Review

Gene-environment interactions in considering physical activity for the prevention of dementia

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Abstract: Alzheimer’s disease (AD), the most common neurodegenerative disease worldwide, ranks as one of the most feared diseases in the world. Similarly, recent studies suggest that AD may be the third leading cause of death in the United States, behind heart disease and cancer. In the absence of a cure or effective treatment, strategies to prevent or delay the onset and progression of the disease are desperately needed. Decades of research have identified key risk and protective factors including genetic polymorphism in the APOE gene, age and lifestyle factors. Physical activity (PA) is emerging as an attractive primary prevention strategy. This review will summarise the latest findings supporting the role of physical activity in the prevention of AD, including possible mechanisms and the influence of genetics on disease prevention. Given that AD and other dementias are recognised as a world health priority, public health strategies are needed to incorporate promoting the health benefits of physical activity across the lifespan.

Keywords: Alzheimer's disease; physical activity; apolipoprotein E

1. What is Alzheimer’s disease?

Alzheimer’s disease (AD) is a devastating neurodegenerative disease named after the German Psychiatrist Dr Alois Alzheimer who first described the condition over 100 years ago [1]. Present estimates put the number of people living with dementia worldwide at 47 million and the majority of these people will have AD [2]. In the absence of an effective treatment or cure, that number is projected to triple by 2050, meaning that 1 in 85 adults will be living with AD [3], thus constituting a massive economic and emotional burden on society.
AD is characterised histopathologically by the abnormal deposition of two proteins, amyloid-beta (Aβ) [4,5] and hyperphosphorylated tau [6,7]. Traditionally, a definitive diagnosis of AD was only possible upon post-mortem analysis, but recent neuro-imaging techniques are making it possible to detect Aβ deposition decades before the onset of symptoms [8] and can therefore assist in identifying at-risk individuals and monitor disease progression. Tau radioisotopes for PET imaging are also an area of intense research activity (e.g. [9,10]. Clinically, AD is characterised by problems with specific aspects of learning and memory that progress to more global cognitive decline in the advanced stages, however accurate diagnosis based on clinical symptoms alone, particularly in the early stages of the disease is problematic [11].

Lastly, AD can be broadly categorised into two groups based on age of onset, late-onset AD, which occurs over the age of 65, and early-onset AD. Late-onset AD constitutes the vast majority of AD cases and is multifactorial in nature [12,13], however no known cause has yet been identified. Early-onset AD is much more rare and caused by autosomal dominant inheritance of mutations in three known genes, amyloid precursor protein (APP), presenilin-1 (PSEN1) and presenilin-2 (PSEN2) [14]. Down syndrome (trisomy 21) is also linked with AD, because a significant number of affected individuals develop the neuropathology of AD by the fifth decade of life. Over-production of APP and Aβ [15,16] by virtue of the location of the gene on Chromosome 21, is thought to contribute to the increased incidence of AD in people with Down syndrome.

2. Known risk and protective factors

2.1. Risk and protective factors

It is clear that AD is a multifactorial disease, with a convergence of genetic, environmental and lifestyle factors involved in the disease process. Given the multitude of factors, it is useful to categorise them into modifiable or non-modifiable factors. For the purposes of this review, non-modifiable factors will include genetics, age and gender, whereas modifiable factors include lifestyle factors such as physical activity (PA), diet, cigarette smoking, depression, uncontrolled type 2 diabetes (T2D) and obesity.

2.2. Examples of non-modifiable risk factors

In terms of non-modifiable factors, age is the biggest risk for AD [17,18], but it is important to remember that AD is not a part of normal ageing. The prevalence of AD increases with increasing age, where the latest rates from the United States indicate that 1 in 9 people over the age of 65 with AD, increasing to over 80% of people with AD being over the age of 75 years [18,19]. It is still unknown why the risk of AD increases with age, however reduced anti-oxidant capacity [20,21] and increased inflammation [22] are two age-related phenomena that may contribute to the pathogenesis of AD [23].

Women appear to be at greater risk of developing AD than men, even after controlling for sex-differences in life expectancy [24]. The risk may be age-dependent; with increasing age, women are more likely than men to develop AD [19]. Furthermore, the progression of AD in women may be faster than men, particularly at these older ages [25]. One hypothesis for this association is the reduction in gonadal hormones as a consequence of menopause, because gonadal hormones are
known to have numerous neuroprotective actions in the CNS [26–28]. Though as is the case for ageing, the cause for this relationship is not completely understood. Genetic polymorphism in the apolipoprotein E (APOE) gene is the strongest genetic risk factor for AD identified to date. The APOE ε4 allele is associated with increased risk for late-onset AD [29,30], in a gene-dose specific manner [31]. APOE ε4 has in turn been shown to influence elements of AD pathology including interactions with Aβ, tau and synaptic function [32–37] and also response to potential therapies [38–40]. Recent genome-wide association studies (GWAS) have identified numerous risk loci, however the risk conferred by these loci is much smaller than that of APOEε4 [41].

