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Chronic physical activity and the prevention of Alzheimer's disease

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A B S T R A C T

The growing population of older adults and the lack of cure for Alzheimer's disease (AD) has resulted in researchers identifying modifiable lifestyle factors that might prevent or slow the progression of the disease. Prospective studies exploring the relationship between baseline physical activity (PA) and the subsequent risk of a diagnoses of AD and randomized controlled trials (RCTs) testing the effects of aerobic exercise (AE) and resistance exercise (RE) on cognitive performance, blood-based biomarkers of AD, and neuroimaging measures of brain health provide some intriguing results. Exemplars of these studies and results from meta-analytic reviews (when available) are presented to provide an overview of the state of the science. In general, results from prospective studies show that PA is protective, and results from RCTs show that AE improves cognitive performance by older adults who are cognitively normal and by those with mild cognitive impairment. Promising results have been observed for AE on measures of brain health, and studies exploring the effects on biomarkers have yielded some intriguing results but are less consistent to date. Studies testing the effects of RE also find benefits for cognitive performance by older adults and consistently show improvements in brain health. In conclusion, results from prospective studies and RCTs demonstrate the potential of exercise to improve cognition, brain health, and, to a lesser extent, blood-based biomarkers. Future research linking the magnitude of the findings from RCTs with evidence from prospective studies will advance our understanding of the potential of exercise to reduce the risk of AD.

With advancing age, small declines in cognitive performance are typical. However, for some older adults, these small changes may portend an accelerating decline in brain health, ultimately resulting in dementia. Dementia is defined as "a clinical syndrome characterized by progressive cognitive decline that interferes with the ability to function independently" (Duong et al., 2017, p. 118). Within the broad category of dementia, Alzheimer's disease (AD) is the most common form accounting for 60–70% of cases (World Health Organization, 2023). Given the anticipated increase in the population of older adults, it is expected that worldwide cases of AD will increase from 57.4 million in 2019 to 83.2 million in 2030, 116 million in 2040, and 152.8 million in 2050 (Nichols et al., 2022).

AD is a neurodegenerative disease characterized behaviorally by decrements in short-term memory and biologically by the accumulation of amyloid beta (Aβ) and tau proteins which damage the neurons of the brain. AD is currently thought to progress from preclinical to mild cognitive impairment (MCI) to dementia (Alzheimer's Association, 2024). Interestingly, even during the asymptomatic stages, differences in brain health can be observed in those individuals who are most likely to convert to AD. For example, evidence supports that abnormal levels of Aβ (Gordon et al., 2018), neurofilament light chain protein (Quiroz et al., 2020), and tau protein, decreases in glucose metabolism, and increases in brain atrophy can be observed 13–22 years in advance of symptom onset (Barthélemy et al., 2020). This is important because it suggests the potential value of intervening early with individuals who are at greatest risk for AD.

The growing challenge that society will face due to AD has resulted in a robust response by scientists focused on advancing our understanding of the disease and on disease treatment and prevention. However, there is currently no known cure for AD. Researchers have identified numerous putative pathways to target with pharmacological interventions, but thus far effectiveness has been limited, and there have been concerns about the risk of severe side effects (Alzheimer's Association, 2024). Although there is great potential in AD therapeutics research, scientists are also focusing on modifiable risk factors for AD as a way of delaying or preventing AD.

In the most recent report provided by the Lancet Standing Commission on Dementia (Livingston et al., 2024), the authors identified 14 potentially modifiable risk factors for dementia, accounting for 45.3% of the weighted population-level risk for dementia. During midlife (defined as 18–65 years old), these include several risk factors related to energy balance, including high LDL cholesterol, physical inactivity, diabetes, hypertension, and obesity that account for a combined 14% of the weighted population-level risk for dementia. Participation in regular

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exercise during midlife is therefore implicated as a potential intervention to reduce the risk of AD.

