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REVIEW ARTICLE

Physical Activity in Preventing Alzheimer's Disease and Cognitive Decline: A Narrative Review

Stefano Brini[1,2,7] · Hamid R. Sohrabi[3,4,6] · Jeremiah J. Peiffer[1] · Mira Karrasch[5] · Heikki Hämäläinen[2,7] · Ralph N. Martins[3,4,6] · Timothy J. Fairchild[1]

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Abstract A large body of epidemiological and experimental data exploring the relationship between physical activity (PA) and Alzheimer's disease (AD) are now available. Despite observational evidence supporting a role for PA in delaying the onset of AD, randomised controlled trials have reported mixed findings, likely due to the heterogeneity in study cohorts, outcome measures, and the adopted PA intervention. The primary objective of this narrative review is to evaluate the extant evidence on the relationship between PA, cognitive decline and AD in older populations. The interaction between PA and the putative mechanisms underlying AD progression, including genetic factors and amyloid-β levels will be explored. In this context, particular attention will be given to studies assessing PA in the early clinical and preclinical, asymptomatic stages of AD. Based on current evidence, clinical considerations for implementation of exercise-based interventions are discussed, along with limitations of previous research and directions for future studies.

Key Points

There is observational evidence suggesting that higher levels of physical activity, particularly early in life, delays the onset of Alzheimer's disease.

While exercise has not been found to be harmful in randomised controlled trials in elderly participants, the benefits of exercise on cognitive performance have been mixed.

Engagement in regular exercise comprising of both aerobic and non-aerobic activities, and which are supported by one or more types of recreational activities, are likely to benefit cognition in elderly individuals and should be supported in public health programmes.

1 Introduction

Dementia is an umbrella term encompassing many neurodegenerative disorders, including Alzheimer's disease (AD). The global estimated costs of dementia in 2015 were US$818 billion annually and these are expected to extend to US$2 trillion by the year 2030 [1]. Without a treatment or cure, the worldwide estimated prevalence of dementia will be 115.5 million people by the year 2050 [2]. Consequently, the World Health Organization (WHO) has labelled dementia a public health priority [3].

✉ Timothy J. Fairchild
T.Fairchild@murdoch.edu.au

1 School of Psychology and Exercise Science, Murdoch University, Room 2.042, Social Sciences Building, 90 South Street, Murdoch, Perth, WA 6150, Australia

2 Department of Psychology and Speech-Language Pathology, University of Turku, Turku, Finland

3 School of Medical and Health Sciences, Edith Cowan University, Perth, WA, Australia

4 Department of Biomedical Sciences, Macquarie University, Sydney, NSW, Australia

5 Department of Psychology, Åbo Akademi University, Turku, Finland

6 Australian Alzheimer's Research Foundation, Perth, WA, Australia

7 Turku Brain and Mind Center, University of Turku, Turku, Finland

The most common form of dementia is AD, which accounts for 60–70% of all dementia cases and for which no treatment or cure currently exists [4, 5]. While most individuals experience subtle decreases in cognitive performance with advancing age [6], the pronounced cognitive deterioration resulting from AD is not part of the normal ageing process [7]. Cognitive decline associated with AD can be divided into three stages: a preclinical, asymptomatic stage referred to as subjective cognitive decline (SCD) [8, 9]; a symptomatic, preclinical stage of mild cognitive impairment (MCI) [10], and AD, which is characterised by cognitive impairment and significant dysfunction in daily living activities [7]. Importantly, SCD or MCI are not always considered as part of the preclinical phase of AD since many individuals with SCD or MCI do not always progress to AD [11].

Research has traditionally focused on tertiary preventions aiming to alleviate or slow the pathogenic processes in the symptomatic preclinical and clinical stages of AD. However interventions in these stages have, to a large degree, been unsuccessful in achieving these aims [4, 7, 12]. This is likely due to the presence of advanced neuronal damage in individuals within symptomatic stages, and this neuronal damage has proven difficult to reverse with current interventions [12, 13]. Administering disease-modifying interventions such as increasing levels of physical activity (PA) in the asymptomatic stage (i.e. SCD) may be an important strategy in delaying the onset or slowing the progression of AD pathogenesis before neurodegeneration becomes irreversible [9, 13, 14]. Specifically, a 5-year delay in the onset of AD could reduce the number of AD patients by 57% and the associated economic costs by half [15].

2 The Pathophysiology of Alzheimer's Disease (AD)

AD is a complex neurodegenerative disorder with a clinical phenotype characterised by insidious and progressive decline in episodic memory, attention, executive functions, language, and praxis, followed by loss of motor control, resulting in complete dependence and ultimately death [16]. A definitive diagnosis for AD can only be achieved histopathologically at post-mortem. For many years, the *amyloid cascade hypothesis* was the prevailing explanation for the pathogenesis of AD [17]. This hypothesis arose from histopathological observations showing accumulation of intra- and extracellular misfolded proteins called amyloids, which contain phosphorylated tau and amyloid plaques, comprising of β-amyloid (Aβ) peptides. The accumulation of these Aβ peptides was observed to exacerbate synaptic dysfunction, resulting in tau hyperphosphorylation that aggregates and deposits intracellularly, ultimately leading to synaptic loss and neuronal death [18]. This process can be confirmed during post-mortem examination of AD brain tissues that reveals microscopic lesions such as senile plaques and neurofibrillary tangles across the central nervous system, particularly in the cerebral cortex. Gross inspection of the AD brain post-mortem also reveals normally distributed and hemi-symmetrical atrophy of the neocortex, suggesting neurodegeneration [17].

This cascade of neuropathological events arising from the abnormal accumulation of the Aβ peptide is thought to be a central event in AD pathophysiology, indicating that selectively targeting Aβ with pharmacotherapy would successfully treat AD [18]. Consequently, the *amyloid cascade hypothesis* was used as a benchmark from which therapeutic interventions were developed [17], many of which however have not been successful [4, 19]. Indeed, it now appears the AD pathophysiology cannot be reduced to a single aetiology as had been previously hypothesized; rather, it likely arises from several toxic pathogenic processes [5, 16].