2.2. Modifiable risk factors

In 2011, Deborah Barnes and Kristine Yaffe published a review of the available literature pertaining to risk factors for AD. The paper suggested that up to half of all AD could be attributable to seven preventative risk factors [13]. Their findings were exciting not only because of the potential to prevent one, but multiple diseases, by modifying lifestyle choices. The seven factors identified by this study were diabetes, midlife hypertension, midlife obesity, smoking, depression, cognitive inactivity or low educational attainment, and physical inactivity [13]. An updated analysis concluded that after taking into account the inter-relationships between these factors, approximately one third of AD could be prevented by improved access to educational opportunities and improved cardiovascular health [42]. Other important modifiable risk factors that have been identified in observational studies include traumatic brain injury [43] and cholesterol level fluctuations over the life span [44]. Exposure to environmental pollutants such as heavy metals and pesticides are also attracting attention as possible risk factors for neurodegenerative diseases, including AD [45].

PA is defined by the World Health Organization as “any bodily movement produced by skeletal muscles that requires energy expenditure” [46] and therefore includes exercise (a planned, structured, repetitive activity for the improvement or maintenance of physical fitness), but also activity that occurs as a consequence of house work chores, playing, working, active transportation and recreational activities. PA is an attractive target because this factor can contribute to reducing the risk of developing diabetes, preventing hypertension and obesity and also affects brain function—4 of the remaining 7 factors [47]. Because of this multitude of beneficial effects, PA is the focus of this review.

3. Physical activity has multiple effects on brain function

Exactly how regular PA confers protection against AD is not fully understood, however it is likely that PA has multiple direct and indirect beneficial effects that together contribute to brain health. Importantly, evidence is emerging that “its never too late” to benefit from increased PA in terms of AD prevention. A recent meta-analysis of 9 studies involving over 20,000 participants confirmed that PA corresponds to a statistically significant reduction in risk of AD in older adults (over the age of 65 years). This meta-analysis also demonstrated a relationship between the level of PA and reduction in risk for AD in 6 out of the 9 studies analysed [48]. In other words, the more physically active you are, the less likely you are to develop AD. Furthermore, previous studies have reported long-lasting benefits, in terms of AD-risk reduction, of engaging in PA throughout the
lifespan (as reviewed in [49]). It is apparent that PA exerts peripheral and central effects on brain function; outlined below are some of the ways that PA can influence brain function by altering psychological, biochemical and physiological parameters to ultimately improve cognitive performance.

Traditionally, studies have focussed on the relationship between PA and cardiovascular/aerobic fitness. However it is important to remember that improvements in health status can occur in the absence of measurable change in aerobic fitness such as cardiac output and oxidative potential [50]. For example, musculoskeletal fitness is strongly related to the ability of elderly people to maintain functional independence (reviewed in [47]) and reduces risks of falls [51], osteoporosis [52] and osteoarthritis [53]. Osteoporosis is also linked to increased risk for AD, possibly mediated by estrogen exposure in post-menopausal women [54–56].

Regular PA is known to reduce central adiposity and obesity, leading to reduced body fat and increased muscle mass (commonly measured as reduced body mass index-BMI) [49]. High BMI is in turn associated with poorer cognitive function and cerebral atrophy [57,58]. Central adiposity, as measured by waist-to-hip ratio is also associated with increased likelihood of neuropathological markers using brain imaging techniques [59]. Obesity at midlife significantly increases the risk of developing AD [60] and dementia [61]. Conversely, lean body mass and increased bone mineral density is associated with improved cognitive performance in healthy, older people [62]. The underlying mechanism linking body composition and brain health is not definitively known, however high-density lipoprotein (HDL) may be a major contributing factor. The evidence for this is four-fold; 1) HDL can bind to and facilitate clearance of $\alpha\beta$ [63,64], 2) PA can raise circulating HDL [65], 3) HDL is correlated with lower circulating $\alpha\beta$ [66] and 4) better cognitive performance in healthy aged people [67–70].

