, C., Fanon, J.L., Lang, P.O., 2020. Effect of 9 weeks continuous vs. interval aerobic training on plasma BDNF levels, aerobic fitness, cognitive capacity and quality of life among seniors with mild to moderate Alzheimer's disease: a randomized controlled trial. Eur. Rev. Aging Phys. Act. 17, 2. https://doi.org/10.1186/s11556-019-0234-1.
Engeroff, T., Ingmann, T., Banzer, W., 2018. Physical activity throughout the adult life span and domain-specific cognitive function in old age: a systematic review of cross-sectional and longitudinal data. Sports Med. 48, 1405–1436. https://doi.org/10.1007/s40279-018-0920-6.
Erickson, K.I., Raji, C.A., Lopez, O.L., Becker, J.T., Rosano, C., Newman, A.B., Gach, H. M., Thompson, P.M., Ho, A.J., Kuller, L.H., 2010. Physical activity predicts gray matter volume in late adulthood: the Cardiovascular Health Study. Neurology 75, 1415–1422. https://doi.org/10.1212/WNL.0b013e3181f88359.
Erickson, K.I., Prakash, R.S., Voss, M.W., Chaddock, L., Heo, S., McLaren, M., Pence, B. D., Martin, S.A., Vieira, V.J., Woods, J.A., McAuley, E., Kramer, A.F., 2010. Brain-derived neurotrophic factor is associated with age-related decline in hippocampal volume. J. Neurosci. 30, 5368–5375. https://doi.org/10.1523/jneurosci.6251-09.2010.
Erickson, K.I., Voss, M.W., Prakash, R.S., Basak, C., Szabo, A., Chaddock, L., Kim, J.S., Heo, S., Alves, H., White, S.M., Wojcicki, T.R., Mailey, E., Vieira, V.J., Martin, S.A., Pence, B.D., Woods, J.A., McAuley, E., Kramer, A.F., 2011. Exercise training increases size of hippocampus and improves memory. Proc. Natl. Acad. Sci. USA 108, 3017–3022. https://doi.org/10.1073/pnas.1015950108.
Eriksson, P.S., Perfilieva, E., Björk-Eriksson, T., Alborn, A.M., Nordborg, C., Peterson, D. A., Gage, F.H., 1998. Neurogenesis in the adult human hippocampus. Nat. Med. 4, 1313–1317. https://doi.org/10.1038/3305.

Fabel, K., Fabel, K., Tam, B., Kaufer, D., Baiker, A., Simmons, N., Kuo, C.J., Palmer, T.D., 2003. VEGF is necessary for exercise-induced adult hippocampal neurogenesis. Eur. J. Neurosci. 18, 2803–2812.

Fang, E.F., Hou, Y., Palikaras, K., Adriaanse, B.A., Kerr, J.S., Yang, B., Lautrup, S., Hasan-Olive, M.M., Caponio, D., Dan, X., Rocktäschel, P., Croteau, D.L., Akbari, M., Greig, N.H., Fladby, T., Nilsen, H., Cader, M.Z., Mattson, M.P., Tavernarakis, N., Bohr, V.A., 2019. Mitophagy inhibits amyloid-beta and tau pathology and reverses cognitive deficits in models of Alzheimer's disease. Nat. Neurosci. 22, 401–412. https://doi.org/10.1038/s41593-018-0332-9.

Farmer, J., Zhao, X., van Praag, H., Wodtke, K., Gage, F.H., Christie, B.R., 2004. Effects of voluntary exercise on synaptic plasticity and gene expression in the dentate gyrus of adult male Sprague-Dawley rats in vivo. Neuroscience 124, 71–79. https://doi.org/10.1016/j.neuroscience.2003.09.029.

Fedewa, M.V., Hathaway, E.D., Ward-Ritacco, C.L., 2017. Effect of exercise training on C reactive protein: a systematic review and meta-analysis of randomised and non-randomised controlled trials. Br. J. Sports Med. 51, 670–676. https://doi.org/10.1136/bjsports-2016-095999.

Firth, J., Stubbs, B., Vancampfort, D., Schuch, F., Lagopoulos, J., Rosenbaum, S., Ward, P.B., 2018. Effect of aerobic exercise on hippocampal volume in humans: a systematic review and meta-analysis. Neuroimage 166, 230–238. https://doi.org/10.1016/j.neuroimage.2017.11.007.

Fonte, C., Smania, N., Pedrinolla, A., Munari, D., Gandolfi, M., Picelli, A., Varalta, V., Benetti, M.V., Brugnera, A., Federico, A., Muti, E., Tamburin, S., Schena, F., Venturelli, M., 2019. Comparison between physical and cognitive treatment in patients with MCI and Alzheimer's disease. Aging 11, 3138–3155. https://doi.org/10.18632/aging.101970.

Frederiksen, K.S., Madsen, K., Andersen, B.B., Beyer, N., Garde, E., Høgh, P., Waldemar, G., Hasselbalch, S.G., Law, I., 2019. Moderate- to high-intensity exercise does not modify cortical beta-amyloid in Alzheimer's disease. Alzheimers Dement 5, 208–215. https://doi.org/10.1016/j.trci.2019.04.006.

Fulgenzi, G., Hong, Z., Tomassoni-Ardori, F., Barella, L.F., Becker, J., Barrick, C., Swing, D., Yanpallewar, S., Croix, B.S., Wess, J., Gavrilova, O., Tessarollo, L., 2020. Novel metabolic role for BDNF in pancreatic β-cell insulin secretion. Nat. Commun. 11, 1950. https://doi.org/10.1038/s41467-020-15833-5.

Gaitán, J.M., Boots, E.A., Dougherty, R.J., Oh, J.M., Ma, Y., Edwards, D.F., Christian, B. T., Cook, D.B., Okonkwo, O.C., 2019. Brain glucose metabolism, cognition, and cardiorespiratory fitness following exercise training in adults at risk for alzheimer's disease. Brain Plast. 5, 83–95. https://doi.org/10.3233/bpl-190093.

Gaitán, J.M., Moon, H.Y., Stremlau, M., Dubal, D.B., Cook, D.B., Okonkwo, O.C., van Praag, H., 2021. Effects of aerobic exercise training on systemic biomarkers and cognition in late middle-aged adults at risk for Alzheimer's disease. Front. Endocrinol. 12, 660181 https://doi.org/10.3389/fendo.2021.660181.

Garber, C.E., Blissmer, B., Deschenes, M.R., Franklin, B.A., Lamonte, M.J., Lee, I.M., Nieman, D.C., Swain, D.P., American College of Sports, M., 2011. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med. Sci. Sports Exerc. 43, 1334–1359. https://doi.org/10.1249/MSS.0b013e318213fefb.

Gardner, J.C., Dvoretskiy, S.V., Yang, Y., Venkataraman, S., Lange, D.A., Li, S., Boppart, A.L., Kim, N., Rendeiro, C., Boppart, M.D., Rhodes, J.S., 2020. Electrically stimulated hind limb muscle contractions increase adult hippocampal astrogliogenesis but not neurogenesis or behavioral performance in male C57BL/6J mice. Sci. Rep. 10, 19319. https://doi.org/10.1038/s41598-020-76356-z.

González, H.M., Tarraf, W., Harrison, K., Windham, B.G., Tingle, J., Alonso, A., Griswold, M., Heiss, G., Knopman, D., Mosley, T.H., 2018. Midlife cardiovascular health and 20-year cognitive decline: atherosclerosis risk in communities study results. Alzheimer'S. Dement. J. Alzheimer'S. Assoc. 14, 579–589. https://doi.org/10.1016/j.jalz.2017.11.002.

Grammatikopoulou, M.G., Goulis, D.G., Gkiouras, K., Theodoridis, X., Gkouskou, K.K., Evangeliou, A., Dardiotis, E., Bogdanos, D.P., 2020. To keto or not to keto? a systematic review of randomized controlled trials assessing the effects of ketogenic therapy on alzheimer disease. Adv. Nutr. 11, 1583–1602. https://doi.org/10.1093/advances/nmaa073.

Green, D.J., Maiorana, A., O'Driscoll, G., Taylor, R., 2004. Effect of exercise training on endothelium-derived nitric oxide function in humans. J. Physiol. 561, 1–25. https://doi.org/10.1113/jphysiol.2004.068197.

Groot, C., Hooghiemstra, A.M., Raijmakers, P.G., van Berckel, B.N., Scheltens, P., Scherder, E.J., van der Flier, W.M., Ossenkoppele, R., 2016. The effect of physical activity on cognitive function in patients with dementia: a meta-analysis of randomized control trials. Ageing Res. Rev. 25, 13–23. https://doi.org/10.1016/j.arr.2015.11.005.

Guadagni, V., Drogos, L.L., Tyndall, A.V., Davenport, M.H., Anderson, T.J., Eskes, G.A., Longman, R.S., Hill, M.D., Hogan, D.B., Poulin, M.J., 2020. Aerobic exercise improves cognition and cerebrovascular regulation in older adults. Neurology 94, e2245–e2257. https://doi.org/10.1212/wnl.0000000000009478.

Guerrieri, D., van Praag, H., 2015. Exercise-mimetic AICAR transiently benefits brain function. Oncotarget 6, 18293–18313. https://doi.org/10.18632/oncotarget.4715.

Guure, C.B., Ibrahim, N.A., Adam, M.B., Said, S.M., 2017. Impact of physical activity on cognitive decline, dementia, and its subtypes: meta-analysis of prospective studies. Biomed. Res. Int. 2017, 9016924 https://doi.org/10.1155/2017/9016924.

Hakala, J.O., Rovio, S.P., Pahkala, K., Nevalainen, J., Juonala, M., Hutri-Kähönen, N., Heinonen, O.J., Hirvensalo, M., Telama, R., Viikari, J., Tammelin, T.H., Raitakari, O. T., 2019. Physical activity from childhood to adulthood and cognitive performance in midlife. Med. Sci. Sports Exerc. 51, 882–890. https://doi.org/10.1249/mss.0000000000001862.

Hamer, M., Chida, Y., 2009. Physical activity and risk of neurodegenerative disease: a systematic review of prospective evidence. Psychol. Med 39, 3–11. https://doi.org/10.1017/s0033291708003681.

Hanseeuw, B.J., Betensky, R.A., Jacobs, H., Schultz, A.P., Sepulcre, J., Becker, J.A., Cosio, D., Farrell, M., Quiroz, Y.T., Mormino, E.C., Buckley, R.F., Papp, K.V., Amariglio, R.A., Dewachter, I., Ivanoiu, A., Huijbers, W., Hedden, T., Marshall, G.A., Chhatwal, J.P., Rentz, D.M., Sperling, R.A., Johnson, K., 2019. Association of amyloid and tau with cognition in preclinical alzheimer disease: a longitudinal study. JAMA Neurol. 76, 915–924. https://doi.org/10.1001/jamaneurol.2019.1424.

Hanyu, H., Sato, T., Hirao, K., Kanetaka, H., Iwamoto, T., Koizumi, K., 2010. The progression of cognitive deterioration and regional cerebral blood flow patterns in Alzheimer's disease: a longitudinal SPECT study. J. Neurol. Sci. 290, 96–101. https://doi.org/10.1016/j.jns.2009.10.022.

Harber, M.P., Kaminsky, L.A., Arena, R., Blair, S.N., Franklin, B.A., Myers, J., Ross, R., 2017. Impact of cardiorespiratory fitness on all-cause and disease-specific mortality: advances since 2009. Prog. Cardiovasc. Dis. 60, 11–20. https://doi.org/10.1016/j.pcad.2017.03.001.