3 Risk Factors for AD

3.1 Subjective Cognitive Decline as a Risk Factor for AD

SCD and subjective memory complaints (SMC) are used interchangeably in the literature. While SMC remains the prominent feature during the asymptomatic, preclinical stage of AD, researchers have preferentially adopted SCD when referring to this stage. The prevalence of SCD among individuals aged 60 years and over ranges between 25 and 50% [20], with the prevalence increasing concurrently with age [21]. A person with SCD experiences subjective impairment in memory and cognitive functions, but these subjective impairments cannot be detected by objective measures [22]. The conversion rate from SCD to MCI in studies conducted over 4 years was 24.4%, while the conversion rate to dementia over this time period was 10.9%, compared with 4.6% in individuals without SCD [11]. Overall, individuals with SCD (but without objectively measurable complaints) have twice the risk of developing dementia than those without SCD [11]. Structural magnetic resonance imaging (MRI) has also indicated that participants with SCD have a significantly smaller mean left hippocampal volume [$n = 20$; 2.0 (0.4) cm^3] compared with control participants [$n = 28$; 2.3 (0.4) cm^3] without memory complaints [23]. Consequently, SCD is an

important risk indicator in the natural history across the AD spectrum [24].

There is experimental evidence indicating that PA interventions may be more successful when delivered in the early preclinical (Table 1) [25–27] and early clinical populations [28], as opposed to the latter clinical phase of AD (Table 2) [29]. For example, in a randomised controlled trial, Lautenschlager et al. [25] tested the effects of increased PA levels on cognition among individuals with SCD and MCI and found a significant improvement in cognition as measured by the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog). This difference was still detectable at the 18-month follow-up. Another trial comparing an active control (regular health advice) and a multidomain intervention comprising diet, exercise, and cognitive training among AD at-risk individuals across 2 years, revealed that the multidomain intervention improved memory and processing speed tasks [27]. Similarly, Shah et al. [26] demonstrated that in older individuals at risk of AD but without SCD or MCI, a combination of PA and computer-based cognitive training improved cognition and cerebral glucose metabolism, which is a marker of cognitive performance, more than each intervention alone. Finally, that early intervention is likely associated with improved cognitive outcomes is supported by systematic reviews that PA interventions seem to be more successful when delivered during the MCI stage rather than at the AD stage (Tables 2, 3) [28].

3.2 Cardiovascular Diseases and Low Physical Activity (PA) as Risk Factors for AD

Several modifiable, cardiovascular risk factors have been associated with increased risk of AD, including obesity and obesity-related diseases such as type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD). While individuals with obesity have a higher risk of AD [30–32], the magnitude of the association, independently of other risk factors, remains a matter of debate. Nevertheless, two systematic reviews with meta-analyses have since confirmed overweight and obesity in mid-life as independent risk factors for AD [33, 34], while obesity later in life has been associated with a lower risk of AD [35], although the strength of these relationships was found to be less than the relationshhip with apolipoprotein E (APOE), which is a major genetic risk factor for AD [34]. T2DM has also been associated with poorer cognitive performance in working memory, executive functions, and attention in older adults [36, 37], as well as immediate and delayed verbal recall, and verbal fluency among elderly women [38, 39], which are cognitive abilities that are strongly affected by AD. Moreover, improving glycaemic control has been shown to improve cognitive performance [40]. That T2DM has been found to accelerate cognitive decline and increase AD risk independently of other comorbid factors (e.g. obesity) [34, 41] is therefore unsurprising. Similarly, individuals with CVD have an elevated risk for AD [42–44]. The independent and direct relationship between CVD and AD is likely related to hypoperfusion and microemboli, which may present in CVD and can accelerate the pathogenesis of AD [44, 45]. In addition, reduced PA and

Table 1 Experimental trials investigating the effects of PA programmes on preclinical AD

Study	*N*; mean age, years (SD)	Type of PA programme	Neurological condition	Findings
Lautenschlager et al. [25]	170; PA 68.6 (8.7), controls 68.7 (8.5)	Three 50-min home-based sessions/week of moderate intensity PA	SCD, MCI	Tx ↑ 0.26 ADAS-Cog Cx ↓ 1.04 ADAS-Cog Between-group difference (Tx and Cx): ↓ 1.3 points
Shah et al. [26]	224; 67.6 (5.42)	PA: 48 walking sessions 60 min/day, 3 days/week, and 32 resistance training sessions 40/day, 2 days/week; CS: 40 sessions at 60 min/day for 5 days/week for the auditory-based Brain Fitness Program and the visual-based Insight Program; PA+CS: both PA and CS sessions	Elderly individuals at a higher risk of AD	NS ↑ in cognition in the PA or CS groups Significant ↑ in the RAVLT:LTDR in the PA + CS group relative to controls
Ngandu et al. [27]	1260; 69.4 (4.7) years	Progressive muscle strength training (1–3 times/week), aerobic exercise (2–5 times/week), and exercises to enhance postural balance	Elderly individuals at a higher risk of AD	Tx *Z* scores ↑ 0.20 NTB Cx *Z* scores ↑ 0.16 NTB Between-group difference (Tx and Cx): 0.022

AD Alzheimer's disease, *ADAS-Cog* Alzheimer's disease assessment scale-cognitive subscale, *CS* cognitive stimulation, *Cx* control, *MCI* mild cognitive impairment, *NS* no significant, *NTB* neuropsychological test battery, *PA* physical activity, *RAVLT:LTDR* rey auditory verbal learning test: long-term delayed recall, *SCD* subjective cognitive decline, *SD* standard deviation, *Tx* treatment, ↑ indicates increased, ↓ indicates decreased