T2D and insulin resistance are also associated with increased risk for future AD [71]. There are many ways by which T2D may increase susceptibility to AD: through its association with other factors relating to “metabolic syndrome” (e.g. dyslipidemia, hypertension) [72], the toxic effects of prolonged exposure to high glucose levels [73] and through the neurobiological effects of insulin itself [74–76]. Regardless of the mechanism linking AD and T2D, studies suggest that PA has a role to play in the prevention of T2D [77,78], thus providing further support for the role of PA in the prevention of AD.

The beneficial effects of PA on the brain may also be mediated by increased production of growth factors such as brain derived neurotrophic factor (BDNF) and insulin-like growth factor (IGF1) [79]. BDNF is a molecule central to the processes of learning and memory, hippocampal function and depression and anxiety [80]. PA has been consistently shown to up-regulate BDNF expression in several brain regions, particularly the hippocampus [81,82]. A series of elegant experiments over a number of years in animal models have demonstrated the central role of BDNF in mediating the improved learning response after PA. When rats are deprived of voluntary PA (i.e. wheel-running), the genes for both BDNF and its receptor (TrkB) are down-regulated [83]. Blocking the interaction of BDNF and TrkB receptors prevents the acquisition and retention of learning tasks [84] and also attenuates the induction of synaptic protein expression by PA in rodent models [85]. There may even be long-lasting effects of PA on BDNF signalling because mice that have been selectively bred for high wheel running have larger brain regions, higher BDNF levels, increased hippocampal neurogenesis and higher vascular endothelial growth factor (VEGF) levels and capillary density [86]. IGF1 is another growth factor that is up-regulated by PA [87]. Interestingly, IGF1 and BDNF act
synergistically to mediate the effects of PA on the hippocampus [88,89]. Furthermore, IGF1 can also influence brain amyloidosis and tau hyperphosphorylation, key features of AD pathology [90].

Self-reported PA is associated with larger brain volumes, as measured by brain imaging techniques, compared to participants who report little or no PA [91]. Frontal lobe and medial temporal lobe structures are preferentially affected by PA in older adults [92]. The positive relationship between PA and brain volume also remains in patients with mild cognitive impairment (MCI) and AD [93]. Self-reported PA at midlife is associated with long-term benefits in terms of brain volume, particularly grey matter volume in the frontal areas, after a 21-year follow-up period [94], reinforcing the concept that lifetime engagement in PA can result in long-term health benefits. A randomised controlled trial utilising an aerobic-based PA program showed an increase in hippocampal volume and higher serum BDNF levels in the exercise compared to control groups in older adults [95]. In patients with early-stage AD, objective measures of PA (cardiovascular fitness) are associated with reduced brain atrophy [96] and preservation of medial temporal lobe structures [97], indicating that maintaining PA even through the onset of disease, can provide some benefit.

In rodents, voluntary PA has been shown to enhance hippocampal function by increasing learning rate in older animals [98,99]. A number of meta-analyses have been conducted to determine whether PA can influence cognitive performance (recently reviewed in [100]). The positive influence of PA on cognition remains for older adults with and without cognitive impairment [101] and appears to be greatest for executive functions, such as planning, working with memory and multi-tasking [102]. PA may also help prevent loss of spatial ability with age [103]. Recent studies have demonstrated that physically active younger adults have a higher degree of functional connectivity between brain regions than their more sedentary counterparts [104]. An aerobic exercise intervention program in older adults (aged 70–85 years) also resulted in greater brain network connectivity than sedentary controls over a 4 month period [105]. PA interventions can also induce plasticity in functional networks and brain activation patterns resulting in improved cognitive performance in cognitively healthy older adults [106]. Whilst these initial studies are on a small sample group, they do suggest that engaging in PA can enhance efficiency of brain networks, thus altering the functional connectivity and structure of the brain.

PA can influence mood and reduce depressive symptoms, both of which are known to influence cognitive performance and risk of later decline. PA has been shown to reduced the risk of both prevalent and incident depression in older adults over a 5 year follow-up period [107]. Reduced mobility is associated with increased risk of depression [108], indicating that keeping people active is an important intervention to be considered for people with disability [109]. The protective effect of PA against depression is also observed when objective measures of PA are used for elderly subjects [110]. PA is also associated with lower depressive symptoms and improved perception of quality of life for residents of institutionalised care facilities [111]. The protective benefit of PA remains after controlling for confounding demographic variables such as ethnicity, socioeconomic status, smoking and BMI [112]. Relatively simple PA interventions, for example, walking have been shown to reduce the severity of symptoms for older people with depression [113], and there is a suggestion that aerobic, rather than resistance exercise may be most beneficial for ameliorating depression [114]. PA can also reduce the severity of symptoms for elderly people with anxiety disorders [115].