Hardy, J.A., Higgins, G.A., 1992. Alzheimer's disease: the amyloid cascade hypothesis. Science 256, 184–185. https://doi.org/10.1126/science.1566067.

He, X.F., Liu, D.X., Zhang, Q., Liang, F.Y., Dai, G.Y., Zeng, J.S., Pei, Z., Xu, G.Q., Lan, Y., 2017. Voluntary exercise promotes glymphatic clearance of amyloid beta and reduces the activation of astrocytes and microglia in aged mice. Front Mol. Neurosci. 10, 144. https://doi.org/10.3389/fnmol.2017.00144.

Henstridge, C.M., Hyman, B.T., Spires-Jones, T.L., 2019. Beyond the neuron-cellular interactions early in Alzheimer disease pathogenesis. Nat. Rev. Neurosci. 20, 94–108. https://doi.org/10.1038/s41583-018-0113-1.

Heppner, F.L., Ransohoff, R.M., Becher, B., 2015. Immune attack: the role of inflammation in Alzheimer disease. Nat. Rev. Neurosci. 16, 358–372. https://doi.org/10.1038/nrn3880.

Hoffmann, K., Sobol, N.A., Frederiksen, K.S., Beyer, N., Vogel, A., Vestergaard, K., Brændgaard, H., Gottrup, H., Lolk, A., Wermuth, L., Jacobsen, S., Laugesen, L.P., Gergelyffy, R.G., Høgh, P., Bjerregaard, E., Andersen, B.B., Siersma, V., Johannsen, P., Cotman, C.W., Waldemar, G., Hasselbalch, S.G., 2016. Moderate-to-high intensity physical exercise in patients with Alzheimer's disease: a randomized controlled trial. J. Alzheimers Dis. 50, 443–453. https://doi.org/10.3233/jad-150817.

Hong, J., Hong, S.G., Lee, J., Park, J.Y., Eriksen, J.L., Rooney, B.V., Park, Y., 2020. Exercise training ameliorates cerebrovascular dysfunction in a murine model of Alzheimer's disease: role of the P2Y2 receptor and endoplasmic reticulum stress. Am. J. Physiol. Heart Circ. Physiol. 318, H1559–h1569. https://doi.org/10.1152/ajpheart.00129.2020.

Hörder, H., Johansson, L., Guo, X., Grimby, G., Kern, S., Östling, S., Skoog, I., 2018. Midlife cardiovascular fitness and dementia: a 44-year longitudinal population study in women. Neurology 90, e1298–e1305. https://doi.org/10.1212/wnl.0000000000005290.

Horgusluoglu-Moloch, E., Risacher, S.L., Crane, P.K., Hibar, D., Thompson, P.M., Saykin, A.J., Nho, K., Alzheimer's Disease Neuroimaging Initiative, (, 2019. Genome-wide association analysis of hippocampal volume identifies enrichment of neurogenesis-related pathways. Sci. Rep. 9, 14498. https://doi.org/10.1038/s41598-019-50507-3.

Horowitz, A.M., Fan, X., Bieri, G., Smith, L.K., Sanchez-Diaz, C.I., Schroer, A.B., Gontier, G., Casaletto, K.B., Kramer, J.H., Williams, K.E., Villeda, S.A., 2020. Blood factors transfer beneficial effects of exercise on neurogenesis and cognition to the aged brain. Science 369, 167–173. https://doi.org/10.1126/science.aaw2622.

Hu, J., Cai, M., Shang, Q., Li, Z., Feng, Y., Liu, B., Xue, X., Lou, S., 2021. Elevated lactate by high-intensity interval training regulates the hippocampal bdnf expression and the mitochondrial quality control system. Front. Physiol. 12, 629914 https://doi.org/10.3389/fphys.2021.629914.

Huang, Y., Happonen, K.E., Burrola, P.G., O'Connor, C., Hah, N., Huang, L., Nimmerjahn, A., Lemke, G., 2021. Microglia use TAM receptors to detect and engulf amyloid β plaques. Nat. Immunol. 22, 586–594. https://doi.org/10.1038/s41590-021-00913-5.

Ingelsson, M., Fukumoto, H., Newell, K.L., Growdon, J.H., Hedley-Whyte, E.T., Frosch, M.P., Albert, M.S., Hyman, B.T., Irizarry, M.C., 2004. Early Abeta accumulation and progressive synaptic loss, gliosis, and tangle formation in AD brain. Neurology 62, 925–931. https://doi.org/10.1212/01.wnl.0000115115.98960.37.

Islam, M.R., Valaris, S., Young, M.F., Haley, E.B., Luo, R., Bond, S.F., Mazuera, S., Kitchen, R.R., Caldarone, B.J., Bettio, L., Christie, B.R., Schmider, A.B., Soberman, R. J., Besnard, A., Jedrychowski, M.P., Kim, H., Tu, H., Kim, E., Choi, S.H., Tanzi, R.E., Spiegelman, B.M., Wrann, C.D., 2021. Exercise hormone irisin is a critical regulator of cognitive function. Nat. Metab. 3, 1058–1070. https://doi.org/10.1038/s42255-021-00438-z.

Iturria-Medina, Y., Sotero, R.C., Toussaint, P.J., Mateos-Perez, J.M., Evans, A.C., 2016. Early role of vascular dysregulation on late-onset Alzheimer's disease based on multifactorial data-driven analysis. Nat. Commun. 7, 11934. https://doi.org/10.1038/ncomms11934.

Jack CR, Jr, Petersen, R.C., Xu, Y., O'Brien, P.C., Smith, G.E., Ivnik, R.J., Tangalos, E.G., Kokmen Jr., E., 1998. Rate of medial temporal lobe atrophy in typical aging and Alzheimer's disease. Neurology 51, 993–999. https://doi.org/10.1212/wnl.51.4.993.

Jack CR, Jr, Petersen, R.C., Xu, Y., O'Brien, P.C., Smith, G.E., Ivnik, R.J., Boeve, B.F., Tangalos, E.G., Kokmen Jr., E., 2000. Rates of hippocampal atrophy correlate with change in clinical status in aging and AD. Neurology 55, 484–489. https://doi.org/10.1212/wnl.55.4.484.

Jack CR, Jr, Knopman, D.S., Jagust, W.J., Petersen, R.C., Weiner, M.W., Aisen, P.S., Shaw, L.M., Vemuri, P., Wiste, H.J., Weigand, S.D., Lesnick, T.G., Pankratz, V.S., Donohue, M.C., Trojanowski Jr., J.Q., 2013. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. Lancet Neurol. 12, 207–216. https://doi.org/10.1016/s1474-4422(12)70291-0.

Jackson, A.S., Sui, X., Hebert, J.R., Church, T.S., Blair, S.N., 2009. Role of lifestyle and aging on the longitudinal change in cardiorespiratory fitness. Arch. Intern. Med. 169, 1781–1787. https://doi.org/10.1001/archinternmed.2009.312.

Jacobs, K.R., Lim, C.K., Blennow, K., Zetterberg, H., Chatterjee, P., Martins, R.N., Brew, B.J., Guillemin, G.J., Lovejoy, D.B., 2019. Correlation between plasma and CSF concentrations of kynurenine pathway metabolites in Alzheimer's disease and relationship to amyloid-β and tau. Neurobiol. Aging 80, 11–20. https://doi.org/10.1016/j.neurobiolaging.2019.03.015.

Jia, R.X., Liang, J.H., Xu, Y., Wang, Y.Q., 2019. Effects of physical activity and exercise on the cognitive function of patients with Alzheimer disease: a meta-analysis. BMC Geriatr. 19, 181. https://doi.org/10.1186/s12877-019-1175-2.

Jin, K., Zhu, Y., Sun, Y., Mao, X.O., Xie, L., Greenberg, D.A., 2002. Vascular endothelial growth factor (VEGF) stimulates neurogenesis in vitro and in vivo. Proc. Natl. Acad. Sci. USA 99, 11946–11950. https://doi.org/10.1073/pnas.182296499.

Joisten, N., Kummerhoff, F., Koliamitra, C., Schenk, A., Walzik, D., Hardt, L., Knoop, A., Thevis, M., Kiesl, D., Metcalfe, A.J., Bloch, W., Zimmer, P., 2020. Exercise and the Kynurenine pathway: current state of knowledge and results from a randomized cross-over study comparing acute effects of endurance and resistance training. Exerc Immunol. Rev. 26, 24–42.

Kandimalla, R., Manczak, M., Yin, X., Wang, R., Reddy, P.H., 2018. Hippocampal phosphorylated tau induced cognitive decline, dendritic spine loss and mitochondrial abnormalities in a mouse model of Alzheimer's disease. Hum. Mol. Genet. 27, 30–40. https://doi.org/10.1093/hmg/ddx381.

Karlsson, L., González-Alvarado, M.N., Motalleb, R., Blomgren, K., Börjesson, M., Kuhn, H.G., 2019. Constitutive PGC-1α overexpression in skeletal muscle does not protect from age-dependent decline in neurogenesis. Sci. Rep. 9, 12320. https://doi.org/10.1038/s41598-019-48795-w.

Karlsson, L., González-Alvarado, M.N., Motalleb, R., Wang, Y., Wang, Y., Börjesson, M., Zhu, C., Kuhn, H.G., 2020. Constitutive PGC-1α Overexpression in skeletal muscle does not contribute to exercise-induced neurogenesis. Mol. Neurobiol. 58, 1465–1481. https://doi.org/10.1007/s12035-020-02189-6.

Katsimpardi, L., Litterman, N.K., Schein, P.A., Miller, C.M., Loffredo, F.S., Wojtkiewicz, G.R., Chen, J.W., Lee, R.T., Wagers, A.J., Rubin, L.L., 2014. Vascular and neurogenic rejuvenation of the aging mouse brain by young systemic factors. Science 344, 630–634. https://doi.org/10.1126/science.1251141.

Katsouri, L., Lim, Y.M., Blondrath, K., Eleftheriadou, I., Lombardero, L., Birch, A.M., Mirzaei, N., Irvine, E.E., Mazarakis, N.D., Sastre, M., 2016. PPARγ-coactivator-1α gene transfer reduces neuronal loss and amyloid-β generation by reducing β-secretase in an Alzheimer's disease model. Proc. Natl. Acad. Sci. USA 113, 12292–12297. https://doi.org/10.1073/pnas.1606171113.

Kempermann, G., Kuhn, H.G., Gage, F.H., 1998. Experience-induced neurogenesis in the senescent dentate gyrus. J. Neurosci. 18, 3206–3212.

Keren-Shaul, H., Spinrad, A., Weiner, A., Matcovitch-Natan, O., Dvir-Szternfeld, R., Ulland, T.K., David, E., Baruch, K., Lara-Astaiso, D., Toth, B., Itzkovitz, S., Colonna, M., Schwartz, M., Amit, I., 2017. A unique microglia type associated with restricting development of alzheimer's disease. Cell 169 (1276–1290), e1217–1290. e17. https://doi.org/10.1016/j.cell.2017.05.018.

Khodadadi, D., Gharakhanlou, R., Naghdi, N., Salimi, M., Azimi, M., Shahed, A., Heysieattalab, S., 2018. Treadmill exercise ameliorates spatial learning and memory deficits through improving the clearance of peripheral and central amyloid-beta levels. Neurochem. Res. 43, 1561–1574. https://doi.org/10.1007/s11064-018-2571-2.

Kim, D., Cho, J., Kang, H., 2019. Protective effect of exercise training against the progression of Alzheimer's disease in 3xTg-AD mice. Behav. Brain Res. 374, 112105 https://doi.org/10.1016/j.bbr.2019.112105.