Table 2 Systematic reviews of intervention studies investigating the effects of increased PA on cognitive decline/dementia

Study	Design; *N*	Assessment of PA	Neurological condition	Findings
Öhman et al. [28]	22 RCTs; 1699	Walking, Tai Chi, ergocycling, and strength training lasting from 6 to 12 months	MCI, dementia	PA ↑ global cognition, executive function, attention, and delayed recall in MCI subjects NS effects on cognition in subjects with dementia
Forbes et al. [29]	17 RCTs; 1067	Tx: any combination of aerobic, strength, or balance training, vs. Cx: usual care, or social contact/activities; PA programmes; frequency (range 2–5 times/week, to daily, from 20 to 75 mins/session, from 2 weeks to 18 months	Dementia	NS effects on cognitive performance
Groot et al. [73]	18 RCTs; 802	(1) Aerobic only; (2) non-aerobic; and (3) combined aerobic with non-aerobic exercise; high and low frequency	Dementia, AD	PA ↑ cognitive function in AD- and non-AD-related dementia Greater ↑ for combined PA than aerobic only NS effect for non-aerobic PA Both high and low frequency ↑ cognition
van Uffelen et al. [153]	8 RCTs; 543	Aerobic exercise only, strength exercise, strength and balance exercise, all-round exercise, including aerobic, strength, balance, and flexibility training, from 6 to 52 weeks of 20–65 min sessions at a frequency of 1–3 times/week	CD, dementia	Significant ↑ in general cognitive function, executive functions, and memory

AD Alzheimer's disease, *CD* cognitive decline, *Cx* control, *MCI* mild cognitive impairment, *NS* no significant, *PA* physical activity, *PD* Parkinson's disease, *RCTs* randomised controlled trials, *Tx* treatment, ↑ indicates increase

Table 3 Systematic reviews on epidemiological studies investigating the relationship between PA and cognitive decline/impairment/dementia

Study	Design; *N*	Assessment of PA	Neurological condition	Findings
Sofi et al. [55]	15 prospective studies (12 cohorts); 33,816 without CI at baseline, followed for 1–12 years	Self-report PA	CD or CI	PA ↓ CI risk by 35% vs. sedentary individuals High-intensity PA by 38% vs. sedentary individuals
Hamer and Chida [57]	16 prospective studies, 163,797 without dementia at baseline	Self-report PA	Dementia, AD, PD	PA associated 28% ↓ dementia risk and 45% AD risk NS association between PA and PD

AD Alzheimer's disease, *CD* cognitive decline, *CI* cognitive impairment, *NS* no significant, *PA* physical activity, *PD* Parkinson's disease, ↓ indicates decreased

sedentary behaviour are strongly associated with obesity [46], T2DM, and CVD [43, 46, 47], which have been identified as key contributing causes of each AD risk factor [48–50]. Indeed, a sedentary lifestyle is associated with increased AD risk [51], with physical inactivity being the single largest modifiable risk factor for AD, while increased PA is considered protective against AD [52].

3.2.1 PA, Cognition and Risk of AD: Epidemiological Findings

The epidemiological evidence (Table 4) suggests a strong association between moderate or high levels of PA and improved cognitive performance later in life [53], even after adjusting for factors such as sex, age, baseline cognitive status, and depression. Women who reported being physically active at different ages (30, 50 years, and late life) had a reduced likelihood of developing cognitive impairment later in life compared with physically inactive women, particularly when they engaged in higher PA in their earlier years [54]. A meta-analysis of prospective studies confirmed a consistent protection of PA against cognitive impairment later in life and this protection occurred at all levels of PA (Table 3) [55]. The beneficial effects of PA have also been extended to a reduced risk of all-cause dementia and AD [56], a finding confirmed in a

Table 4 Epidemiological studies investigating the relationship between PA and cognitive decline/impairment as well as dementia

Study	*N*	Assessment of PA	Neurological condition	Findings
Etgen et al. [53]	3903	No activity, moderate activity (< 3 times/week), and high activity (≥ 3 times/week)	Incident CI at 2-year follow-up	Baseline moderate or high PA was associated with ↓ incident CI risk, compared with no PA
Middleton et al. [54]	9344	Current (late life) yearly frequencies of low- (e.g. walking or gardening), moderate- (e.g. dancing or tennis), or high-intensity (jogging or skiing) PA; modified Paffenbarger questionnaire	CI	PA during youth, age 30 and 50 years, and late life was associated with a ↓ likelihood of CI later in life compared with physical inactivity
Laurin et al. [56]	6434	Combination of two questions from a risk factor questionnaire: frequency (low, moderate, or high: ≥ 3 times per week, weekly, or less than weekly) and intensity (more vigorous, equal to, or less vigorous than walking)	Incident CI and dementia	High PA was associated with ↓ risk of CI, AD, and dementia of any type
Buchman et al. [58]	716	Actigraphy for 10 days (total daily PA)	AD at 4-year follow-up	Lowest 10th PA percentile compared with highest 90th was associated with ↑ AD risk
Sturman et al. [63]	4055	US Health Interview Survey (walking for exercise, jogging, yard work, etc.); PA was measured as hours/week	CD	Each additional hour of PA/week was associated with ↓ rate of CD
Wang et al. [64]	776	Mental, physical, social, productive, and recreational activities; social and leisure activity data were gathered during personal interview with trained nurses	Dementia	Mental, social, or productive activity associated with ↓ dementia risk
Niti et al. [65]	1635	Social activities (attending church/temple/mosque), productive activities (shopping, hobbies), PA activities (walking, jogging, sports)	CD	Higher LA was associated with ↓ CD risk more than PA or SA
Podewils et al. [66]	5888	MLTAQ (walking, household chores, mowing, raking, gardening, etc.)	Dementia	Highest PA quartile was associated with ↓ dementia risk vs. lowest PA quartile Engaging in ≥ 4 activities was associated with ↓ dementia risk than 0–1 activity

AD Alzheimer's disease, *CD* cognitive decline, *CI* cognitive impairment, *LA* leisure activity, *MLTAQ* Minnesota Leisure Time Activity Questionnaire, *PA* physical activity, *SA* social activity, ↓ indicates decreased, ↑ indicates increased

systematic review of prospective studies demonstrating a link between increased PA and a lower risk of dementia and AD [57]. Of particular note is one study adopting actigraphy to objectively measure PA, as opposed to self-reported PA, which found that high total daily PA was associated with a lower risk of AD [58]. Compared with self-report, actigraphy is a valid and objective measure of PA in aging [59, 60] and does not rely on participants' subjective recall of previous PA levels, which is often challenging and inaccurate [61].