Early research in the area of exercise psychology demonstrated that chronic physical activity benefits cognitive performance across all ages. This work was summarized meta-analytically yielding an overall effect size of Hedges's $g = 0.33$ with the largest effects observed for older adults (45–60 years, $g = 1.02$) and smaller effects reported for the oldest adults (60–90 years, $g = 0.19$) and adults (30–45 years, $g = 0.06$) (Etnier et al., 1997). In a subsequent meta-analysis focused exclusively on older adults (>55 years), Colcombe and Kramer (2003) reported an overall effect size of Hedges's $g = 0.48$ for all exercise studies. Since that time, numerous empirical studies have been conducted and meta-analyses have consistently reported small-to-moderate beneficial effects for exercise on cognitive performance. These promising results have led scientists to begin to specifically explore the potential role of physical activity (PA) as a means of protecting against AD. In more recent years, researchers have used prospective designs to test the effects of physical activity (PA) at one point in time on subsequent risk for AD, have worked to understand potential differences in benefits as a function of PA modality (e.g., aerobic exercise, resistance exercise), have begun to explore underlying mechanisms and putative AD biomarkers, and have examined the benefits of PA for persons with MCI or relative to their genetic risk for AD.

1. Prospective studies and AD prevention

Yaffe et al. (2001) conducted the first prospective study establishing a link between PA and the prevention of AD. Participants (n = 5925) were women free of cognitive impairments at baseline and were tested again after a 6- to 8-year follow-up. The authors assessed PA by recording the number of blocks (1 block ≈ 160 m) each participant walked daily, either for exercise or as part of her normal routine, along with the number of flights of stairs climbed each day. Self-report data were also collected using the modified Paffenbarger Scale, which computes total PA (kilocalories per week). PA data was summarized into quartiles for all measurements, ranging from the lowest to the highest. The authors found that the odds of cognitive decline were reduced by 37% and 35% for women in the highest quartile of blocks walked and total kilocalories expended, respectively, compared to those in the lowest quartile.

Since this first study, numerous prospective studies have been conducted with reviews (Stephen et al., 2017) and meta-analyses (Beckett et al., 2015; Hamer & Chida, 2009; Sofi et al., 2011; Yu et al., 2020) generally supporting a protective effect of PA for subsequent AD. For instance, Hamer and Chida were the first to perform a meta-analysis quantifying the associations between PA and risk of neurodegenerative disease, including incident dementia, AD, and Parkinson's disease. The included studies examined non-demented men and women at baseline, with no restrictions on age. The pooled relative risk (RR) among participants who engaged in higher levels of PA was 0.72 for overall dementia and was 0.55 for AD. Sofi et al. analyzed data from 33, 816 participants from 15 prospective studies who were followed for 1–12 years. High levels of PA were associated with a 38% reduction in the risk of cognitive decline, while low-to-moderate PA also conferred significant protection, reducing the risk by 35%. Beckett et al. provided further evidence from nine prospective studies, including 20,326 participants aged 65 years or older who were dementia-free at baseline. In their analyses, they adjusted for age, sex, years of higher education, presence of the APOE epsilon 4 (ε4) allele (a genetic risk factor for AD), body mass index (BMI), and depression and found that physically active older adults had a lower risk of AD compared to their non-active counterparts (RR = 0.61). Stephen et al. included 24 prospective studies in their review, with sample sizes ranging from 176 to 5698 and follow-up periods from 1 to 34 years. An interesting aspect of this paper is that the authors broadened their definition of PA to capture PA from various domains, including sports, leisure, hobbies, and work-related. They concluded that leisure PA consistently demonstrated a protective effect against AD, whereas other forms of PA did not. Thus, across numerous meta-analytic reviews of prospective studies, findings consistently support a reduction in the risk of clinical cognitive decline for individuals who are more physically active 1–34 years earlier.

This evidence underscores the importance of PA as a protective factor. However, one of the challenges of prospective studies relates to the variability in the length of follow-up periods. For example, Sofi et al. (2011) reported follow-up durations ranging from 1 to 12 years, while Stephen et al. (2017) included follow-ups ranging from 1 to 34 years—resulting in a 22-year difference in the upper limits of these studies. Given that AD can begin developing up to 10 years (Sabia et al., 2017) or even 20 years before the onset of overt symptoms (Bateman et al., 2012; Ryman et al., 2014), studies with shorter follow-ups may fail to capture the long-term protective effects of PA against AD. Instead, they may introduce variability by including individuals already in the preclinical stages of the disease. The reverse causality hypothesis proposes that AD progression leads to reduced PA engagement rather than PA protecting against AD (See Fig. 1). Supporting this theory, research suggests that declining PA levels may reflect early neurodegenerative changes that limit PA participation (Kivimäki et al., 2019; Sato et al., 2021). Consequently, studies with follow-ups of less than 10 years may include participants who already present preclinical AD.