Kim, T.W., Park, S.S., Park, J.Y., Park, H.S., 2020. Infusion of plasma from exercised mice ameliorates cognitive dysfunction by increasing hippocampal neuroplasticity and mitochondrial functions in 3xTg-AD mice. Int J. Mol. Sci. 21 https://doi.org/10.3390/ijms21093291.

Kisler, K., Nelson, A.R., Montagne, A., Zlokovic, B.V., 2017. Cerebral blood flow regulation and neurovascular dysfunction in Alzheimer disease. Nat. Rev. Neurosci. 18, 419–434. https://doi.org/10.1038/nrn.2017.48.

Kivimäki, M., Singh-Manoux, A., Pentti, J., Sabia, S., Nyberg, S.T., Alfredsson, L., Goldberg, M., Knutsson, A., Koskenvuo, M., Koskinen, A., Kouvonen, A., Nordin, M., Oksanen, T., Strandberg, T., Suominen, S.B., Theorell, T., Vahtera, J., Väänänen, A., Virtanen, M., Westerholm, P., Westerlund, H., Zins, M., Seshadri, S., Batty, G.D., Sipilä, P.N., Shipley, M.J., Lindbohm, J.V., Ferrie, J.E., Jokela, M., IPD-Work, c, 2019. Physical inactivity, cardiometabolic disease, and risk of dementia: an individual-participant meta-analysis. Bmj 365, l1495. https://doi.org/10.1136/bmj.l1495.

Kobro-Flatmoen, A., Lagartos-Donate, M.J., Aman, Y., Edison, P., Witter, M.P., Fang, E. F., 2021. Re-emphasizing early Alzheimer's disease pathology starting in select entorhinal neurons, with a special focus on mitophagy. Ageing Res. Rev. 67, 101307 https://doi.org/10.1016/j.arr.2021.101307.

Kodama, S., Saito, K., Tanaka, S., Maki, M., Yachi, Y., Asumi, M., Sugawara, A., Totsuka, K., Shimano, H., Ohashi, Y., Yamada, N., Sone, H., 2009. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. Jama 301, 2024–2035. https://doi.org/10.1001/jama.2009.681.

Kovacevic, A., Fenesi, B., Paolucci, E., Heisz, J.J., 2019. The effects of aerobic exercise intensity on memory in older adults. Appl. Physiol. Nutr. Metab. 45, 591–600. https://doi.org/10.1139/apnm-2019-0495.

Kuhn, H.G., Dickinson-Anson, H., Gage, F.H., 1996. Neurogenesis in the dentate gyrus of the adult rat: age-related decrease of neuronal progenitor proliferation. J. Neurosci. 16, 2027–2033.

Kujach, S., Olek, R.A., Byun, K., Suwabe, K., Sitek, E.J., Ziemann, E., Laskowski, R., Soya, H., 2019. Acute sprint interval exercise increases both cognitive functions and peripheral neurotrophic factors in humans: the possible involvement of lactate. Front. Neurosci. 13, 1455. https://doi.org/10.3389/fnins.2019.01455.

Kulmala, J., Solomon, A., Kåreholt, I., Ngandu, T., Rantanen, T., Laatikainen, T., Soininen, H., Tuomilehto, J., Kivipelto, M., 2014. Association between mid- to late life physical fitness and dementia: evidence from the CAIDE study. J. Intern. Med. 276, 296–307. https://doi.org/10.1111/joim.12202.

Kurl, S., Laukkanen, J.A., Lonnroos, E., Remes, A.M., Soininen, H., 2018. Cardiorespiratory fitness and risk of dementia: a prospective population-based cohort study. Age Ageing 47, 611–614. https://doi.org/10.1093/ageing/afy060.

Lamb, S.E., Sheehan, B., Atherton, N., Nichols, V., Collins, H., Mistry, D., Dosanjh, S., Slowther, A.M., Khan, I., Petrou, S., Lall, R., DAPA Trial, I., 2018. Dementia And Physical Activity (DAPA) trial of moderate to high intensity exercise training for people with dementia: randomised controlled trial. Bmj 361, k1675. https://doi.org/10.1136/bmj.k1675.

Lane, C.A., Barnes, J., Nicholas, J.M., Sudre, C.H., Cash, D.M., Malone, I.B., Parker, T.D., Keshavan, A., Buchanan, S.M., Keuss, S.E., James, S.N., Lu, K., Murray-Smith, H., Wong, A., Gordon, E., Coath, W., Modat, M., Thomas, D., Richards, M., Fox, N.C., Schott, J.M., 2019. Associations between vascular risk across adulthood and brain pathology in late life: evidence from a british birth cohort. JAMA Neurol. 77, 1–9. https://doi.org/10.1001/jamaneurol.2019.3774.

Law, L.L., Rol, R.N., Schultz, S.A., Dougherty, R.J., Edwards, D.F., Koscik, R.L., Gallagher, C.L., Carlsson, C.M., Bendlin, B.B., Zetterberg, H., Blennow, K., Asthana, S., Sager, M.A., Hermann, B.P., Johnson, S.C., Cook, D.B., Okonkwo, O.C., 2018. Moderate intensity physical activity associates with CSF biomarkers in a cohort at risk for Alzheimer's disease. Alzheimers Dement 10, 188–195. https://doi.org/10.1016/j.dadm.2018.01.001.

Lev-Vachnish, Y., Cadury, S., Rotter-Maskowitz, A., Feldman, N., Roichman, A., Illouz, T., Varvak, A., Nicola, R., Madar, R., Okun, E., 2019. L-Lactate promotes adult hippocampal neurogenesis. Front. Neurosci. 13, 403. https://doi.org/10.3389/fnins.2019.00403.

Li, B., Liang, F., Ding, X., Yan, Q., Zhao, Y., Zhang, X., Bai, Y., Huang, T., Xu, B., 2019. Interval and continuous exercise overcome memory deficits related to beta-Amyloid accumulation through modulating mitochondrial dynamics. Behav. Brain Res. 112171, 112171 https://doi.org/10.1016/j.bbr.2019.112171.

Li, X., Tsolis, K.C., Koper, M.J., Ronisz, A., Ospitalieri, S., von Arnim, C., Vandenberghe, R., Tousseyn, T., Scheuerle, A., Economou, A., Carpentier, S., Otto, M., Thal, D.R., 2021. Sequence of proteome profiles in preclinical and symptomatic Alzheimer's disease. Alzheimer'S. Dement. J. Alzheimer'S. Assoc. 17, 946–958. https://doi.org/10.1002/alz.12345.

Liang, K.Y., Mintun, M.A., Fagan, A.M., Goate, A.M., Bugg, J.M., Holtzman, D.M., Morris, J.C., Head, D., 2010. Exercise and Alzheimer's disease biomarkers in cognitively normal older adults. Ann. Neurol. 68, 311–318. https://doi.org/10.1002/ana.22096.

Lin, X., Zhang, X., Guo, J., Roberts, C.K., McKenzie, S., Wu, W.C., Liu, S., Song, Y., 2015. Effects of exercise training on cardiorespiratory fitness and biomarkers of cardiometabolic health: a systematic review and meta-analysis of randomized controlled trials. J. Am. Heart Assoc. 4 https://doi.org/10.1161/jaha.115.002014.

Lipnicki, D.M., Makkar, S.R., Crawford, J.D., Thalamuthu, A., Kochan, N.A., Lima-Costa, M.F., Castro-Costa, E., Ferri, C.P., Brayne, C., Stephan, B., Llibre-Rodriguez, J. J., Llibre-Guerra, J.J., Valhuerdi-Cepero, A.J., Lipton, R.B., Katz, M.J., Derby, C.A., Ritchie, K., Ancelin, M.L., Carrière, I., Scarmeas, N., Yannakoulia, M., Hadjigeorgiou, G.M., Lam, L., Chan, W.C., Fung, A., Guaita, A., Vaccaro, R., Davin, A., Kim, K.W., Han, J.W., Suh, S.W., Riedel-Heller, S.G., Roehr, S., Pabst, A., van Boxtel, M., Köhler, S., Deckers, K., Ganguli, M., Jacobsen, E.P., Hughes, T.F., Anstey, K.J., Cherbuin, N., Haan, M.N., Aiello, A.E., Dang, K., Kumagai, S., Chen, T., Narazaki, K., Ng, T.P., Gao, Q., Nyunt, M., Scazufca, M., Brodaty, H., Numbers, K., Trollor, J.N., Meguro, K., Yamaguchi, S., Ishii, H., Lobo, A., Lopez-Anton, R., Santabárbara, J., Leung, Y., Lo, J.W., Popovic, G., Sachdev, P.S., for Cohort Studies of Memory in an International Consortium, (, 2019. Determinants of cognitive performance and decline in 20 diverse ethno-regional groups: a COSMIC collaboration cohort study. PLoS Med. 16, e1002853 https://doi.org/10.1371/journal.pmed.1002853.

Liu, H.L., Zhao, G., Zhang, H., Shi, L.D., 2013. Long-term treadmill exercise inhibits the progression of Alzheimer's disease-like neuropathology in the hippocampus of APP/PS1 transgenic mice. Behav. Brain Res. 256, 261–272. https://doi.org/10.1016/j.bbr.2013.08.008.

Livingston, G., Sommerlad, A., Orgeta, V., Costafreda, S.G., Huntley, J., Ames, D., Ballard, C., Banerjee, S., Burns, A., Cohen-Mansfield, J., Cooper, C., Fox, N., Gitlin, L. N., Howard, R., Kales, H.C., Larson, E.B., Ritchie, K., Rockwood, K., Sampson, E.L., Samus, Q., Schneider, L.S., Selbæk, G., Teri, L., Mukadam, N., 2017. Dementia prevention, intervention, and care. Lancet 390, 2673–2734. https://doi.org/10.1016/s0140-6736(17)31363-6.

Livingston, G., Huntley, J., Sommerlad, A., Ames, D., Ballard, C., Banerjee, S., Brayne, C., Burns, A., Cohen-Mansfield, J., Cooper, C., Costafreda, S.G., Dias, A., Fox, N., Gitlin, L.N., Howard, R., Kales, H.C., Kivimäki, M., Larson, E.B., Ogunniyi, A., Orgeta, V., Ritchie, K., Rockwood, K., Sampson, E.L., Samus, Q., Schneider, L.S., Selbæk, G., Teri, L., Mukadam, N., 2020. Dementia prevention, intervention, and

care: 2020 report of the Lancet Commission. Lancet 396, 413–446. https://doi.org/10.1016/s0140-6736(20)30367-6.

Long, J.M., Holtzman, D.M., 2019. Alzheimer disease: an update on pathobiology and treatment strategies. Cell 179, 312–339. https://doi.org/10.1016/j.cell.2019.09.001.

Long, Z., Chen, J., Zhao, Y., Zhou, W., Yao, Q., Wang, Y., He, G., 2020. Dynamic changes of autophagic flux induced by Abeta in the brain of postmortem Alzheimer's disease patients, animal models and cell models. Aging 12, 10912–10930. https://doi.org/10.18632/aging.103305.

Lopez-Lopez, C., LeRoith, D., Torres-Aleman, I., 2004. Insulin-like growth factor I is required for vessel remodeling in the adult brain. Proc. Natl. Acad. Sci. USA 101, 9833–9838. https://doi.org/10.1073/pnas.0400337101.