While the association between PA and lower risk of AD is well-established, this effect might be mediated or moderated by additional factors not easily accounted for, such as social engagement, educational level, depression, cognitive activity, and the number of different types of activities (as opposed to total duration alone) performed [55, 62]. Indeed, some studies have found that a previously significant relationship between PA and cognitive impairment became non-significant after adjusting for such factors [63–66]. For example, Podewils et al. [66] found that individuals engaging in a greater number of activities (≥ 4) had a significantly lower relative risk of dementia and AD than those engaging in 0–1 activities; individuals with the highest quartile of energy expenditure were not protected from relative risk of dementia after multivariate adjustment. Overall, the epidemiological data suggest a strong association between higher PA levels and a lower risk of cognitive impairment and AD later in life [54, 55], even after multivariate adjustment. However, due to the clustering of multiple risk factors with lower levels of PA, the magnitude of the independent association of PA with cognitive impairment and AD remains equivocal.

3.2.2 *PA and Cognition in Dementia: Experimental Findings*

Whether PA interventions improve cognition in clinical populations with existing AD is also contentious [28, 29].

Additional details regarding the methodologies and findings of studies can be found in Table 5. A two-point increase in Mini-Mental State Examination (MMSE) scores has been observed following a 3-month music-based exercise intervention in a clinical population with moderate dementia, which ranges from 10 to 18 MMSE points [67]. However, when considering a 2-point increase from baseline (M 12.87; SD 5.01) in the experimental group, at the end of the trial participants were still in the moderate phase of dementia, therefore the clinical implications of these findings are likely limited. Using treadmill walking, Arcoverde et al. [68] found that MMSE scores remained similar from baseline to post-intervention, while the control group experienced a decrease in MMSE scores, suggesting exercise slowed the rate of cognitive decline in this clinical AD group. Similarly, Venturelli et al. [69] found that aerobic walking significantly slowed cognitive decline when global cognition was measured with the Cambridge Cognitive Examination (CAMCOG) but not with the MMSE in individuals with borderline moderate–severe AD. This is likely explained on the basis that the MMSE has low sensitivity in detecting changes across periods of fewer than 6 months [70], which could explain why Venturelli et al. [69] observed significant changes in the

Table 5 Experimental trials investigating the effects of single-intervention PA programmes on clinical dementia

Study	*N*; mean age, years (SD)	Type of PA programme	Neurological condition	Findings
Van de Winckel et al. [67]	25; PA: 81.33 (4.24); controls: 81.90 (4.18)	Daily face-to-face 30-min PA sessions focusing on upper and lower body strengthening, balance, trunk movements, and flexibility training, which was supported by music such as folkloric accordion songs, including polka, folk, country, and western music	AD, MID	Tx ↑ from 12.87 to 15.53 MMSE Cx ↑ from 10.80 to 11.00 MMSE
Arcoverde et al. [68]	20; PA: 79 (74.7–82.2); controls: 78.5 (64–81.2)*	PA on a treadmill for 30 mins, twice weekly at moderate intensity (60% VO_{2max}) for 3 months	AD	Tx ↑ 6.10 (6.7) CAMCOG Cx ↓ 6.10 (4.3) CAMCOG NS effects on MMSE
Venturelli et al. [69]	24; PA: 83 (6); controls: 85 (5)	At least 30 mins of moderate aerobic exercise (walking) 4 times/week for 6 months	AD	Tx showed slower ↓ (−13%) compared with Cx (−47%) in MMSE
Eggermont et al. [71]	97; PA: NA; NA	Walking for 30 mins, 5 days/week, for 6 weeks	Dementia	NS effects on cognitive performance
Bossers et al. [72]	109; Combined group: 85.7 (5.1); aerobic group: 85.4 (5.4); social group: 85.4 (5.0)	Combined group: strength exercises (lower-limb strengthening) and aerobic exercise (moderate- to high-intensity walking); aerobic group received only the aerobic exercise; social group: social and intellectual engagement (30-min one-to-one social visits); intervention lasted 9 weeks	Dementia	Combined Tx ↑ 2.3 MMSE Aerobic Tx ↑ 1 MMSE Cx ↑ 0.72 MMSE
Steinberg et al. [74]	37; home safety 74.0 (8.1), exercise 76.5 (3.9)	Combined group = aerobic fitness (brisk walking), strength training (major muscle groups), balance and flexibility training (shifting centre of gravity, tandem walks, forward and backward walks, and chair sit to stands); daily exercises for 12 weeks; control group = home safety assessments	Probable AD	Combined Tx showed NS ↑ in primary outcome (global cognition) Combined Tx showed worse depression and QOL Combined Tx ↑ JTT after controlling for MMSE scores
Miu et al. [75]	85; Combined group: 75 (7); control group: 78 (6)	Combined group = treadmill, bicycle and arm ergometry, and 10-min flexibility training (at the start of each session) for 3 months, twice/week for 45–60 mins	Dementia	NS effects on cognitive performance Combined Tx showed ↑ in physical function

AD Alzheimer's disease, *CAMCOG* Cambridge Cognitive Examination, *JTT* Jebsen Total Time, *MID* multi-infarct dementia, *MMSE* Mini-Mental State Examination, *NA* not available, *NS* no significant, *PA* physical activity, *QOL* quality of life, *Tx* treatment, ↑ indicates increased, ↓ indicates decreased

* range

CAMCOG scores but not in the MMSE scores. However, aerobic walking was found not to improve global cognition in nursing-home residents with moderate dementia, but the intervention in this study lasted only 6 weeks [71].