Kivimäki et al. (2019) specifically tested this empirical question relative to the duration of the follow-up period and found evidence supporting the reverse causality hypothesis. They included 19 prospective observational cohort studies with 404,840 participants who were free of dementia at baseline. Among participants under 65 years of age, they found a significant association between physical inactivity and dementia (hazard ratio [HR] 1.40 for all-cause dementia and 1.36 for AD) when inactivity was assessed <10 years prior to diagnosis. However, this association disappeared with assessments >10 years before diagnosis (1.01 vs. 0.96 for all-cause dementia and AD, respectively), suggesting that early preclinical dementia stages influence inactivity. In contrast, Iso-Markku et al. (2022) and Zhang, Li, et al. (2023) did not find evidence that early AD symptoms affect participation in PA. Specifically, Iso-Markku et al. conducted a meta-analysis of 58 studies involving 257,983 participants aged 20–65 years of age, all free of dementia at baseline. The mean follow-up time was divided into two categories for each disease: one included all studies and the other included only those with follow-ups longer than 20 years. PA was associated with a decreased risk of all-cause dementia (RR = 0.80), AD (RR = 0.86), and vascular dementia (RR = 0.79) across all studies. The protective association remained significant even in studies with follow-ups exceeding 20 years for all-cause dementia (RR = 0.89) and AD (RR = 0.89). The analyses were controlled for age at baseline, follow-up length, study quality, and APOE-ε4 carrier status. Thus, the findings support the causal direction of PA protecting against dementia, AD, and vascular dementia, while early AD symptoms do not appear to limit participation in PA. Zhang, Li et al. report similar findings from their meta-analysis of 29 prospective cohort studies with 2,068,519 participants aged 65 years or older who were cognitively normal at baseline. The mean follow-up was 14.9 years (range: 3.9–44 years). After adjusting for covariates including age, baseline cognition, chronic disease, education, sex, vascular risk factors, and APOE-ε4, crude HR (cHR) and adjusted HR (aHR) were computed. Results showed higher PA levels significantly reduced AD incidence (cHR = 0.72; aHR = 0.85). An inverse dose-response relationship indicated greater protection with moderate (cHR = 0.86) to high (cHR = 0.56) PA levels. Counter to the reverse causality hypothesis, the protective effect was stronger (<5 years: HR 0.56; 5–10 years: HR 0.47; 10–15 years: HR 0.78) in shorter follow-ups (<15 years) than in longer follow-ups (HR 1.00).

In summary, meta-analytic reviews of prospective studies consistently support a protective effect of PA in terms of reduction in the risk for AD in future years. Although it is important to consider the possibility of the reverse causality hypothesis in studies using shorter follow-