Lourenco, M.V., Frozza, R.L., de Freitas, G.B., Zhang, H., Kincheski, G.C., Ribeiro, F.C., Gonçalves, R.A., Clarke, J.R., Beckman, D., Staniszewski, A., Berman, H., Guerra, L. A., Forny-Germano, L., Meier, S., Wilcock, D.M., de Souza, J.M., Alves-Leon, S., Prado, V.F., Prado, M., Abisambra, J.F., Tovar-Moll, F., Mattos, P., Arancio, O., Ferreira, S.T., De Felice, F.G., 2019. Exercise-linked FNDC5/irisin rescues synaptic plasticity and memory defects in Alzheimer's models. Nat. Med. 25, 165–175. https://doi.org/10.1038/s41591-018-0275-4.

Lourenco, M.V., Ribeiro, F.C., Sudo, F.K., Drummond, C., Assunção, N., Vanderborght, B., Tovar-Moll, F., Mattos, P., De Felice, F.G., Ferreira, S.T., 2020. Cerebrospinal fluid irisin correlates with amyloid-β, BDNF, and cognition in Alzheimer's disease. Alzheimers Dement 12, e12034. https://doi.org/10.1002/dad2.12034.

Lourida, I., Hannon, E., Littlejohns, T.J., Langa, K.M., Hyppönen, E., Kuzma, E., Llewellyn, D.J., 2019. Association of lifestyle and genetic risk with incidence of dementia. Jama 322, 430. https://doi.org/10.1001/jama.2019.9879.

Lu, X., Moeini, M., Li, B., de Montgolfier, O., Lu, Y., Bélanger, S., Thorin, É., Lesage, F., 2020. Voluntary exercise increases brain tissue oxygenation and spatially homogenizes oxygen delivery in a mouse model of Alzheimer's disease. Neurobiol. Aging 88, 11–23. https://doi.org/10.1016/j.neurobiolaging.2019.11.015.

Lu, Y., Dong, Y., Tucker, D., Wang, R., Ahmed, M.E., Brann, D., Zhang, Q., 2017. Treadmill exercise exerts neuroprotection and regulates microglial polarization and oxidative stress in a streptozotocin-induced rat model of sporadic Alzheimer's disease. J. Alzheimer'S. Dis. JAD 56, 1469–1484. https://doi.org/10.3233/jad-160869.

Maass, A., Düzel, S., Goerke, M., Becke, A., Sobieray, U., Neumann, K., Lövden, M., Lindenberger, U., Bäckman, L., Braun-Dullaeus, R., Ahrens, D., Heinze, H.J., Müller, N.G., Düzel, E., 2015. Vascular hippocampal plasticity after aerobic exercise in older adults. Mol. Psychiatry 20, 585–593. https://doi.org/10.1038/mp.2014.114.

Maass, A., Düzel, S., Brigadski, T., Goerke, M., Becke, A., Sobieray, U., Neumann, K., Lövdén, M., Lindenberger, U., Bäckman, L., Braun-Dullaeus, R., Ahrens, D., Heinze, H.J., Müller, N.G., Lessmann, V., Sendtner, M., Düzel, E., 2016. Relationships of peripheral IGF-1, VEGF and BDNF levels to exercise-related changes in memory, hippocampal perfusion and volumes in older adults. Neuroimage 131, 142–154. https://doi.org/10.1016/j.neuroimage.2015.10.084.

Magistretti, P.J., Allaman, I., 2018. Lactate in the brain: from metabolic end-product to signalling molecule. Nat. Rev. Neurosci. 19, 235–249. https://doi.org/10.1038/nrn.2018.19.

Manczak, M., Kandimalla, R., Yin, X., Reddy, P.H., 2018. Hippocampal mutant APP and amyloid beta-induced cognitive decline, dendritic spine loss, defective autophagy, mitophagy and mitochondrial abnormalities in a mouse model of Alzheimer's disease. Hum. Mol. Genet. 27, 1332–1342. https://doi.org/10.1093/hmg/ddy042.

Marinus, N., Hansen, D., Feys, P., Meesen, R., Timmermans, A., Spildooren, J., 2019. The impact of different types of exercise training on peripheral blood brain-derived neurotrophic factor concentrations in older adults: a meta-analysis. Sports Med. 49, 1529–1546. https://doi.org/10.1007/s40279-019-01148-z.

McLean, C.A., Cherny, R.A., Fraser, F.W., Fuller, S.J., Smith, M.J., Beyreuther, K., Bush, A.I., Masters, C.L., 1999. Soluble pool of Abeta amyloid as a determinant of severity of neurodegeneration in Alzheimer's disease. Ann. Neurol. 46, 860–866. https://doi.org/10.1002/1531-8249(199912)46:6<860::aid-ana8>3.0.co;2-m.

Middeldorp, J., Lehallier, B., Villeda, S.A., Miedema, S.S., Evans, E., Czirr, E., Zhang, H., Luo, J., Stan, T., Mosher, K.I., Masliah, E., Wyss-Coray, T., 2016. Preclinical assessment of young blood plasma for Alzheimer Disease. JAMA Neurol. 73, 1325–1333. https://doi.org/10.1001/jamaneurol.2016.3185.

Middleton, L.E., Barnes, D.E., Lui, L.Y., Yaffe, K., 2010. Physical activity over the life course and its association with cognitive performance and impairment in old age. J. Am. Geriatr. Soc. 58, 1322–1326. https://doi.org/10.1111/j.1532-5415.2010.02903.x.

Minn, Y.K., Choi, S.H., Suh, Y.J., Jeong, J.H., Kim, E.J., Kim, J.H., Park, K.W., Park, M.H., Youn, Y.C., Yoon, B., Choi, S.J., Oh, Y.K., Yoon, S.J., 2018. Effect of physical activity on the progression of alzheimer's disease: the clinical research center for dementia of south korea study. J. Alzheimer'S. Dis. JAD 66, 249–261. https://doi.org/10.3233/jad-180333.

Mizoguchi, Y., Yao, H., Imamura, Y., Hashimoto, M., Monji, A., 2020. Lower brain-derived neurotrophic factor levels are associated with age-related memory impairment in community-dwelling older adults: the sefuri study. Sci. Rep. 10, 16442. https://doi.org/10.1038/s41598-020-73576-1.

Monnier, A., Prigent-Tessier, A., Quirié, A., Bertrand, N., Savary, S., Gondcaille, C., Garnier, P., Demougeot, C., Marie, C., 2017. Brain-derived neurotrophic factor of the cerebral microvasculature: a forgotten and nitric oxide-dependent contributor of brain-derived neurotrophic factor in the brain. Acta Physiol. 219, 790–802. https://doi.org/10.1111/apha.12743.

Moon, H.Y., Becke, A., Berron, D., Becker, B., Sah, N., Benoni, G., Janke, E., Lubejko, S. T., Greig, N.H., Mattison, J.A., Duzel, E., van Praag, H., 2016. Running-induced systemic cathepsin b secretion is associated with memory function. Cell Metab. 24, 332–340. https://doi.org/10.1016/j.cmet.2016.05.025.

Moore, K.M., Girens, R.E., Larson, S.K., Jones, M.R., Restivo, J.L., Holtzman, D.M., Cirrito, J.R., Yuede, C.M., Zimmerman, S.D., Timson, B.F., 2016. A spectrum of exercise training reduces soluble Abeta in a dose-dependent manner in a mouse model of Alzheimer's disease. Neurobiol. Dis. 85, 218–224. https://doi.org/10.1016/j.nbd.2015.11.004.

Morena, F., Argentati, C., Trotta, R., Crispoltoni, L., Stabile, A., Pistilli, A., di Baldassarre, A., Calafiore, R., Montanucci, P., Basta, G., Pedrinolla, A., Smania, N., Venturelli, M., Schena, F., Naro, F., Emiliani, C., Rende, M., Martino, S., 2017. A Comparison of lysosomal enzymes expression levels in peripheral blood of mild- and severe-Alzheimer's disease and mci patients: implications for regenerative medicine approaches. Int J. Mol. Sci. 18 https://doi.org/10.3390/ijms18081806.

Moreno-Jiménez, E.P., Flor-García, M., Terreros-Roncal, J., Rábano, A., Cafini, F., Pallas-Bazarra, N., Ávila, J., Llorens-Martín, M., 2019. Adult hippocampal neurogenesis is abundant in neurologically healthy subjects and drops sharply in patients with Alzheimer's disease. Nat. Med. 25, 554–560. https://doi.org/10.1038/s41591-019-0375-9.

Morland, C., Andersson, K.A., Haugen, Ø.P., Hadzic, A., Kleppa, L., Gille, A., Rinholm, J. E., Palibrk, V., Diget, E.H., Kennedy, L.H., Stølen, T., Hennestad, E., Moldestad, O., Cai, Y., Puchades, M., Offermanns, S., Vervaeke, K., Bjørås, M., Wisløff, U., Storm-Mathisen, J., Bergersen, L.H., 2017. Exercise induces cerebral VEGF and angiogenesis via the lactate receptor HCAR1. Nat. Commun. 8, 15557. https://doi.org/10.1038/ncomms15557.

Morris, J.K., Vidoni, E.D., Johnson, D.K., Van Sciver, A., Mahnken, J.D., Honea, R.A., Wilkins, H.M., Brooks, W.M., Billinger, S.A., Swerdlow, R.H., Burns, J.M., 2017. Aerobic exercise for Alzheimer's disease: a randomized controlled pilot trial. PloS One 12, e0170547. https://doi.org/10.1371/journal.pone.0170547.

Müller, J., Chan, K., Myers, J.N., 2017. Association between exercise capacity and late onset of dementia, alzheimer disease, and cognitive impairment. Mayo Clin. Proc. 92, 211–217. https://doi.org/10.1016/j.mayocp.2016.10.020.

Myers, J., Prakash, M., Froelicher, V., Do, D., Partington, S., Atwood, J.E., 2002. Exercise capacity and mortality among men referred for exercise testing. New Engl. J. Med. 346, 793–801. https://doi.org/10.1056/NEJMoa011858.

Nagahara, A.H., Tuszynski, M.H., 2011. Potential therapeutic uses of BDNF in neurological and psychiatric disorders. Nat. Rev. Drug Disco 10, 209–219. https://doi.org/10.1038/nrd3366.

Näslund, J., Haroutunian, V., Mohs, R., Davis, K.L., Davies, P., Greengard, P., Buxbaum, J.D., 2000. Correlation between elevated levels of amyloid beta-peptide in the brain and cognitive decline. Jama 283, 1571–1577. https://doi.org/10.1001/jama.283.12.1571.

Nelson, P.T., Alafuzoff, I., Bigio, E.H., Bouras, C., Braak, H., Cairns, N.J., Castellani, R.J., Crain, B.J., Davies, P., Del Tredici, K., Duyckaerts, C., Frosch, M.P., Haroutunian, V., Hof, P.R., Hulette, C.M., Hyman, B.T., Iwatsubo, T., Jellinger, K.A., Jicha, G.A., Kövari, E., Kukull, W.A., Leverenz, J.B., Love, S., Mackenzie, I.R., Mann, D.M., Masliah, E., McKee, A.C., Montine, T.J., Morris, J.C., Schneider, J.A., Sonnen, J.A., Thal, D.R., Trojanowski, J.Q., Troncoso, J.C., Wisniewski, T., Woltjer, R.L., Beach, T. G., 2012. Correlation of Alzheimer disease neuropathologic changes with cognitive status: a review of the literature. J. Neuropathol. Exp. Neurol. 71, 362–381. https://doi.org/10.1097/NEN.0b013e31825018f7.

Ng, T.K.S., Ho, C.S.H., Tam, W.W.S., Kua, E.H., Ho, R.C., 2019. Decreased Serum Brain-Derived Neurotrophic Factor (BDNF) levels in patients with Alzheimer's Disease (AD): a systematic review and meta-analysis. Int. J. Mol. Sci. 20 https://doi.org/10.3390/ijms20020257.