Arguably, some of the most exciting data to date has shown that PA has disease-modifying capabilities. In 2005, Lazarov and colleagues demonstrated that environmental enrichment, including
provision of running wheels, led to a reduction in Aβ load in a transgenic mouse model [116]. In the same year, Adlard and colleagues showed that voluntary exercise alone was sufficient to reduce amyloid load in transgenic mouse models [117], although to date, no studies have demonstrated that PA can remove pre-existing Aβ load.

Similar results are seen in human studies, where higher levels of physical activity are correlated with improved AD-associated biomarker panels such as CSF Aβ and tau and brain amyloid load as measured by carbon 11-labelled Pittsburgh Compound B-positron emission tomography [118–120] imaging [121], although not all studies find a relationship between PA and AD-associated biomarkers [122]. Subsequently, results from the Australian Imaging and Biomarkers and Lifestyle study of ageing demonstrated that higher self-reported levels of physical activity in cognitively healthy older adults is associated with lower blood plasma levels and reduced brain burden of Aβ [123]. PA has also been shown to attenuate age-related alterations in AD-associated biomarkers in people at risk for AD by nature of family history or APOEε4 polymorphism [124].

In summary, there is a large body of evidence to suggest that PA has multiple beneficial effects on cognitive function, through both direct and systemic/peripheral effects. PA is a factor that can be modified, but is there an interaction between PA and genetic risk for AD?

4. Gene × environment interactions in the prevention of AD by physical activity—“exercise genetics”

As discussed above, polymorphism in the APOE gene is the strongest genetic risk factor identified for AD. Apolipoprotein E has a further link to the relationship of PA to brain health because of its function as a lipid-transport protein [125–128]. A number of studies have sought to assess whether various potential protective strategies, for example estrogen replacement [38,129], anti-inflammatory [130] and antihypertensive [131] therapy can mitigate genetic risk of AD, in terms of APOEε4 carriage.

Similar analyses have also been conducted around the world to determine whether PA can still offer protection from AD in APOEε4 carriers. The results have been mixed with some studies finding greater benefit of PA in terms of cognitive health and reduced risk for AD for APOEε4 carriers [132–139], non-carriers [140] and no effect of APOE genotype [141–143]. The differences maybe due to methodological issues in assessing PA levels, the age of the cohorts, study design or the ethnicity of the various cohorts, however the overall protective effect of PA against cognitive decline remains.

More recent studies have begun to elucidate whether APOEε4 influences the impact of PA on potential AD-associated biomarkers. PA has been shown to confer protection against hippocampal atrophy in cognitively healthy older adults [144]. A recent analysis of cognitively normal older adults demonstrated that a sedentary lifestyle is associated with higher amyloid burden (PiB-PET imaging) amongst APOEε4 carriers but not non-carriers [145], suggesting that PA maybe particularly important in reducing AD-biological markers for people at genetic risk for AD. The greater improvement in cognitive performance and neuroplasticity as a result of PA for APOEε4 carriers is also found in transgenic mouse models [146].

It’s not entirely clear how possession of the APOEε4 allele confers increased risk for AD, however it is associated with reduced synaptic plasticity [37], reduced cholinergic functioning [147,148], reduced neuronal activity [149–151], impaired clearance of Aβ [152,153] and can also influence the
inflammatory cascade and oxidative stress [32,154,155]. In addition to APOE ε4 polymorphism, the levels of apolipoprotein E itself may be important in the pathogenesis of AD [156], with an APOE promoter polymorphism associated with increased risk for AD [157–159].

Given the effect of PA on BDNF levels, one may expect that genetic polymorphism in the BDNF gene may also influence the protective benefits conferred by PA. In humans, a Val66Met polymorphism in the BDNF gene (rs6265) has been associated with reduced secretion of BDNF, poorer cognitive performance and smaller hippocampal volume [160,161]. This particular polymorphism is also associated with increased risk for AD [162]. A recent cross-sectional analysis from the AIBL study group has found an associated between BDNF polymorphism, hippocampal volume and physical activity such that high levels of PA reduced the volume of the temporal lobe in BDNF Met carriers (i.e. the risk allele) [163]. This finding suggests that Val carriers are better able to derive the benefits of PA on BDNF levels than Met carriers, who may produce altered binding of BDNF to TrkB receptors, but not p75 receptors [164].