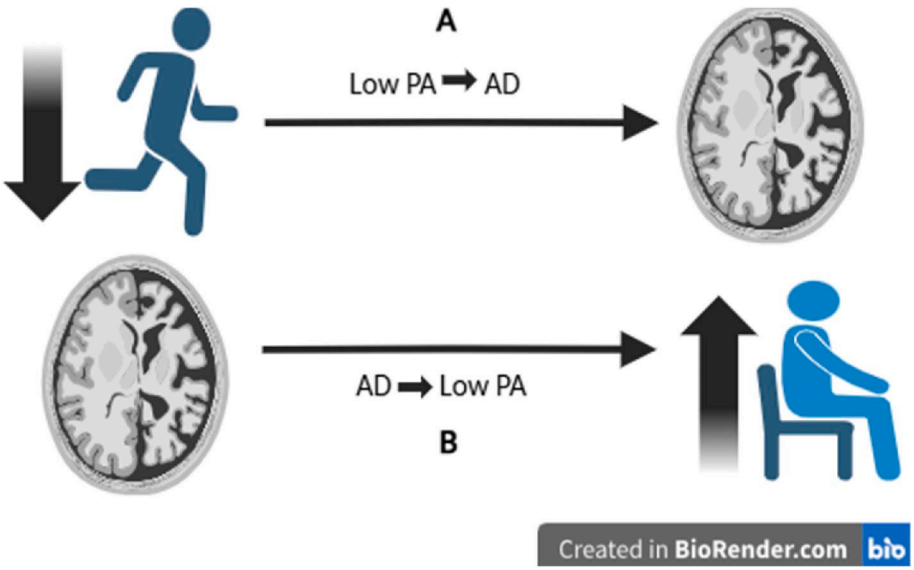

Fig. 1. Two hypotheses linking physical activity (PA) and Alzheimer's disease (AD).
NoteA = predicted causal path (i.e., physical inactivity as a risk factor for AD). B = reverse causality hypothesis (i.e., the onset of AD symptoms reducing PA).

up periods (Kivimäki et al., 2019), researchers who have considered the length of follow-up as a moderator argue against reverse causality (Iso-Markku et al., 2022; Zhang, Li, et al., 2023), highlighting PA's role as a protective factor against AD. Nevertheless, further research is needed to clarify the interaction between PA and AD while recognizing that pre-clinical changes may be occurring decades in advance of a clinical diagnosis of MCI or AD. Prospective studies serve as a starting point in science to study the relationship between variables of interest. Randomized clinical trials (RCTs) provide an opportunity to more directly assess the causal relationship between PA and AD.

2. Clinical trials and pre-cursors of AD

In RCTs, participants are randomly assigned to an exercise condition or a control condition to test the causal link between PA and outcomes related to dementia. Given the practicalities of conducting an RCT (e.g., cost, compliance, sustainability), these clinical trials are typically relatively short in duration (e.g., 6 months to 1 year) relative to the time course of AD. As such, scientists have measured outcomes that are themselves predictive of AD rather than conducting longer interventions that would allow them to actually follow participants through to diagnosis. In terms of cognitive outcomes, researchers have largely focused on global cognition or on the cognitive domains of memory (the primary domain impacted by AD) and executive function (EF, a cognitive domain linked to frontal-lobe function which is also implicated in AD). Neuroimaging studies have examined the volume of brain structures known to be linked to AD such as the hippocampus (important for memory) and have assessed pre-clinical changes linked to AD such as white matter lesions. Researchers have also looked at blood-based biomarkers including neurotrophic factors known to predict brain health (e.g., brain-derived neurotrophic factor [BDNF], vascular endothelial growth factor [VEGF]), with a more recent focus on biomarkers directly linked to AD (e.g., phosphorylated tau [p-tau], Aβ).

2.1. Aerobic exercise

The most studied modality of exercise has been aerobic exercise (AE) which has consistently demonstrated efficacy in enhancing cognitive performance, particularly in domains susceptible to early decline in AD, such as memory and EF (Baker et al., 2010; Erickson et al., 2011; Morris et al., 2017). These improvements have been observed across diverse populations, study designs, and intervention protocols, underscoring AE's potential as a non-pharmacological strategy to mitigate AD risk. Researchers in this area have explored AE's impact on cognitive performance, brain structure, and biomarkers, emphasizing its neuroprotective potential, and have tested interventions with cognitively normal individuals and in those with MCI to explore potential protective effects.

Cognition. Research indicates that AE can enhance cognitive performance in cognitively normal older adults. For example, Albinet et al. (2016) investigated the effects of a five-month AE program (aqua aerobics) on EF in sedentary older adults. The researchers randomly assigned participants to either an AE group (n = 19) or a stretching control group (n = 17). The AE group participated in two 1-h weekly swimming sessions (40–65% of individual heart rate reserve, HRR), while the control group engaged in a stretching program. By the end of the intervention, the AE group demonstrated significant improvements in EF, particularly in inhibitory control and working memory, compared to the control group. Similarly, Langlois et al. (2013) examined the effects of a 12-week AE program. The researchers randomly assigned older adults to either an AE group (n = 36) or a control group (n = 36). The AE group participated in a moderate to high intensity supervised exercise program, while the control group maintained their usual activity levels. At the end of the intervention, the AE group exhibited significant improvements in cognitive function, particularly in EF, processing speed, and working memory.