Ngandu, T., Lehtisalo, J., Solomon, A., Levälahti, E., Ahtiluoto, S., Antikainen, R., Bäckman, L., Hänninen, T., Jula, A., Laatikainen, T., Lindström, J., Mangialasche, F., Paajanen, T., Pajala, S., Peltonen, M., Rauramaa, R., Stigsdotter-Neely, A., Strandberg, T., Tuomilehto, J., Soininen, H., Kivipelto, M., 2015. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. Lancet 385, 2255–2263. https://doi.org/10.1016/s0140-6736(15)60461-5.

Nigam, S.M., Xu, S., Kritikou, J.S., Marosi, K., Brodin, L., Mattson, M.P., 2017. Exercise and BDNF reduce Aβ production by enhancing α-secretase processing of APP. J. Neurochem. 142, 286–296. https://doi.org/10.1111/jnc.14034.

Nilsson, J., Ekblom, Ö., Ekblom, M., Lebedev, A., Tarassova, O., Moberg, M., Lövdén, M., 2020. Acute increases in brain-derived neurotrophic factor in plasma following physical exercise relates to subsequent learning in older adults. Sci. Rep. 10, 4395. https://doi.org/10.1038/s41598-020-60124-0.

Noda, Y., Kuzuya, A., Tanigawa, K., Araki, M., Kawai, R., Ma, B., Sasakura, Y., Maesako, M., Tashiro, Y., Miyamoto, M., Uemura, K., Okuno, Y., Kinoshita, A., 2018. Fibronectin type III domain-containing protein 5 interacts with APP and decreases amyloid β production in Alzheimer's disease. Mol. Brain 11, 61. https://doi.org/10.1186/s13041-018-0401-8.

Northey, J.M., Cherbuin, N., Pumpa, K.L., Smee, D.J., Rattray, B., 2018. Exercise interventions for cognitive function in adults older than 50: a systematic review with meta-analysis. Br. J. Sports Med. 52, 154–160. https://doi.org/10.1136/bjsports-2016-096587.

Nortley, R., Korte, N., Izquierdo, P., Hirunpattarasilp, C., Mishra, A., Jaunmuktane, Z., Kyrargyri, V., Pfeiffer, T., Khennouf, L., Madry, C., Gong, H., Richard-Loendt, A., Huang, W., Saito, T., Saido, T.C., Brandner, S., Sethi, H., Attwell, D., 2019. Amyloid beta oligomers constrict human capillaries in Alzheimer's disease via signaling to pericytes. Science 365. https://doi.org/10.1126/science.aav9518.

Norton, S., Matthews, F.E., Barnes, D.E., Yaffe, K., Brayne, C., 2014. Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. Lancet Neurol. 13, 788–794. https://doi.org/10.1016/s1474-4422(14)70136-x.

Ogino, E., Manly, J.J., Schupf, N., Mayeux, R., Gu, Y., 2019. Current and past leisure time physical activity in relation to risk of Alzheimer's disease in older adults. Alzheimers Dement 15, 1603–1611. https://doi.org/10.1016/j.jalz.2019.07.013.

Öhman, H., Savikko, N., Strandberg, T.E., Kautiainen, H., Raivio, M.M., Laakkonen, M.L., Tilvis, R., Pitkälä, K.H., 2016. Effects of exercise on cognition: the finnish alzheimer disease exercise trial: a randomized, controlled trial. J. Am. Geriatr. Soc. 64, 731–738. https://doi.org/10.1111/jgs.14059.

Okonkwo, O.C., Schultz, S.A., Oh, J.M., Larson, J., Edwards, D., Cook, D., Koscik, R., Gallagher, C.L., Dowling, N.M., Carlsson, C.M., Bendlin, B.B., LaRue, A., Rowley, H. A., Christian, B.T., Asthana, S., Hermann, B.P., Johnson, S.C., Sager, M.A., 2014. Physical activity attenuates age-related biomarker alterations in preclinical AD. Neurology 83, 1753–1760. https://doi.org/10.1212/wnl.0000000000000964.

Olaya, B., Moneta, M.V., Bobak, M., Haro, J.M., Demakakos, P., 2019. Cardiovascular risk factors and memory decline in middle-aged and older adults: the english longitudinal study of ageing. BMC Geriatr. 19, 337. https://doi.org/10.1186/s12877-019-1350-5.

Palmer, T.D., Willhoite, A.R., Gage, F.H., 2000. Vascular niche for adult hippocampal neurogenesis. J. Comp. Neurol. 425, 479–494.

Pang, R., Wang, X., Pei, F., Zhang, W., Shen, J., Gao, X., Chang, C., 2019. Regular exercise enhances cognitive function and intracephalic GLUT expression in Alzheimer's disease model mice. J. Alzheimer'S. Dis. JAD 72, 83–96. https://doi.org/10.3233/jad-190328.

Pani, J., Reitlo, L.S., Evensmoen, H.R., Lydersen, S., Wisløff, U., Stensvold, D., Håberg, A. K., 2021. Effect of 5 Years of exercise intervention at different intensities on brain structure in older adults from the general population: a generation 100 substudy. Clin. Inter. Aging 16, 1485–1501. https://doi.org/10.2147/cia.S318679.

Park, H.S., Park, S.S., Kim, C.J., Shin, M.S., Kim, T.W., 2019a. Exercise alleviates cognitive functions by enhancing hippocampal insulin signaling and neuroplasticity in high-fat diet-induced obesity. Nutrients 11. https://doi.org/10.3390/nu11071603.

Park, J., Kim, J., Mikami, T., 2021. Exercise-induced lactate release mediates mitochondrial biogenesis in the hippocampus of mice via monocarboxylate transporters. Front. Physiol. 12, 736905 https://doi.org/10.3389/fphys.2021.736905.

Park, J.H., Hong, J.H., Lee, S.W., Ji, H.D., Jung, J.A., Yoon, K.W., Lee, J.I., Won, K.S., Song, B.I., Kim, H.W., 2019b. The effect of chronic cerebral hypoperfusion on the pathology of Alzheimer's disease: a positron emission tomography study in rats. Sci. Rep. 9, 14102. https://doi.org/10.1038/s41598-019-50681-4.

Parodi-Rullan, R., Sone, J.Y., Fossati, S., 2019. Endothelial mitochondrial dysfunction in cerebral amyloid angiopathy and alzheimer's disease. J. Alzheimer'S. Dis. JAD 72, 1019–1039. https://doi.org/10.3233/jad-190357.

Pase, M.P., Beiser, A., Enserro, D., Xanthakis, V., Aparicio, H., Satizabal, C.L., Himali, J. J., Kase, C.S., Vasan, R.S., DeCarli, C., Seshadri, S., 2016. Association of ideal cardiovascular health with vascular brain injury and incident dementia. Stroke 47, 1201–1206. https://doi.org/10.1161/strokeaha.115.012608.

Pase, M.P., Davis-Plourde, K., Himali, J.J., Satizabal, C.L., Aparicio, H., Seshadri, S., Beiser, A.S., DeCarli, C., 2018. Vascular risk at younger ages most strongly associates with current and future brain volume. Neurology 91, e1479–e1486. https://doi.org/10.1212/wnl.0000000000006360.

Patterson, C., 2018. World Alzheimer Report 2018. Alzheimer's Disease International, London.

Pedrinolla, A., Schena, F., Venturelli, M., 2017. Resilience to Alzheimer's disease: the role of physical activity. Curr. Alzheimer Res. 14, 546–553. https://doi.org/10.2174/1567205014666170111145817.

Pedrinolla, A., Venturelli, M., Fonte, C., Munari, D., Benetti, M.V., Rudi, D., Tamburin, S., Muti, E., Zanolla, L., Smania, N., Schena, F., 2018. Exercise training on locomotion in patients with Alzheimer's disease: a feasibility study. J. Alzheimers Dis. 61, 1599–1609. https://doi.org/10.3233/jad-170625.

Pedrinolla, A., Venturelli, M., Tamburin, S., Fonte, C., Stabile, A.M., Galazzo, I.B., Ghinassi, B., Venneri, M.A., Pizzini, F.B., Muti, E., Smania, N., Di Baldassarre, A., Naro, F., Rende, M., Schena, F., 2019. Non-Aβ-dependent factors associated with global cognitive and physical function in Alzheimer's disease: a pilot multivariate analysis. J. Clin. Med 8. https://doi.org/10.3390/jcm8020224.

Pedrinolla, A., Venturelli, M., Fonte, C., Tamburin, S., Di Baldassarre, A., Naro, F., Varalta, V., Giuriato, G., Ghinassi, B., Muti, E., Smania, N., Schena, F., 2020. Exercise training improves vascular function in patients with Alzheimer's disease. Eur. J. Appl. Physiol. 120, 2233–2245. https://doi.org/10.1007/s00421-020-04447-w.

Peng, H., Wang, Q., Lou, T., Qin, J., Jung, S., Shetty, V., Li, F., Wang, Y., Feng, X.H., Mitch, W.E., Graham, B.H., Hu, Z., 2017. Myokine mediated muscle-kidney crosstalk suppresses metabolic reprogramming and fibrosis in damaged kidneys. Nat. Commun. 8, 1493. https://doi.org/10.1038/s41467-017-01646-6.

Pentikäinen, H., Savonen, K., Ngandu, T., Solomon, A., Komulainen, P., Paajanen, T., Antikainen, R., Kivipelto, M., Soininen, H., Rauramaa, R., 2019. Cardiorespiratory fitness and cognition: longitudinal associations in the FINGER study. J. Alzheimer'S. Dis. JAD 68, 961–968. https://doi.org/10.3233/jad-180897.

Pereira, A.C., Huddleston, D.E., Brickman, A.M., Sosunov, A.A., Hen, R., McKhann, G.M., Sloan, R., Gage, F.H., Brown, T.R., Small, S.A., 2007. An in vivo correlate of exercise-induced neurogenesis in the adult dentate gyrus. Proc. Natl. Acad. Sci. USA 104, 5638–5643. https://doi.org/10.1073/pnas.0611721104.

Pini, L., Pievani, M., Bocchetta, M., Altomare, D., Bosco, P., Cavedo, E., Galluzzi, S., Marizzoni, M., Frisoni, G.B., 2016. Brain atrophy in Alzheimer's Disease and aging. Ageing Res. Rev. 30, 25–48. https://doi.org/10.1016/j.arr.2016.01.002.

Powers, R.K., Culp-Hill, R., Ludwig, M.P., Smith, K.P., Waugh, K.A., Minter, R., Tuttle, K. D., Lewis, H.C., Rachubinski, A.L., Granrath, R.E., Carmona-Iragui, M., Wilkerson, R. B., Kahn, D.E., Joshi, M., Lleó, A., Blesa, R., Fortea, J., D'Alessandro, A., Costello, J. C., Sullivan, K.D., Espinosa, J.M., 2019. Trisomy 21 activates the kynurenine pathway via increased dosage of interferon receptors. Nat. Commun. 10, 4766. https://doi.org/10.1038/s41467-019-12739-9.

Rabin, J.S., Klein, H., Kirn, D.R., Schultz, A.P., Yang, H.S., Hampton, O., Jiang, S., Buckley, R.F., Viswanathan, A., Hedden, T., Pruzin, J., Yau, W.W., Guzmán-Vélez, E., Quiroz, Y.T., Properzi, M., Marshall, G.A., Rentz, D.M., Johnson, K.A., Sperling, R.A., Chhatwal, J.P., 2019. Associations of physical activity and β-amyloid with longitudinal cognition and neurodegeneration in clinically normal older adults. JAMA Neurol. 76, 1203–1210. https://doi.org/10.1001/jamaneurol.2019.1879.