There is experimental evidence that also shows that combining aerobic with non-aerobic exercise (i.e. resistance or strength exercises) can improve cognition more than aerobic exercise alone [72, 73]. For example, global cognition, executive functions, and verbal and visual memory were improved more in individuals with dementia combining 9 weeks of aerobic (walking) and non-aerobic exercise (strength exercises) than individuals completing aerobic-based exercises only [72]. However, despite similar methodology and good adherence, Steinberg et al. [74] showed only modest (non-significant) improvements in global cognition following a multimodal exercise programme by the end of the study [74]. Similarly, Miu et al. [75] did not detect improvements in global cognition following a combination of treadmill, bicycle, and arm ergometry relative to controls, among individuals with dementia. Recently, a meta-analysis revealed that although aerobic-based PA interventions were beneficial in AD patients, the combination of aerobic with non-aerobic exercise produced greater effects on cognition [73]. However, a systematic review by Forbes et al. [29] reported a similar effect size for exercise on cognition as was observed by Groot et al. [73], but concluded that a meta-analysis could not be conducted due to substantial unexplained statistical heterogeneity ($I^2 = 80$).

To date, there is promising evidence supporting a role for exercise in improving cognition in individuals with dementia, but the field does have several studies yielding conflicting results [29]. There appear to be several key elements required for a PA intervention to demonstrate significant and clinically meaningful improvements in cognition among individuals with AD. These include multimodal PA interventions with at least one aerobic component [73] consisting of at least 150 min during the week, and which is delivered for longer than 10 weeks [28, 76]. The exercise intervention should be supported by additional PA (incidental) throughout the day to improve global cognition [77]. Moreover, since physical exercise likely affects particular dementia subtypes in different ways, the specific programming (duration, intensity, type, frequency) of exercise is likely to be an important consideration for studies in individuals with existing AD [28, 29, 78].

3.3 Genetic Markers and Risk of Cognitive Decline and AD

Several genetic markers have been associated with increased AD risk, including *APOE*, *klotho*, WW domain-containing protein 1 (*WWC1*), and brain-derived neurotrophic factor (*BDNF*). Although *klotho* (encoding the transmembrane protein klotho [79]) and *WWC1* (encoding the KIBRA protein [80]) have both been implicated in cognitive impairment, their involvement in cognitive decline and AD development are equivocal [81, 82]. As such, *BDNF* and *APOE* have garnered the greatest attention in this field.

The *APOE* gene is polymorphic, with three major alleles, namely ε2, ε3, and ε4, with a global prevalence of 8.4, 77.9, and 13.7%, respectively; the ε4 is approximately 40% prevalent among individuals with AD [83]. The presence of at least one copy of the ε4 allele (ε2/ε4; ε3/ε4) increases the risk of AD by odds ratios (ORs) of 2.6 and 3.2, respectively, while two copies (ε4/ε4) increases the risk of AD by an OR of 14.9 among Caucasian people [83]. Furthermore, the presence of one or two *APOE* ε4 alleles can trigger the onset of AD 5 or 10 years earlier, respectively [84]. Therefore, the *APOE* ε4 is a major non-modifiable risk factor for AD and is associated with a younger age of onset [85]. While the *APOE* ε4 is a risk factor for CVD [86], coronary heart disease [87], and higher amyloid aggregation, which is in itself a risk factor for AD [88], the exact mechanisms explaining the link between *APOE* ε4 and increased AD risk are still unclear. Of particular relevance to this review, individuals with SCD who are also carriers of the *APOE* ε4 allele are twice as likely to progress to AD than those without SCD and the *APOE* ε4 allele, suggesting that both factors produce an additive effect in cognitive decline [89]. Additionally, SCDs that test positive for the *APOE* ε4 allele demonstrate glucose hypometabolism in brain areas typically affected by AD, such as the parieto-temporal lobe, when compared with non-carriers [90].

The *BDNF* gene encodes the BDNF, which is a growth factor in the central nervous system that has been shown to regulate neuronal growth, promote neuronal survival, and regulate synaptic plasticity [91]. In addition, BDNFs may regulate neuroplastic processes such as long-term potentiation in the hippocampus [92], and, as such, BDNFs may play an important role in the pathogenesis of AD [93]. Phillips et al. [94] were the first to show reduced post-mortem in situ expression of BDNF messenger RNA (mRNA) in the hippocampal formation of nine AD patients compared with six control donors. Since then, several studies have shown decreased BDNF serum levels among individuals in the preclinical [95] and clinical phases of AD [96, 97], and that the BDNF levels correlate with the degree of cognitive impairment [98]. A large cross-sectional study including 4463 community-living elderly participants found that after adjusting for covariates, lower serum BDNF levels were associated with a decline in memory performance and with an elevated risk for MCI

[99]. Importantly, circulating BDNF is generally accepted as a suitable surrogate marker of total (central and peripheral) BDNF concentration; however, the short half-life and low blood–brain barrier perfusion capacity of BDNF [100] require further investigation.