Research not only shows improvements in cognitively normal older adults, but also in older adults with MCI. Two studies provide exemplars of research conducted with persons with MCI. Baker et al. (2010) conducted a six-month high-intensity AE intervention (75%–85% of HRR) in older adults with MCI and reported significant sex-specific cognitive benefits. Participants were randomly placed into either an AE group (n = 19) or a stretching group (n = 10). Following the intervention, women exhibited improvements in multiple EF tests (Symbol-Digit Modalities, Verbal Fluency, Stroop, and Task Switching), while men showed gains in only one test of EF (Trails B), potentially suggesting distinct pathways through which AE benefits cognitive domains in men and women. Morris et al. (2017) expanded on these findings by examining a 26-week supervised AE regimen in individuals with MCI. Participants were randomized into an AE group (n = 37) or a stretching and toning group (n = 39). They observed that AE led to significant improvements in functional ability, while primary cognitive outcomes (e.g., memory and EF) and

depressive symptoms showed no significant group differences. However, secondary analyses revealed that increases in cardiorespiratory fitness were positively correlated with enhanced memory performance and reduced bilateral hippocampal atrophy, highlighting the potential neuroprotective effects of AE.

When this literature has been reviewed meta-analytically, results consistently support cognitive benefits. Colcombe and Kramer (2003) reported an average effect of 0.41 in response to AE. Angevaren et al. (2008) also reported significant benefits for cognitive speed (ES = 0.26), delayed memory (ES = 0.50), and visual attention (ES = 0.26) for older adults who are cognitively normal (ES = 0.40) and for those with MCI (ES = 0.59). More recent meta-analyses support these findings. Xu et al. (2023) reported significant improvement in cognitive ability with AE, including increases on the Mini-Mental State Examination (mean difference, MD = 2.65), Montreal Cognitive Assessment (MD = 2.58), Wechsler Adult Intelligence Scale (MD = 2.13), Wisconsin Card Sorting Test (MD = 5.31), and the Stroop Color and Word Test (MD = 5.31). Additionally, Zhang, Li, et al. (2023) demonstrated that AE positively impacted multiple cognitive domains in cognitively healthy adults (ES = 0.44). These findings highlight the importance of AE for maintaining cognitive health in aging.

Neuroimaging. Neuroimaging studies provide compelling evidence for the impact of AE on brain structure and cognitive function in older adults. In a seminal study, Colcombe et al. (2006) examined whether AE could increase brain volume in aging populations. In a six-month RCT, 59 sedentary older adults were randomly assigned to either an AE group or a toning/stretching control group. Magnetic resonance imaging (MRI) scans taken before and after the intervention showed that the AE group experienced significant increases in both grey and white matter volume, particularly in the prefrontal and temporal cortices, regions crucial for EF, decision-making, and attentional control. Similarly, Erickson et al. (2011) investigated the effects of AE on hippocampal volume and memory in a one-year RCT with older adults. Participants were randomly assigned to either an AE group (n = 60) or a stretching control group (n = 60). Results showed that AE increased hippocampal volume by 2%, effectively reversing one to two years of age-related atrophy. Since the hippocampus is essential for memory and spatial navigation and is particularly vulnerable in the early stages of AD, this finding highlights the potential of AE to counteract neurodegenerative processes. Notably, these structural changes were accompanied by significant improvements in spatial memory and increased serum levels of BDNF. Together, these findings suggest that AE preserves memory-related structures and maintains brain health and cognitive resilience in aging populations.

In addition to promoting neuroplasticity in cognitively normal older adults, AE has been shown to benefit brain health in populations at higher risk for cognitive decline. Morris et al. (2017) reported benefits in response to a 26-week supervised AE intervention evaluated in individuals with MCI. Results from this RCT revealed that AE participants (n = 37) experienced less hippocampal atrophy compared to a control group (n = 39) engaged in stretching and toning exercises. Improvements in cardiorespiratory fitness strongly correlated with reductions in hippocampal atrophy, suggesting a link between physical fitness and neuroprotection. Additionally, the AE group demonstrated better performance on memory tasks, aligning with structural brain changes observed in imaging data. These results underscore the potential of AE to attenuate hippocampal degeneration in at-risk populations, highlighting its role as a non-pharmacological strategy for neuroprotection.