Genetic polymorphism for other molecules affected by PA, such as IDE [165] and IGF-1 [166] are also associated with increased risk for AD, but whether these polymorphisms also alter the efficacy of PA for preventing AD is unknown. Inflammation is another key process that is likely to be influenced by engaging in PA [79,167]. Because inflammatory genetic polymorphisms are also linked with AD risk [168–178], inflammation provides another avenue for investigation into the concept of genetic exercise. Lastly, a recent study has demonstrated that engaging in PA can reduce the risk conferred by other AD-risk alleles—PICALM, CLU and BIN1 [179], possibly by mediating Aβ clearance and tau pathology [180,181].

Another intriguing element to the concept of exercise genetics is the concept that PA can regulate epigenetic control of gene expression, in other words, exercise can change your DNA. Epigenetics is the study of changes in gene function that are heritable, but not related to a change in the sequence of DNA. Such modifications can occur through mechanisms such as DNA methylation and can either activate or suppress gene transcription. Exercise during pregnancy has been shown to mitigate AD-pathology in offspring of transgenic mice [182] and also to increase BDNF expression in rat pups [183]. Recent literature reviews have highlighted the link between PA and epigenetic control of a number of genes linked with AD including inflammatory genes and BDNF [184–186]. These studies suggest that PA may induce long-term and heritable alterations in DNA and offer new insights into how PA and interact with the genome to reduce risk for future AD (Figure 1).
Figure 1. Simplified diagrammatic representation of the bi-directional interaction between genes and the environment with respect to PA. PA can influence aging, psychological wellbeing, disease processes and biochemical pathways, all of which influence epigenetic mechanisms. Therefore there are multiple ways through which PA can potentially protect against age-related and AD-related cognitive decline. For the sake of simplicity, the inter-relationships between the outer-circles have not been shown.

5. Directions for future research—relationship status: its complicated

Despite numerous studies supporting the role for PA in the prevention of AD, there remain some issues that will need to be addressed before the full potential of PA can be realised. As a starting point, it is recommended by health authorities that people follow PA guidelines relevant to their age group. The Global Recommendations on Physical Activity, developed by the WHO are divided into three categories according to age group; children aged 5–17 years, adults aged 18–64 years and adults aged 65 and above, and are valid for all people unless specific medical conditions are contraindicated (Table 1).
Table 1. World Health Organization (WHO) Global Recommendations on Physical Activity* for Health (2015) for Adults. Pregnant and post-partum women and all adults with heart conditions are advised to seek medical advice prior to commencing a PA program. Recommendations are made for all healthy adults unless specific medical conditions indicate otherwise (adapted from http://www.who.int/dietphysicalactivity/factsheet_recommendations/en/).

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Age Group</th>
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<tr>
<td>At least 150 minutes of moderate-intensity OR</td>
<td>✓</td>
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<tr>
<td>At least 75 minutes of vigorous-intensity OR</td>
<td>✓</td>
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<tr>
<td>An equivalent combination of moderate- and vigorous-intensity aerobic PA/week.</td>
<td>✓</td>
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<tr>
<td>Activity should be performed in bouts of at least 10 minutes duration.</td>
<td>✓</td>
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<tr>
<td>For additional health benefits, adults should increase their moderate-intensity to 300 minutes OR</td>
<td>✓</td>
</tr>
<tr>
<td>Engage in 150 minutes of vigorous-intensity OR</td>
<td>✓</td>
</tr>
<tr>
<td>An equivalent combination of moderate- and vigorous-intensity activity aerobic PA/week.</td>
<td>✓</td>
</tr>
<tr>
<td>Muscle-strengthening activities should be done involving major muscle groups on 2 or more days a week.</td>
<td>✓</td>
</tr>
<tr>
<td>Older adults, with poor mobility, should perform physical activity to enhance balance and prevent falls on 3 or more days per week.</td>
<td>✓</td>
</tr>
<tr>
<td>When older adults cannot do the recommended amounts of physical activity due to health conditions, they should be as physically active as their abilities and conditions allow.</td>
<td>✓</td>
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*PA includes leisure time physical activity, transportation (e.g. walking or cycling), occupational (i.e. work), household chores, or planned exercise/sports, in the context of daily, family, and community activities.