3.3.1 Apolipoprotein ε4 Allele and PA

Given that presence of at least one of the *APOE* ε4 alleles is associated with poorer performance on cognitive tasks [101] and an increased risk of AD [84], researchers have assessed whether cognitive benefits arising from PA are moderated by *APOE* ε4 allele status. Indeed, evidence indicates that PA levels have a greater effect on cognitive function and future incidence of cognitive decline among individuals who carry at least one copy of the *APOE* ε4 allele [102–104], although some researchers have not observed the same relationship [66]. For example, less than an hour/day of PA was associated with an increased risk of cognitive decline [$N = 347$; OR 2.0, 95% confidence interval (CI) 0.9–4.8], and this effect was stronger in *APOE* ε4 allele carriers (adjusted OR 3.7, 95% CI 1.1–12.6), even after adjusting for additional confounders [102]. Similarly, a longitudinal population-based survey (mean follow-up period 21 years) found that the beneficial effects of PA on dementia risk were more robust between *APOE* ε4 allele carriers (OR 0.23) and non-carriers (OR 0.59) among 1449 older adults (age range 65–79 years) [105]. However, in contrast, Podewils et al. [66] found an inverse association between PA and dementia risk for *APOE* ε4 non-carriers, but found no association for *APOE* ε4 carriers in their prospective study including 3075 men and women (age $\geq$ 65 years, mean follow-up 5.4 years). In this study, PA levels were obtained via self-report and via the kcal/week and number of activities (range 0–14) performed in the previous 2 weeks reported. It was interesting to note that participation in multiple ($\geq$ 4) different types of activities appeared to be as important, if not more important, than the self-reported PA levels in this cohort [66].

3.3.2 Brain-Derived Neurotrophic Factors (BDNF) and PA

There is evidence [106, 107] suggesting a possible association between habitual PA or cardiorespiratory fitness (CRF) and BDNF concentration, although this is not consistently observed [108–111]. For example, Zoladz et al. [107] found that basal BDNF concentration was significantly higher in trained athletes ($n = 16$) compared with untrained individuals ($n = 13$), which agrees with the findings of Correia et al. [106] in international- and domestic-level sprinters (vs. sedentary individuals). However, in contrast, Winker et al. [111] found no difference in BDNF concentration between active elderly marathon runners and cyclists ($n = 56$) matched for age, sex, and years of education to sedentary individuals ($n = 58$), while Nofuji et al. [110] found basal BDNF concentrations were lower in a group of trained males ($n = 12$) compared with a group of sedentary males ($n = 14$). In line with this view, Chan et al. [108] and Jung et al. [109] observed an inverse relationship between BDNF concentrations and PA level ($n = 85$) and CRF ($n = 995$), respectively. Therefore, based on the current evidence, a clear relationship between PA or CRF and BDNF cannot be made [112]. While these mixed findings may be attributed to several potential confounders, the circadian variation in circulating BDNF concentrations (typically reflecting cortisol concentration) in both men [113] and women [114] may partly explain some of the variance in study outcomes.

Findings from prospective research assessing the effects of aerobic exercise on serum BDNF concentration have also been mixed, with resting BDNF concentration remaining largely unchanged in response to chronic exercise training despite acute exercise yielding substantial transient increases in BDNF concentration [112]. Aerobic exercise training (3 or 5 weeks) did not alter basal BDNF concentrations in 47 sedentary adult males [115]. Likewise, a 6-month longitudinal intervention testing the effects of low and moderate PA in 62 cognitively healthy elderly subjects found only a non-significant positive trend between BDNF and PA [116]. More specific to the current review is the finding that in individuals with amnestic MCI ($N = 33$), chronic (6 months, 4 days/week, supervised) aerobic exercise did not significantly alter BDNF levels, although a potential sex difference has been proposed [117]. In contrast, a robust albeit transient increase in BDNF concentration has been observed in response to acute aerobic exercise [112] and this has occurred concomitant with improved cognitive performance. For example, acute cycling [118–122], stepping [123], and rowing [124] have been shown to increase serum BDNF levels in healthy and clinical populations with major depression [120] and individuals with spinal cord injury [122]. There is evidence that the magnitude of change in BDNF concentration is intensity-dependent, with acute high-intensity exercise having a greater effect on peripheral BDNF concentration compared with acute low-intensity exercise [112, 118, 121]. For example, Ferris et al. [118] showed a pre-post significant increase in serum BDNF concentration following 30 min of cycling at 10% above, but not at 20% below, ventilatory threshold. Nevertheless, increases in peripheral BDNF following acute exercise seem to be transient since concentrations in BDNF return to baseline during passive recovery [125]. Moreover, Ferris et al. [118] and Griffin et al. [115] also observed improvements in cognitive performance (as assessed using

the Stroop colour/word test and face-name matching task, respectively); however, Ferris et al. [118] lacked a control group and cognitive scores did not correlate with circulating BDNF levels. It is worth noting that some of these studies had small sample sizes including eight [124], 11 [119], and 15 [118] participants. Nevertheless, a recent review concluded that acute ($n = 14$ studies) and chronic ($n = 6$ studies) aerobic exercise increased peripheral BDNF concentrations [112], albeit this effect was more robust for the transient increase in response to acute exercise.

There is currently little evidence to suggest that resistance training performed in isolation will increase BDNF concentration [112]. However, in a convenience sample of 48 elderly women, Coelho et al. [126] found increases in plasma BDNF levels following resistance training three times/week for 10 weeks, while Yarrow et al. [127] found transient increases in serum BDNF after an acute bout of resistance training in 20 males, but did not observe changes in resting BDNF levels after 5 weeks of training. The lack of effect on serum BDNF following acute resistance training has been replicated in healthy males ($N = 16$) [128], sports students ($N = 19$; 12 weeks) [129], and untrained older individuals [mean age 50.9 years (6.2)] who trained three times/week for 10 weeks [130].

In sum, observational and experimental evidence in healthy and cognitively impaired populations suggest that increased PA is associated with increases in basal BDNF levels. These increases may be moderated by the type of exercise, with aerobic exercise generating more robust effects on BDNFs, and by a dose–response relationship that may be intensity-dependent [112, 118, 121], but the observed increases return to baseline (15–60 min) during passive recovery [125]. In some cases, increases in BDNF levels correlate with improved cognitive performance [115], while in others they do not [118]. It is worth mentioning that blood processing (serum: clotting time and temperature; plasma: platelet stores) [131], circadian rhythms [113, 114], and phases of the menstrual cycle [114] may affect BDNF concentrations.