A meta-analysis by Firth et al. (2018) examined the effects of AE on hippocampal volume in humans. The study found that while AE did not significantly affect total hippocampal volume across all participants (ES = 0.15), it had significant positive effects on left hippocampal volume compared to control conditions (ES = 0.36). Similarly, Balbim et al. (2024) conducted a meta-analysis investigating the effects of AE on hippocampal volume. Despite improvements in fitness levels (ES = 0.30), no significant effects of AE on hippocampal volume were found (ES = 0.10). Although results are promising, the inconsistency in findings suggests that future work is needed in this area to better understand AE's effects on the brain.

Blood-Based Biomarkers. Blood-based biomarkers can also provide valuable insight into the neurobiological effects of AE on neurodegenerative disease processes, including AD (Sewell et al., 2024). These biomarkers can offer non-invasive measures to track disease progression and the effects of interventions. Several studies have examined the effects of exercise on biomarkers associated with cognitive decline or with AD.

Sewell et al. (2024) conducted a 6-month intervention examining the effects of exercise on blood biomarkers, including plasma Aβ, phosphorylated tau (p-tau181), glial fibrillary acidic protein (GFAP), and neurofilament light (NfL), in cognitively unimpaired older adults. Elevated levels of p-tau181, GFAP, and NfL are linked to neurodegeneration and AD pathology, while lower Aβ levels in the blood may indicate increased accumulation in the brain, a hallmark of AD. The intervention involved moderate- or high-intensity cycling two times a week for six months. Cognitively healthy older adults were randomly assigned to either an inactive control group (n = 32), a high-intensity group (n = 33), or a moderate-intensity group (n = 34). Despite improvements in cardiorespiratory fitness, no significant changes in any of the plasma biomarkers were observed from baseline to post-intervention. Notably, higher baseline levels of NfL were associated with poorer cognition, and exploratory analyses suggested that higher cardiorespiratory fitness correlated with higher NfL and GFAP levels in APOE-ε4 non-carriers. However, this relationship was mediated by BMI, suggesting that body composition may play a role in modulating the effects of fitness on these biomarkers. This finding underscores the complexity of the relationship between fitness, neurodegeneration markers, and cognitive health.

Yu et al. (2020) also investigated the effects of exercise on plasma biomarkers in individuals with AD in their FIT-AD pilot study. The study explored how moderate-intensity cycling (n = 18) and low-intensity stretching (n = 8) impacted plasma levels of Aβ, p-tau181, and total tau (t-tau) over six months. While no significant differences between groups were observed, within-group analyses indicated a moderate effect size for increased p-tau181 levels in the stretching group (ES = 0.43) and a small effect size for reduced t-tau levels in the cycling group (ES = −0.35). Overall, exercise did not significantly impact AD biomarkers. However, exploratory analyses suggested that biomarker levels may be influenced by factors such as age and APOE genotype, underscoring the need for further investigation. Together, these studies suggest that AE's direct effects on blood-based biomarkers related to AD remain inconclusive. Future research is needed to determine the most effective exercise regimens for modulating these biomarkers and improving brain health in at-risk populations.

2.2. Resistance exercise

Resistance exercise (RE) is an effective standalone modality of exercise with broad health benefits including improved cardiovascular (Ashton et al., 2018), skeletal muscle (Geng et al., 2023), and cognitive health (Zhang, Jia, et al., 2023). RE consists of performing muscle contractions against an external force for various sets and repetitions often using bodyweight, bands, machines, or free weights to increase muscle size or strength. This exercise modality is a preference for many and is recommended by multiple public health authorities (ACSM, 2022; WHO, 2020). In this subsection, findings from landmark clinical trials investigating the role of RE in AD risk prevention are presented, emphasizing the cognitive and neuroprotective benefits.