5.1. Physical activity—a prescription for AD?

Given the positive effects of PA on cognition, a number of randomised trials have been conducted that use an exercise intervention in patients at risk, or with dementia. A recent meta-analysis of 14 of such trials has indicated that PA intervention results in cognitive improvements across a range of domains including attention, executive function and fluid intelligence, as well as improvements on clinical dementia ratings [187]. The PA interventions included both aerobic and resistance exercises and also solely home-based interventions. PA interventions may also improve functional abilities and stabilise care-giver burden for patients with AD [188]. Clinical trials are currently underway to determine the effects of PA and genetics on cognitive performance in older adults [189], however there is currently no gold-standard for outcome measures in dementia prevention.
5.2. Methodological issues

There are also some methodological issues that need to be resolved in order to better clarify and characterised the role of PA in the prevention of AD. To date, a number of studies rely on self-report questionnaires such as the Community Healthy Activities Model Program for Seniors (CHAMPS) (e.g. [190]) or International Physical Activity Questionnaire (e.g. [123]) versus objective measures (e.g. activity monitors [191] or aerobic fitness [134]). This is an important distinction because the results generated vary depending upon the measures used to assess PA engagement [192]. Additionally, the type of PA in regards to leisure-time versus other forms of PA such as occupational are important considerations when interpreting data. Leisure-time PA may include a cognitively stimulating and social-interaction component which may confer additional protective benefits than PA alone [136,193–198]. Lastly, there remains to be a detailed characterisation of the intensity and duration of PA that is required for maximal benefit. This is not only and important economic question for public health advocates, but it may be that too much PA could actually contribute to AD pathology, rather than mitigate it [92]. This knowledge will also assist in minimising environmental (such as feelings of safety, places to rest etc. [199]) and cultural barriers to engaging in PA [200].

5.3. Multivariate approaches—variety is the spice of life

Evidence from animal models suggests that a range of environmental enrichment opportunities result in the greatest protection of the brain from age and disease-related effects [201,202]. In this context, environments rich in motor, sensory and cognitive stimulation have been shown to enhance synaptic plasticity and cognitive performance as well as providing a disease-modification effect.

With this in mind, a number of studies have reported benefits from mentally stimulating activities on improving cognitive function and brain plasticity measures in healthy older people (e.g. [203–205], those with MCI [206] and with AD [207,208]. These sorts of cognitive training interventions are also associated with reduced risk for AD [209,210]. A recent Australian study showed that participation in a combination of PA and computerised cognitive stimulation improved cognitive performance and enhanced brain glucose metabolism for healthy older adults compared to single-mode stimulation or controls [211]. Whilst these studies are encouraging, they are still preliminary in nature and additional randomised, large-scale clinical trials are clearly warranted to determine the optimal intervention programs, whether there are long-lasting improvements and if any benefits of training are transferable to non-trained cognitive domains [212].

The idea that a multi-modal intervention may provide maximal benefit for AD has been taken one step further in the design of the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER)—a randomised controlled trial of diet, exercise, cognitive stimulation and blood pressure monitoring in older adults. This intervention resulted in a reduction in cognitive deterioration and a particular effect on executive functioning and processing speed and changes in lifestyle choices such as diet, PA and BMI [213]. Further follow-up studies are planned to determine whether the FINGER intervention had any effect on incident AD and dementia. In a similar vein, large prospective cohort studies such as AIBL [214] and the Alzheimer’s Disease Neuroimaging Initiative [215] provide further opportunities to interrogate the relationship between PA and AD. In addition, investigation of protective factors in cohorts of people who will develop AD by way of possessing an AD-causing genetic mutation (i.e. the Dominantly Inherited Alzheimer’s
Network-DIAN) will provide valuable insights into the biological mechanisms affected by PA [216].

5.4. Genetic and gender effects?

Evidence from animal models suggests that the effects of APOEε4 may be more pronounced in females than males [217]. Indeed female APOEε4 carriers are at greater risk of future AD than male APOEε4 carriers [218]. Aerobic fitness in APOEε4 carriers is associated with better cognitive performance in healthy older women [134], yet APOEε4 carriage has no impact on the net protective benefit of PA in men [143]. This sex-genetic interaction needs to be better explored and characterised for PA intervention studies [24].

6. Conclusion

In summary, there are numerous lines of evidence strongly supportive for a role of PA in the prevention and possibly slowing the progression of AD. Research is now teasing apart the effect of various genetic factors on the ability of PA to act on various pathological aspects of AD. More studies are required to elucidate the mechanisms underlying the affect of PA on the brain in the hope that exercise prescription may one day become a reality for age-related diseases, including AD.

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Conflict of interest

There are no conflicts of interest to declare.

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