Reas, E.T., Laughlin, G.A., Bergstrom, J., Kritz-Silverstein, D., Richard, E.L., Barrett-Connor, E., McEvoy, L.K., 2019. Lifetime physical activity and late-life cognitive function: the rancho bernardo study. Age Ageing 48, 241–246. https://doi.org/10.1093/ageing/afy188.

Reddy, P.H., Yin, X., Manczak, M., Kumar, S., Pradeepkiran, J.A., Vijayan, M., Reddy, A. P., 2018. Mutant APP and amyloid beta-induced defective autophagy, mitophagy, mitochondrial structural and functional changes and synaptic damage in hippocampal neurons from Alzheimer's disease. Hum. Mol. Genet. 27, 2502–2516. https://doi.org/10.1093/hmg/ddy154.

Redila, V.A., Christie, B.R., 2006. Exercise-induced changes in dendritic structure and complexity in the adult hippocampal dentate gyrus. Neuroscience 137, 1299–1307. https://doi.org/10.1016/j.neuroscience.2005.10.050.

Reiter, K., Nielson, K.A., Smith, T.J., Weiss, L.R., Alfini, A.J., Smith, J.C., 2015. Improved cardiorespiratory fitness is associated with increased cortical thickness in mild cognitive impairment. J. Int. Neuropsychol. Soc. JINS 21, 757–767. https://doi.org/10.1017/s135561771500079x.

Rich, B., Scadeng, M., Yamaguchi, M., Wagner, P.D., Breen, E.C., 2017. Skeletal myofiber vascular endothelial growth factor is required for the exercise training-induced increase in dentate gyrus neuronal precursor cells. J. Physiol. 595, 5931–5943. https://doi.org/10.1113/jp273994.

Roberson, E.D., Scearce-Levie, K., Palop, J.J., Yan, F., Cheng, I.H., Wu, T., Gerstein, H., Yu, G.Q., Mucke, L., 2007. Reducing endogenous tau ameliorates amyloid beta-induced deficits in an Alzheimer's disease mouse model. Science 316, 750–754. https://doi.org/10.1126/science.1141736.

Rosenberg, A., Ngandu, T., Rusanen, M., Antikainen, R., Bäckman, L., Havulinna, S., Hänninen, T., Laatikainen, T., Lehtisalo, J., Levälahti, E., Lindström, J., Paajanen, T., Peltonen, M., Soininen, H., Stigsdotter-Neely, A., Strandberg, T., Tuomilehto, J., Solomon, A., Kivipelto, M., 2018. Multidomain lifestyle intervention benefits a large elderly population at risk for cognitive decline and dementia regardless of baseline characteristics: the FINGER trial. Alzheimer'S. Dement. J. Alzheimer'S. Assoc. 14, 263–270. https://doi.org/10.1016/j.jalz.2017.09.006.

Ross, R., de Lannoy, L., Stotz, P.J., 2015. Separate effects of intensity and amount of exercise on interindividual cardiorespiratory fitness response. Mayo Clin. Proc. 90, 1506–1514. https://doi.org/10.1016/j.mayocp.2015.07.024.

Rovio, S., Spulber, G., Nieminen, L.J., Niskanen, E., Winblad, B., Tuomilehto, J., Nissinen, A., Soininen, H., Kivipelto, M., 2010. The effect of midlife physical activity on structural brain changes in the elderly. Neurobiol. Aging 31, 1927–1936. https://doi.org/10.1016/j.neurobiolaging.2008.10.007.

Ruitenberg, A., den Heijer, T., Bakker, S.L., van Swieten, J.C., Koudstaal, P.J., Hofman, A., Breteler, M.M., 2005. Cerebral hypoperfusion and clinical onset of dementia: the Rotterdam study. Ann. Neurol. 57, 789–794. https://doi.org/10.1002/ana.20493.

Sah, N., Peterson, B.D., Lubejko, S.T., Vivar, C., van Praag, H., 2017. Running reorganizes the circuitry of one-week-old adult-born hippocampal neurons. Sci. Rep. 7, 10903. https://doi.org/10.1038/s41598-017-11268-z.

Samieri, C., Perier, M.C., Gaye, B., Proust-Lima, C., Helmer, C., Dartigues, J.F., Berr, C., Tzourio, C., Empana, J.P., 2018. Association of cardiovascular health level in older age with cognitive decline and incident dementia. Jama 320, 657–664. https://doi.org/10.1001/jama.2018.11499.

Santos-Lozano, A., Pareja-Galeano, H., Sanchis-Gomar, F., Quindós-Rubial, M., Fiuza-Luces, C., Cristi-Montero, C., Emanuele, E., Garatachea, N., Lucia, A., 2016. Physical activity and Alzheimer Disease: a protective association. Mayo Clin. Proc. 91, 999–1020. https://doi.org/10.1016/j.mayocp.2016.04.024.

Savitz, J., 2020. The kynurenine pathway: a finger in every pie. Mol. Psychiatry 25, 131–147. https://doi.org/10.1038/s41380-019-0414-4.

Schiffer, T., Schulte, S., Sperlich, B., Achtzehn, S., Fricke, H., Strüder, H.K., 2011. Lactate infusion at rest increases BDNF blood concentration in humans. Neurosci. Lett. 488, 234–237. https://doi.org/10.1016/j.neulet.2010.11.035.

Schlittler, M., Goiny, M., Agudelo, L.Z., Venckunas, T., Brazaitis, M., Skurvydas, A., Kamandulis, S., Ruas, J.L., Erhardt, S., Westerblad, H., Andersson, D.C., 2016. Endurance exercise increases skeletal muscle kynurenine aminotransferases and plasma kynurenic acid in humans. Am. J. Physiol. Cell Physiol. 310, C836–C840. https://doi.org/10.1152/ajpcell.00053.2016.

Schmidt-Hieber, C., Jonas, P., Bischofberger, J., 2004. Enhanced synaptic plasticity in newly generated granule cells of the adult hippocampus. Nature 429, 184–187. https://doi.org/10.1038/nature02553.

Serra, F.T., Carvalho, A.D., Araujo, B., Torres, L.B., Cardoso, F., Henrique, J.S., Placencia, E., Lent, R., Gomez-Pinilla, F., Arida, R.M., Gomes da Silva, S., 2019. Early exercise induces long-lasting morphological changes in cortical and hippocampal neurons throughout of a sedentary period of rats. Sci. Rep. 9, 13684. https://doi.org/10.1038/s41598-019-50218-9.

Sevigny, J., Chiao, P., Bussière, T., Weinreb, P.H., Williams, L., Maier, M., Dunstan, R., Salloway, S., Chen, T., Ling, Y., O'Gorman, J., Qian, F., Arastu, M., Li, M., Chollate, S., Brennan, M.S., Quintero-Monzon, O., Scannevin, R.H., Arnold, H.M., Engber, T., Rhodes, K., Ferrero, J., Hang, Y., Mikulskis, A., Grimm, J., Hock, C., Nitsch, R.M., Sandrock, A., 2016. The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. Nature 537, 50–56. https://doi.org/10.1038/nature19323.

Sha, S.J., Deutsch, G.K., Tian, L., Richardson, K., Coburn, M., Gaudioso, J.L., Marcal, T., Solomon, E., Boumis, A., Bet, A., Mennes, M., van Oort, E., Beckmann, C.F., Braithwaite, S.P., Jackson, S., Nikolich, K., Stephens, D., Kerchner, G.A., Wyss-Coray, T., 2019. Safety, tolerability, and feasibility of young plasma infusion in the plasma for Alzheimer symptom amelioration study: a randomized clinical trial. JAMA Neurol. 76, 35–40. https://doi.org/10.1001/jamaneurol.2018.3288.

Shah, R.V., Murthy, V.L., Colangelo, L.A., Reis, J., Venkatesh, B.A., Sharma, R., Abbasi, S. A., Goff DC, Jr, Carr, J.J., Rana, J.S., Terry, J.G., Bouchard, C., Sarzynski, M.A., Eisman, A., Neilan, T., Das, S., Jerosch-Herold, M., Lewis, C.E., Carnethon, M., Lewis, G.D., Lima, J.A., 2016. Association of fitness in young adulthood with survival and cardiovascular risk: the coronary artery risk development in young adults (CARDIA) study. JAMA Intern. Med. 176, 87–95. https://doi.org/10.1001/jamainternmed.2015.6309.

Shang, J., Yamashita, T., Zhai, Y., Nakano, Y., Morihara, R., Fukui, Y., Hishikawa, N., Ohta, Y., Abe, K., 2016. Strong impact of chronic cerebral hypoperfusion on neurovascular unit, cerebrovascular remodeling, and neurovascular trophic coupling in Alzheimer's disease model mouse. J. Alzheimer'S. Dis. JAD 52, 113–126. https://doi.org/10.3233/jad-151126.

Shen, J., Wang, D., Wang, X., Gupta, S., Ayloo, B., Wu, S., Prasad, P., Xiong, Q., Xia, J., Ge, S., 2019. Neurovascular coupling in the dentate gyrus regulates adult hippocampal neurogenesis. Neuron 103, 878–890. https://doi.org/10.1016/j.neuron.2019.05.045.

Sheng, B., Wang, X., Su, B., Lee, H.G., Casadesus, G., Perry, G., Zhu, X., 2012. Impaired mitochondrial biogenesis contributes to mitochondrial dysfunction in Alzheimer's disease. J. Neurochem. 120, 419–429. https://doi.org/10.1111/j.1471-4159.2011.07581.x.

Shi, Y., Holtzman, D.M., 2018. Interplay between innate immunity and Alzheimer disease: APOE and TREM2 in the spotlight. Nat. Rev. Immunol. 18, 759–772. https://doi.org/10.1038/s41577-018-0051-1.

Shibata, S., Fujimoto, N., Hastings, J.L., Carrick-Ranson, G., Bhella, P.S., Hearon CM, Jr, Levine, B.D., 2018. The effect of lifelong exercise frequency on arterial stiffness. J. Physiol. 596, 2783–2795. https://doi.org/10.1113/jp275301.

Sleiman, S.F., Henry, J., Al-Haddad, R., El Hayek, L., Abou Haidar, E., Stringer, T., Ulja, D., Karuppagounder, S.S., Holson, E.B., Ratan, R.R., Ninan, I., Chao, M.V., 2016. Exercise promotes the expression of brain derived neurotrophic factor (BDNF) through the action of the ketone body β-hydroxybutyrate. Elife 5. https://doi.org/10.7554/eLife.15092.

Snyder, H.M., Bain, L.J., Brickman, A.M., Carrillo, M.C., Esbensen, A.J., Espinosa, J.M., Fernandez, F., Fortea, J., Hartley, S.L., Head, E., Hendrix, J., Kishnani, P.S., Lai, F., Lao, P., Lemere, C., Mobley, W., Mufson, E.J., Potter, H., Zaman, S.H., Granholm, A. C., Rosas, H.D., Strydom, A., Whitten, M.S., Rafii, M.S., 2020. Further understanding the connection between Alzheimer's disease and down syndrome. Alzheimer'S. Dement. J. Alzheimer'S. Assoc. 16, 1065–1077. https://doi.org/10.1002/alz.12112.

Sobol, N.A., Dall, C.H., Høgh, P., Hoffmann, K., Frederiksen, K.S., Vogel, A., Siersma, V., Waldemar, G., Hasselbalch, S.G., Beyer, N., 2018. Change in fitness and the relation to change in cognition and neuropsychiatric symptoms after aerobic exercise in patients with mild Alzheimer's Disease. J. Alzheimers Dis. 65, 137–145. https://doi.org/10.3233/jad-180253.