Cognition. Clinical trials focusing on RE interventions have often demonstrated positive effects on global cognition and on specific cognitive domains associated with AD risk like EF and memory (Best et al., 2015; Fiatarone Singh et al., 2014; Liu-Ambrose, 2010; Zhao et al., 2022). Liu-Ambrose and colleagues (2010) conducted the *Brain Power*

Study, one of the first large RCTs focused specifically on the effects of RE on cognitive performance. The researchers compared 12 months of once and twice weekly RE with a twice weekly balance and toning control group regarding effects on EF. Cognitively normal women aged 65–75 years were randomly assigned to one of the three conditions (control, n = 49; RE once weekly, n = 54; twice weekly, n = 52). Both RE groups showed significant improvements in EF performance from baseline to intervention completion compared to the control group. Thus, Liu-Ambrose et al. (2010) provided early evidence suggesting that even once weekly RE can benefit cognitive performance and, therefore, potentially mitigate AD risk.

A secondary analysis of the *Brain Power Study* extended Liu-Ambrose and colleagues' (2010) initial findings (Best et al., 2015). The researchers found that improved EF performance was not only maintained at 12-month follow-up (24 months from intervention initiation) in both RE groups, but participants in the twice weekly RE group also experienced memory improvements at this time point. It is important to note that the memory improvements from baseline emerged only at the 12-month follow-up, possibly suggesting delayed neural adaptations. Taken together, the findings related to cognitive outcomes in the *Brain Power Study* (Best et al., 2015; Liu-Ambrose, 2010) offer promising evidence that one to two days of RE per week can improve cognitive performance thus potentially mitigating AD risk. Notably, while both RE frequencies led to cognitive benefits, the twice weekly RE group uniquely demonstrated long-term memory improvements, suggesting that higher frequency may yield greater future cognitive health gains.

While the benefits of RE for cognitively healthy older adults have been demonstrated, its efficacy in populations with existing cognitive impairment is also crucial to explore. To address this, Fiatarone Singh and colleagues (2014) implemented a 6-month 2-3 times per week RE intervention in older adults with MCI. This study, known as *The Study of Mental and Resistance Training (SMART Study)*, investigated RE and cognitive training (CT) through conditions including true interventions and those using sham interventions. Participants were assigned to one of four groups: RE plus sham CT (n = 22), CT plus sham RE (n = 24), combined RE and CT (n = 27), and control (sham CT and sham RE, n = 27). For analysis, the authors examined the outcomes of participants who received RE (i.e., RE plus sham CT and combined RE and CT, n = 49) compared to those who did not (i.e., CT plus sham RE and control, n = 51). After the 6-month intervention, compared to baseline, the proportion of participants with normal global cognition scores (via Alzheimer's Disease Assessment Scale-cognitive; ADAS-Cog) doubled from 24% to 48% in those who received RE, a significant increase compared to those who did not receive RE (20%–27%) (adj OR = 3.50). Given the magnitude of this change, further investigation is warranted to confirm robustness and clinical significance. There was a similar but non-significant trend for EF performance improvement at 6 months. At 12-month follow-up (18 months from intervention initiation), EF performance was significantly improved from baseline. Further, RE was associated with an attenuated decline in visual memory performance, although the opposite was true for delayed auditory memory. To investigate potential mediators, Mavros et al. (2017) conducted a secondary analysis of the *SMART Study,* examining the role of lower, upper, and whole body strength and aerobic capacity. They found that increases in lower, upper, and whole-body strength were associated with improvements in global cognition and EF, while increases in aerobic capacity were not associated with improvements in any cognitive performance measures. Mediation analysis revealed that increases in lower body strength partially explained the association between RE and improvements in global cognition. These findings highlight the critical role of RE in promoting global cognition and EF, suggesting that improvements in strength, particularly lower body strength, may serve as a key target for mitigating cognitive decline and delaying the progression of AD in individuals with MCI. A possible explanation for why strength, rather than aerobic capacity, was associated with cognitive improvements is the magnitude of change observed. While RE led to substantial increases in strength, aerobic capacity improvement was relatively modest, suggesting that the aerobic adaptations may not have been large enough to drive cognitive benefits in this study.