4 Brain Biomarkers in AD Pathophysiology and their Interaction with PA

Pathophysiological abnormalities can occur years before clinical symptoms manifest, which makes neuroimaging techniques particularly useful in the preclinical and early clinical stages of AD [15, 132]. Because a definitive AD diagnosis can only be achieved with histopathological confirmation, the inclusion of neuroimaging methods can increase specificity and diagnostic value in clinical and research settings [133]. Neuroimaging methods used in diagnosing neurodegenerative disorders include structural imaging such as MRI, computer-assisted tomography (CT), functional imaging such as single photon emission tomography (SPECT), and positron emission tomography (PET) [134]. For diagnosing AD, and compared with other neuroimaging techniques, PET has one of the highest rates of sensitivity (86%) and specificity (86%) [135]. Therefore, the following sections will only discuss PET imaging.

4.1 PA Findings on Pittsburgh Compound B-PET

Currently, PET imaging using radioactive tracers are available to detect Aβ deposits in the brain. The Pittsburgh compound B (PiB), which is the analogue of thioflavin T, is the most commonly used tracer for amyloid imaging [136]. In PiB-PET, the compound binds to fibrillar Aβ, but does not bind to diffuse plaques and soluble Aβ, and can be used to differentiate AD and healthy controls [137, 138]. Moreover, individuals with subtle decline in episodic memory—the first cognitive faculty affected by AD—and a PiB-PET-positive scan, have a 50% increased risk of progressing to MCI and AD within 3 years [139]. Nordberg et al. [138] found that individuals with MCI and PiB-PET-positive scans not only had greater memory impairment compared with those with PiB-PET-negative scans at baseline, but also progressed to AD at a rate of approximately 25% per year compared with a 0% conversion rate in those with PiB-PET-negative scans. However, it is worth noting that while some individuals who are PiB positive progress to AD, others do not. Indeed, PiB retention alone does not appear to correlate well with cognitive impairment [140].

There is evidence that PA levels might affect Aβ levels in the brain, cerebrospinal fluid (CSF), and blood. For example, Liang et al. [141] found that individuals ($N = 69$) meeting the American Heart Association guidelines of 7.5 metabolic equivalent (MET) hours/week of exercise showed significantly lower PiB binding and higher levels of $A\beta_{42}$ (considered the more fibrillogenic form of Aβ and more closely associated with disease states) in the CSF. Importantly, $A\beta_{42}$ levels in the CSF are inversely associated with $A\beta_{42}$ aggregation in the brain and, as such, higher levels in the CSF are generally accepted as being indicative of a healthier amyloid profile. In a larger sample ($N = 546$), Brown et al. [142] found that higher PA was negatively associated with lower plasma $A\beta_{1-42/1-40}$ ratio, and, after stratifying participants by *APOE* ε4 allele status, this association was present in *APOE* ε4 allele non-carriers but absent in *APOE* ε4 allele carriers. Conversely, there was an association between higher PA levels and lower amyloid brain load, as measured by PiB-PET, in *APOE* ε4 allele carriers only [142]. Furthermore, in a sample of 201 cognitively intact adults, Head et al. [143] found a sedentary lifestyle was associated with higher PiB binding and

lower CSF $A\beta_{42}$ levels. Moreover, a significant interaction between *APOE* ε4 allele status and exercise engagement for PiB binding was revealed, with a sedentary lifestyle being associated with higher PiB binding in *APOE* ε4 allele carriers ($p = 0.013$), but not for *APOE* ε4 non-carriers.

4.2 PA Findings on [18F]-Fluorodeoxyglucose

At rest, brain activity almost exclusively depends on glucose metabolism; therefore, glucose hypometabolism is considered a more robust surrogate marker of cognitive decline compared with the presence of excessive Aβ [144]. The [18F]-fluorodeoxyglucose (FDG)-PET can be used to generate images of glucose uptake into neural cells in different brain regions. Topographical patterns of reduced uptake, shown by reduced [18F] signal intensity, indicate neurodegeneration even after correcting for cortical atrophy in AD patients [145]. Therefore, FDG-PET can be used to investigate the relationship between PA and glucose metabolism. Deeny et al. [146] found that during a working memory task among individuals with the *APOE* ε4 allele, highly fit (indicative of high PA) compared with low fit (indicative of low PA) elderly females showed greater glucose uptake in the temporal lobe, which is a brain region affected by AD. In contrast, low fit *APOE* ε4 allele carriers showed greater cerebral glucose uptake in the frontal and parietal regions; however, this relationship was not observed during resting glucose metabolism. This indicates that CRF levels likely affect glucose metabolism in the brain in *APOE* ε4 allele carriers compared with non-carriers, which is in line with previous studies having found that the effects of exercise on cognition tend to be more pronounced in *APOE* ε4 allele carriers compared with non-carriers [102, 103]. This conclusion is supported by experimental data showing that a combination of PA and computerised brain training improved glucose metabolism in the left sensorimotor cortex, even after adjusting for age, sex, premorbid IQ, *APOE* ε4 allele status, and history of head injury among non-clinical older individuals [26]. Together, the findings from Shah et al. [26] and Deeny et al. [146] suggest that increased PA may improve cerebral glucose metabolism and counteract the decline in brain glucose uptake that is often present in the preclinical phases of AD.