Sofi, F., Valecchi, D., Bacci, D., Abbate, R., Gensini, G.F., Casini, A., Macchi, C., 2011. Physical activity and risk of cognitive decline: a meta-analysis of prospective studies. J. Intern. Med. 269, 107–117. https://doi.org/10.1111/j.1365-2796.2010.02281.x.

Spartano, N.L., Himali, J.J., Beiser, A.S., Lewis, G.D., DeCarli, C., Vasan, R.S., Seshadri, S., 2016. Midlife exercise blood pressure, heart rate, and fitness relate to brain volume 2 decades later. Neurology 86, 1313–1319. https://doi.org/10.1212/wnl.0000000000002415.

Steen, E., Terry, B.M., Rivera, E.J., Cannon, J.L., Neely, T.R., Tavares, R., Xu, X.J., Wands, J.R., de la Monte, S.M., 2005. Impaired insulin and insulin-like growth factor expression and signaling mechanisms in Alzheimer's disease–is this type 3 diabetes? J. Alzheimer'S. Dis.: JAD 7, 63–80. https://doi.org/10.3233/jad-2005-7107.

Steen Jensen, C., Portelius, E., Siersma, V., Høgh, P., Wermuth, L., Blennow, K., Zetterberg, H., Waldemar, G., Gregers Hasselbalch, S., Hviid Simonsen, A., 2016. Cerebrospinal fluid amyloid beta and tau concentrations are not modulated by 16 weeks of moderate- to high-intensity physical exercise in patients with Alzheimer disease. Dement Geriatr. Cogn. Disord. 42, 146–158. https://doi.org/10.1159/000449408.

Steiner, J.L., Murphy, E.A., McClellan, J.L., Carmichael, M.D., Davis, J.M., 2011. Exercise training increases mitochondrial biogenesis in the brain. J. Appl. Physiol. 111, 1066–1071. https://doi.org/10.1152/japplphysiol.00343.2011.

Stern, Y., Barnes, C.A., Grady, C., Jones, R.N., Raz, N., 2019. Brain reserve, cognitive reserve, compensation, and maintenance: operationalization, validity, and mechanisms of cognitive resilience. Neurobiol. Aging 83, 124–129. https://doi.org/10.1016/j.neurobiolaging.2019.03.022.

Stranahan, A.M., Khalil, D., Gould, E., 2007. Running induces widespread structural alterations in the hippocampus and entorhinal cortex. Hippocampus 17, 1017–1022. https://doi.org/10.1002/hipo.20348.

Suri, S., Topiwala, A., Chappell, M.A., Okell, T.W., Zsoldos, E., Singh-Manoux, A., Kivimäki, M., Mackay, C.E., Ebmeier, K.P., 2019. Association of Midlife cardiovascular risk profiles with cerebral perfusion at older ages. JAMA Netw. Open 2, e195776. https://doi.org/10.1001/jamanetworkopen.2019.5776.

Swain, R.A., Harris, A.B., Wiener, E.C., Dutka, M.V., Morris, H.D., Theien, B.E., Konda, S., Engberg, K., Lauterbur, P.C., Greenough, W.T., 2003. Prolonged exercise induces angiogenesis and increases cerebral blood volume in primary motor cortex of the rat. Neuroscience 117, 1037–1046.

Swerdlow, R.H., 2018. Mitochondria and mitochondrial cascades in Alzheimer's disease. J. Alzheimer'S. Dis.: JAD 62, 1403–1416. https://doi.org/10.3233/jad-170585.

Takimoto, M., Hamada, T., 2014. Acute exercise increases brain region-specific expression of MCT1, MCT2, MCT4, GLUT1, and COX IV proteins. J. Appl. Physiol. 116, 1238–1250. https://doi.org/10.1152/japplphysiol.01288.2013.

Tan, C.H., Low, K.A., Kong, T., Fletcher, M.A., Zimmerman, B., Maclin, E.L., Chiarelli, A. M., Gratton, G., Fabiani, M., 2017a. Mapping cerebral pulse pressure and arterial compliance over the adult lifespan with optical imaging. PloS One 12, e0171305. https://doi.org/10.1371/journal.pone.0171305.

Tan, Z.S., Spartano, N.L., Beiser, A.S., DeCarli, C., Auerbach, S.H., Vasan, R.S., Seshadri, S., 2017b. Physical activity, brain volume, and dementia risk: the framingham study. J. Gerontol. A Biol. Sci. Med. Sci. 72, 789–795. https://doi.org/10.1093/gerona/glw130.

Tari, A.R., Norevik, C.S., Scrimgeour, N.R., Kobro-Flatmoen, A., Storm-Mathisen, J., Bergersen, L.H., Wrann, C.D., Selbæk, G., Kivipelto, M., Moreira, J., Wisløff, U., 2019. Are the neuroprotective effects of exercise training systemically mediated? Prog. Cardiovasc. Dis. 62, 94–101. https://doi.org/10.1016/j.pcad.2019.02.003.

Tari, A.R., Nauman, J., Zisko, N., Skjellegrind, H.K., Bosnes, I., Bergh, S., Stensvold, D., Selbæk, G., Wisløff, U., 2019. Temporal changes in cardiorespiratory fitness and risk of dementia incidence and mortality: a population-based prospective cohort study. Lancet Public Health 4, e565–e574. https://doi.org/10.1016/S2468-2667(19)30183-5.

Tarumi, T., Rossetti, H., Thomas, B.P., Harris, T., Tseng, B.Y., Turner, M., Wang, C., German, Z., Martin-Cook, K., Stowe, A.M., Womack, K.B., Mathews, D., Kerwin, D. R., Hynan, L., Diaz-Arrastia, R., Lu, H., Cullum, C.M., Zhang, R., 2019. Exercise training in amnestic mild cognitive impairment: a one-year randomized controlled trial. J. Alzheimers Dis. 71, 421–433. https://doi.org/10.3233/jad-181175.

Taylor, H.L., Buskirk, E., Henschel, A., 1955. Maximal oxygen intake as an objective measure of cardio-respiratory performance. J. Appl. Physiol. 8, 73–80. https://doi.org/10.1152/jappl.1955.8.1.73.

Thomas, B.P., Tarumi, T., Sheng, M., Tseng, B., Womack, K.B., Cullum, C.M., Rypma, B., Zhang, R., Lu, H., 2020. Brain perfusion change in patients with mild cognitive impairment after 12 months of aerobic exercise training. J. Alzheimer'S. Dis.: JAD 75, 617–631. https://doi.org/10.3233/jad-190977.

Tobin, M.K., Musaraca, K., Disouky, A., Shetti, A., Bheri, A., Honer, W.G., Kim, N., Dawe, R.J., Bennett, D.A., Arfanakis, K., Lazarov, O., 2019. Human Hippocampal neurogenesis persists in aged adults and Alzheimer's disease patients. Cell Stem Cell 24 (974–982), e973–982. https://doi.org/10.1016/j.stem.2019.05.003.

Tomoto, T., Liu, J., Tseng, B.Y., Pasha, E.P., Cardim, D., Tarumi, T., Hynan, L.S., Munro Cullum, C., Zhang, R., 2021. One-year aerobic exercise reduced carotid arterial stiffness and increased cerebral blood flow in amnestic mild cognitive impairment. J. Alzheimer'S. Dis.: JAD 80, 841–853. https://doi.org/10.3233/jad-201456.

Trejo, J.L., Carro, E., Torres-Aleman, I., 2001. Circulating insulin-like growth factor I mediates exercise-induced increases in the number of new neurons in the adult hippocampus. J. Neurosci. 21, 1628–1634. https://doi.org/10.1523/jneurosci.21-05-01628.2001.

Trushina, E., Mielke, M.M., 2014. Recent advances in the application of metabolomics to Alzheimer's disease. Biochim Biophys. Acta 1842, 1232–1239. https://doi.org/10.1016/j.bbadis.2013.06.014.

van der Kleij, L.A., Petersen, E.T., Siebner, H.R., Hendrikse, J., Frederiksen, K.S., Sobol, N.A., Hasselbalch, S.G., Garde, E., 2018. The effect of physical exercise on cerebral blood flow in Alzheimer's disease. NeuroImage. Clin. 20, 650–654. https://doi.org/10.1016/j.nicl.2018.09.003.

van Horssen, J., van Schaik, P., Witte, M., 2019. Inflammation and mitochondrial dysfunction: a vicious circle in neurodegenerative disorders? Neurosci. Lett. 710, 132931 https://doi.org/10.1016/j.neulet.2017.06.050.

van Praag, H., Christie, B.R., Sejnowski, T.J., Gage, F.H., 1999a. Running enhances neurogenesis, learning, and long-term potentiation in mice. Proc. Natl. Acad. Sci. USA 96, 13427–13431. https://doi.org/10.1073/pnas.96.23.13427.

van Praag, H., Kempermann, G., Gage, F.H., 1999b. Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. Nat. Neurosci. 2, 266–270. https://doi.org/10.1038/6368.

van Praag, H., Schinder, A.F., Christie, B.R., Toni, N., Palmer, T.D., Gage, F.H., 2002. Functional neurogenesis in the adult hippocampus. Nature 415, 1030–1034. https://doi.org/10.1038/4151030a.

van Praag, H., Shubert, T., Zhao, C., Gage, F.H., 2005. Exercise enhances learning and hippocampal neurogenesis in aged mice. J. Neurosci. 25, 8680–8685. https://doi.org/10.1523/jneurosci.1731-05.2005.

Vaynman, S., Ying, Z., Gomez-Pinilla, F., 2004. Hippocampal BDNF mediates the efficacy of exercise on synaptic plasticity and cognition. Eur. J. Neurosci. 20, 2580–2590. https://doi.org/10.1111/j.1460-9568.2004.03720.x.

Venturelli, M., Pedrinolla, A., Boscolo Galazzo, I., Fonte, C., Smania, N., Tamburin, S., Muti, E., Crispoltoni, L., Stabile, A., Pistilli, A., Rende, M., Pizzini, F.B., Schena, F., 2018. Impact of nitric oxide bioavailability on the progressive cerebral and peripheral circulatory impairments during aging and alzheimer's disease. Front Physiol. 9, 169. https://doi.org/10.3389/fphys.2018.00169.

Vidoni, E.D., Honea, R.A., Billinger, S.A., Swerdlow, R.H., Burns, J.M., 2012. Cardiorespiratory fitness is associated with atrophy in Alzheimer's and aging over 2 years. Neurobiol. Aging 33, 1624–1632. https://doi.org/10.1016/j.neurobiolaging.2011.03.016.

Vidoni, E.D., Johnson, D.K., Morris, J.K., Van Sciver, A., Greer, C.S., Billinger, S.A., Donnelly, J.E., Burns, J.M., 2015. Dose-response of aerobic exercise on cognition: a community-based, pilot randomized controlled trial. PloS One 10, e0131647. https://doi.org/10.1371/journal.pone.0131647.

Vidoni, E.D., Perales, J., Alshehri, M., Giles, A.M., Siengsukon, C.F., Burns, J.M., 2019. Aerobic exercise sustains performance of instrumental activities of daily living in early-stage alzheimer disease. J. Geriatr. Phys. Ther. 42, E129–e134. https://doi.org/10.1519/jpt.0000000000000172.

Vidoni, E.D., Morris, J.K., Watts, A., Perry, M., Clutton, J., Van Sciver, A., Kamat, A.S., Mahnken, J., Hunt, S.L., Townley, R., Honea, R., Shaw, A.R., Johnson, D.K., Vacek, J., Burns, J.M., 2021. Effect of aerobic exercise on amyloid accumulation in preclinical Alzheimer's: a 1-year randomized controlled trial. PloS One 16, e0244893. https://doi.org/10.1371/journal.pone.0244893.

Villeda, S.A., Luo, J., Mosher, K.I., Zou, B., Britschgi, M., Bieri, G., Stan, T.M., Fainberg, N., Ding, Z., Eggel, A., Lucin, K.M., Czirr, E., Park, J.S., Couillard-Després, S., Aigner, L., Li, G., Peskind, E.R., Kaye, J.A., Quinn, J.F., Galasko, D.R., Xie, X.S., Rando, T.A., Wyss-Coray, T., 2011. The ageing systemic milieu negatively regulates neurogenesis and cognitive function. Nature 477, 90–94. https://doi.org/10.1038/nature10357.

Villeda, S.A., Plambeck, K.E., Middeldorp, J., Castellano, J.M., Mosher, K.I., Luo, J., Smith, L.K., Bieri, G., Lin, K., Berdnik, D., Wabl, R., Udeochu, J., Wheatley, E.G., Zou, B., Simmons, D.A., Xie, X.S., Longo, F.M., Wyss-Coray, T., 2014. Young blood reverses age-related impairments in cognitive function and synaptic plasticity in mice. Nat. Med 20, 659–663. https://doi.org/10.1038/nm.3569.

Vivar, C., Peterson, B.D., van Praag, H., 2016. Running rewires the neuronal network of adult-born dentate granule cells. Neuroimage 131, 29–41. https://doi.org/10.1016/j.neuroimage.2015.11.031.

Wagner, P.D., 2000. New ideas on limitations to VO2max. Exerc. Sport Sci. Rev. 28, 10–14.

Walker, K.A., Gottesman, R.F., Wu, A., Knopman, D.S., Gross, A.L., Mosley TH, Jr, Selvin, E., Windham, B.G., 2019. Systemic inflammation during midlife and cognitive change over 20 years: the ARIC Study. Neurology 92, e1256–e1267. https://doi.org/10.1212/wnl.0000000000007094.

Wang, J., Cui, Y., Yu, Z., Wang, W., Cheng, X., Ji, W., Guo, S., Zhou, Q., Wu, N., Chen, Y., Chen, Y., Song, X., Jiang, H., Wang, Y., Lan, Y., Zhou, B., Mao, L., Li, J., Yang, H., Guo, W., Yang, X., 2019a. Brain endothelial cells maintain lactate homeostasis and control adult hippocampal neurogenesis. Cell Stem Cell 25, e759–767. https://doi.org/10.1016/j.stem.2019.09.009.

Wang, Q., Hu, J., Liu, Y., Li, J., Liu, B., Li, M., Lou, S., 2019b. Aerobic exercise improves synaptic-related proteins of diabetic rats by inhibiting FOXO1/NF-κB/NLRP3 inflammatory signaling pathway and ameliorating PI3K/Akt insulin signaling pathway. J. Mol. Neurosci. 69, 28–38. https://doi.org/10.1007/s12031-019-01302-2.

Wang, Z.H., Xiang, J., Liu, X., Yu, S.P., Manfredsson, F.P., Sandoval, I.M., Wu, S., Wang, J.Z., Ye, K., 2019c. Deficiency in BDNF/TrkB Neurotrophic activity stimulates δ-Secretase by upregulating C/EBPβ in Alzheimer's disease. Cell Rep. 28, 655–669. https://doi.org/10.1016/j.celrep.2019.06.054.

Wendell, C.R., Gunstad, J., Waldstein, S.R., Wright, J.G., Ferrucci, L., Zonderman, A.B., 2014. Cardiorespiratory fitness and accelerated cognitive decline with aging. J. Gerontol. A Biol. Sci. Med Sci. 69, 455–462. https://doi.org/10.1093/gerona/glt144.

Whelton, S.P., Chin, A., Xin, X., He, J., 2002. Effect of aerobic exercise on blood pressure: a meta-analysis of randomized, controlled trials. Ann. Intern. Med. 136, 493–503. https://doi.org/10.7326/0003-4819-136-7-200204020-00006.

Wilckens, K.A., Stillman, C.M., Waiwood, A.M., Kang, C., Leckie, R.L., Peven, J.C., Foust, J.E., Fraundorf, S.H., Erickson, K.I., 2021. Exercise interventions preserve hippocampal volume: a meta-analysis. Hippocampus 31, 335–347. https://doi.org/10.1002/hipo.23292.

Williamson, W., Lewandowski, A.J., Forkert, N.D., Griffanti, L., Okell, T.W., Betts, J., Boardman, H., Siepmann, T., McKean, D., Huckstep, O., Francis, J.M., Neubauer, S., Phellan, R., Jenkinson, M., Doherty, A., Dawes, H., Frangou, E., Malamateniou, C., Foster, C., Leeson, P., 2018. Association of cardiovascular risk factors with mri indices of cerebrovascular structure and function and white matter hyperintensities in young adults. Jama 320, 665–673. https://doi.org/10.1001/jama.2018.11498.

Winblad, B., Amouyel, P., Andrieu, S., Ballard, C., Brayne, C., Brodaty, H., Cedazo-Minguez, A., Dubois, B., Edvardsson, D., Feldman, H., Fratiglioni, L., Frisoni, G.B., Gauthier, S., Georges, J., Graff, C., Iqbal, K., Jessen, F., Johansson, G., Jönsson, L., Kivipelto, M., Knapp, M., Mangialasche, F., Melis, R., Nordberg, A., Rikkert, M.O., Qiu, C., Sakmar, T.P., Scheltens, P., Schneider, L.S., Sperling, R., Tjernberg, L.O., Waldemar, G., Wimo, A., Zetterberg, H., 2016. Defeating Alzheimer's disease and other dementias: a priority for European science and society. Lancet Neurol. 15, 455–532. https://doi.org/10.1016/s1474-4422(16)00062-4.

Wrann, C.D., White, J.P., Salogiannnis, J., Laznik-Bogoslavski, D., Wu, J., Ma, D., Lin, J. D., Greenberg, M.E., Spiegelman, B.M., 2013. Exercise induces hippocampal BDNF through a PGC-1alpha/FNDC5 pathway. Cell Metab. 18, 649–659. https://doi.org/10.1016/j.cmet.2013.09.008.

Xia, E., Xu, F., Hu, C., Kumal, J., Tang, X., Mao, D., Li, Y., Wu, D., Zhang, R., Wu, S., Sun, L., 2019a. Young blood rescues the cognition of Alzheimer's model mice by restoring the hippocampal cholinergic circuit. Neuroscience 417, 57–69. https://doi.org/10.1016/j.neuroscience.2019.08.010.

Xia, J., Li, B., Yin, L., Zhao, N., Yan, Q., Xu, B., 2019b. Treadmill exercise decreases beta-amyloid burden in APP/PS1 transgenic mice involving regulation of the unfolded protein response. Neurosci. Lett. 703, 125–131. https://doi.org/10.1016/j.neulet.2019.03.035.

Xiang, J., Wang, Z.H., Ahn, E.H., Liu, X., Yu, S.P., Manfredsson, F.P., Sandoval, I.M., Ju, G., Wu, S., Ye, K., 2019. Delta-secretase-cleaved Tau antagonizes TrkB neurotrophic signalings, mediating Alzheimer's disease pathologies. Proc. Natl. Acad. Sci. USA 116, 9094–9102. https://doi.org/10.1073/pnas.1901348116.

Xu, W., Wang, H.F., Wan, Y., Tan, C.C., Yu, J.T., Tan, L., 2017. Leisure time physical activity and dementia risk: a dose-response meta-analysis of prospective studies. BMJ Open 7, e014706. https://doi.org/10.1136/bmjopen-2016-014706.

Yan, Q.W., Zhao, N., Xia, J., Li, B.X., Yin, L.Y., 2019. Effects of treadmill exercise on mitochondrial fusion and fission in the hippocampus of APP/PS1 mice. Neurosci. Lett. 701, 84–91. https://doi.org/10.1016/j.neulet.2019.02.030.

Yang, A.C., Stevens, M.Y., Chen, M.B., Lee, D.P., Stähli, D., Gate, D., Contrepois, K., Chen, W., Iram, T., Zhang, L., Vest, R.T., Chaney, A., Lehallier, B., Olsson, N., du Bois, H., Hsieh, R., Cropper, H.C., Berdnik, D., Li, L., Wang, E.Y., Traber, G.M., Bertozzi, C.R., Luo, J., Snyder, M.P., Elias, J.E., Quake, S.R., James, M.L., Wyss-Coray, T., 2020. Physiological blood-brain transport is impaired with age by a shift in transcytosis. Nature 583, 425–430. https://doi.org/10.1038/s41586-020-2453-z.

Yu, F., Vock, D.M., Zhang, L., Salisbury, D., Nelson, N.W., Chow, L.S., Smith, G., Barclay, T.R., Dysken, M., Wyman, J.F., 2021. Cognitive effects of aerobic exercise in alzheimer's disease: a pilot randomized controlled trial. J. Alzheimers Dis. 80, 233–244. https://doi.org/10.3233/jad-201100.

Zhang, J., Guo, Y., Wang, Y., Song, L., Zhang, R., Du, Y., 2018. Long-term treadmill exercise attenuates Abeta burdens and astrocyte activation in APP/PS1 mouse model of Alzheimer's disease. Neurosci. Lett. 666, 70–77. https://doi.org/10.1016/j.neulet.2017.12.025.

Zhang, X.L., Zhao, N., Xu, B., Chen, X.H., Li, T.J., 2019. Treadmill exercise inhibits amyloid-β generation in the hippocampus of APP/PS1 transgenic mice by reducing cholesterol-mediated lipid raft formation. Neuroreport 30, 498–503. https://doi.org/10.1097/wnr.0000000000001230.

Zhao, G., Liu, H.L., Zhang, H., Tong, X.J., 2015. Treadmill exercise enhances synaptic plasticity, but does not alter beta-amyloid deposition in hippocampi of aged APP/PS1 transgenic mice. Neuroscience 298, 357–366. https://doi.org/10.1016/j.neuroscience.2015.04.038.

Zhao, N., Yan, Q.W., Xia, J., Zhang, X.L., Li, B.X., Yin, L.Y., Xu, B., 2020a. Treadmill exercise attenuates abeta-induced mitochondrial dysfunction and enhances mitophagy activity in APP/PS1 transgenic mice. Neurochem. Res. 45, 1202–1214. https://doi.org/10.1007/s11064-020-03003-4.

Zhao, Y., Qian, R., Zhang, J., Liu, F., Iqbal, K., Dai, C.L., Gong, C.X., 2020b. Young blood plasma reduces Alzheimer's disease-like brain pathologies and ameliorates cognitive impairment in 3×Tg-AD mice. Alzheimer'S. Res. Ther. 12, 70. https://doi.org/10.1186/s13195-020-00639-w.

Zhu, N., Jacobs DR, Jr, Schreiner, P.J., Launer, L.J., Whitmer, R.A., Sidney, S., Demerath, E., Thomas, W., Bouchard, C., He, K., Erus, G., Battapady, H., Bryan, R.N., 2015. Cardiorespiratory fitness and brain volume and white matter integrity: the CARDIA study. Neurology 84, 2347–2353. https://doi.org/10.1212/wnl.0000000000001658.

Zotcheva, E., Pintzka, C., Salvesen, Ø., Selbæk, G., Håberg, A.K., Ernstsen, L., 2019. Associations of changes in cardiorespiratory fitness and symptoms of anxiety and depression with brain volumes: the HUNT study. Front Behav. Neurosci. 13, 53. https://doi.org/10.3389/fnbeh.2019.00053.