5 Limitations of Studies on PA and AD with Suggestions for Future Research

5.1 Epidemiological Data

Findings drawn from the epidemiological and experimental literature are limited by several methodological shortcomings. For example, in many observational studies, researchers assessed PA through a single self-report questionnaire [55, 57, 66, 147]. These are susceptible to information bias [148], which threatens internal validity [149], and self-rated fitness has been shown to be inversely related to perceived physical exertion in men and women [150]. Additionally, some epidemiological studies administered PA questionnaires that were not designed for elderly populations [66] or lacked psychometric properties [102, 105, 151]. Several studies have also used different methods to classify duration and intensity of PA or combined frequency, duration, and intensity [55], making it difficult to establish a clear dose–response relationship [152]. From the extant epidemiological literature, it is unclear whether lifelong engagement in high PA is necessary to alter disease-risk profiles due to most studies having focused on elderly populations [55]. Finally, the effects of PA might at least in part be mediated by other factors, including social engagement [62] and number of different activity types [66], which could explain some of the variance in the incidence rate of AD, but this has not been considered in all epidemiological literature [147].

5.2 Experimental Data

A limitation of studies in the field relates to the different types of dementia and the different severity levels being assessed [28, 29], with PA likely affecting different dementia subtypes to a varying extent [78]. In addition, studies included a wide range of different types of exercise programmes that included both supervised and unsupervised training prescribed with different intensities, frequencies, and durations. Similar to the epidemiological studies, the assessment of cognition (e.g. MMSE vs. executive function tasks) and chosen risk markers of AD or cognitive impairment (blood samples vs. CSF samples; neuroimaging techniques vs. protein concentrations) vary widely in the extant literature, making comparisons problematic [29]. In addition to these methodological limitations, some trials did not report intention-to-treat analyses [67, 76] and adherence or attrition rates [76], and were likely statistically underpowered [28, 68, 153], particularly when multivariate adjustments were conducted.

5.3 Suggestions for Future Research

Drawing from the limitations identified above, to improve methodology and decrease the risk of bias, several suggestions for future epidemiological and experimental research are warranted. Since the extant epidemiological evidence has mostly focused on elderly individuals [55], from a public health perspective, it is not possible to generate recommendations for different age groups for mitigating the age-related decline in cognition [6] or alter

risk profiles for dementia. While not without complications, future epidemiological research should focus on exploring the relationship between lifelong exposure to PA and dementia [152] using a validated tool in combination with a CRF test. For example, this could be achieved by linking with existing longitudinal studies that have collected PA levels or data linkage programmes that have access to individuals PA levels. The level of PA needs to be assessed in a more precise way using objective measures such as accelerometry [58] over at least a 2-week period, although these devices are not without shortcomings [154], while, in experimental trials with smaller numbers, direct supervision of exercise participation is critical to generate more precise estimates of PA. Since AD populations find it difficult to adhere to PA interventions [147, 155], it is also important to investigate what type of PA intervention is appropriate for cognitively impaired individuals [147] in prospective studies, particularly since comorbid conditions (e.g. osteoarthritis) often present in the elderly population [156].

Additionally, most experimental studies have focused on cognition as the primary outcome measure, excluding other important variables [29]. The European consensus on endpoints for trials on AD advises the inclusion of functional and proxy endpoints to capture a more comprehensive functioning of the patient [157]. Thus, to render the findings more clinically relevant, the implementation of an exhaustive battery of global functioning (with *a priori* adjustment for type I error), including cognitive and functional tests, is important for establishing whether the intervention has helped the patient to meaningfully regain quality of life [157, 158]. In studies focused on individuals at greater risk of progressing to AD (e.g. SCD), reports of SCDs by proxy (e.g. informant) correlate better with objective performance [159] and are a robust predictor of progression to AD [160] and should therefore be considered. Finally, to assess the role of exercise in altering AD risk and progression in the early stages (e.g. SCD and MCI), adoption of the multiple biomarkers that can better predict AD risk and progression are recommended.

6 Conclusions

There is compelling evidence that exercise improves biomarkers of AD and cognitive performance, and that greater engagement in chronic PA is associated with improved cognition, a later onset of AD, and slowed disease progression; however, conflicting results are prevalent in the extant literature. Epidemiological evidence suggests a clear benefit of PA on improving cognition and reducing AD risk, particularly when the PA is performed at high intensity; however, the magnitude of these associations are typically diminished after analyses are adjusted for the multiple confounding variables (i.e. age, sex, body mass index, *APOE* ε4 status, educational level, smoking, alcohol intake, social support, difficulty in activities of daily living, and instrumental activities of daily living) that often cluster with PA levels.

The experimental studies assessing the impact of acute exercise suggest (1) a transient (minutes to hours) increase in BDNF following aerobic exercise, which is not observed following resistance exercise, (2) greater BDNF responses following higher intensity aerobic exercise, and (3) improvement in executive function tasks; while the experimental studies assessing exercise training suggest (1) improvements in cognition following exercise training in the preclinical and early clinical stages of dementia/AD (i.e. SMC, MCI), but mixed results in individuals with dementia/AD, and (2) greater improvements in cognition across the dementia/AD spectrum when training incorporated a greater frequency of both aerobic and non-aerobic activities. The findings from studies adopting neuroimaging techniques, which are considered more sensitive than other outcome measures, suggest that exercise and PA play an important protective role against AD pathophysiology, particularly in individuals with an *APOE* ε4 allele, which is consistent with the findings from studies using cognitive outcome measures in this cohort. Despite the equivocal nature of the available evidence, it remains noteworthy that a single modifiable risk factor such as PA has largely been shown to affect both the onset and progression of a disease as complex as AD. From a public health perspective, it is important that future research addresses the limitations of previous research and establishes the direct association between PA and AD.

Compliance with Ethical Standards

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Conflicts of interest Ralph N. Martinsis is the founder and Chief Scientific Officer of the biotech company, Alzhyme. Hamid R. Sohrabi has received, and continues to receive, remuneration from activities with Takeda Pharmaceuticals. Stefano Brini, Jeremiah J. Peiffer, Mira Karrasch, Heikki Hämäläinen and Timothy J. Fairchild declare that they have no conflicts of interest.

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