Recently, Zhao et al. (2022) conducted a secondary analysis of the *Graded Resistance Exercise and Type 2 Diabetes in Older Adults (GREAT2DO Study)* to explore the cognitive benefits of RE and body composition improvements. Participants (n = 103, 67.9 ± 5.5 years) engaged in RE 2–3 times per week for 12 months. Of note, the control group performed "sham exercise" sessions that were the same in every way except that they used the lowest possible weight setting over the intervention period. The sham exercise sessions ensured minimal improvement of physiological outcomes (e.g., strength, aerobic capacity) while offering a similar exercise experience. No improvements in global cognition were observed in either group while both groups experienced improvements in EF, memory, and attention at 12 months. Increases in absolute and relative muscle mass and decreases in body fat percentage were associated with memory gains in the RE group, while strength improvements were linked to EF gains, reflecting similar findings observed by Mavros and colleagues (2017). These associations were absent in the control group, which may support the role of RE-induced physical adaptations in driving cognitive benefits. However, it is unclear if the control group also experienced changes in strength or body composition, which limits the ability to conclusively attribute these cognitive improvements to RE alone, especially given the improvements in cognitive performance observed in the control group. Since the sham exercise sessions minimized physiological changes, it is possible that non-exercise factors, like increased socialization, contributed to the improvements in cognitive performance in both groups.

Meta-analytic evidence further reinforces the beneficial effects of RE on cognition. Coelho-Junior and colleagues (2022) found that RE improved global cognition in cognitively healthy (ES = 0.54) and cognitively impaired (ES = 0.60) older adults. RE improved short-term memory when cognitively healthy and impaired samples were combined (ES = 0.30), but the results were not significant when stratified by cognitive status. The benefits to global cognition were associated with interventions lasting at least 16 weeks, performed twice weekly, or conducted at moderate intensity, with similar trends seen for memory benefits. In cognitively impaired samples, benefits were observed with shorter interventions (≤16 weeks), higher frequencies (two to three days per week), or moderate-to-high intensity. In another meta-analysis, Zhang, Jia et al. (2023) found that RE was effective in benefiting various domains of cognition (e.g., global, EF) in cognitively healthy adults (ES = 0.51). They concluded that RE performed in 1–2 sessions per week and lasting ≥60 min at moderate or higher intensity provided cognitive benefits. Overall, landmark studies like the *Brain Power Study* (Best et al., 2015; Liu-Ambrose, 2010) and the SMART Study (Fiatarone Singh et al., 2014; Mavros et al., 2017) along with recent meta-analytic reviews (Coelho-Junior et al., 2022; Zhang, Jia, et al., 2023) have established compelling evidence in support of RE's benefits for global cognition, EF, and memory.

Neuroimaging. In addition to cognitive performance, investigating neuroimaging biomarkers via MRI is also of great interest in assessing the effectiveness of RE in reducing AD risk (Best et al., 2015; Boland-zadeh et al., 2015; Broadhouse et al., 2020; Liu-Ambrose, 2010; Oh et al., 2023; Suo et al., 2016). Interestingly, in the *Brain Power Study,* RE groups experienced 0.32–0.43% decreases in total brain volume, while the control group had no change (Liu-Ambrose, 2010). This was speculated to relate to reduced Aβ load, potentially causing shifts in cerebral fluid resulting in changes to brain volumes assessed via MRI (Fox et al., 2005). The "amyloid-removal-related pseudo-atrophy" hypothesis, an apparent reduction in brain volume observed via MRI following treatments aimed at removing Aβ plaques, may support this speculation (Belder et al., 2024). This phenomenon would not reflect actual neurodegeneration but rather changes in volume associated with the removal or clearance of amyloid deposits; however, it is unknown if this pseudo-atrophy is associated with exercise. In the secondary analysis

from Best et al. (2015), while there was no evidence for reduced cortical grey matter or hippocampal atrophy, there was evidence for reduced cortical white matter atrophy in the twice weekly RE group (0.8%) compared to the control (2%). Bolandzadeh and colleagues (2015) conducted an additional secondary analysis of the *Brain Power Study* including only participants with white matter lesions (WML) at baseline (n = 54). They found that those in the twice weekly RE group had lower WML volumes following the intervention compared to the once weekly RE and control groups. While reduced WML volume is considered to be a positive result and WML volume was associated with maintained gait speed, it was not associated with EF or performance in other cognitive domains.

There have also been neuroimaging-focused secondary analyses of the *SMART Study* (Broadhouse et al., 2020; Suo et al., 2016) yielding promising results. Suo et al. (2016) found that RE was associated with increased grey matter volume in the posterior cingulate, a hippocampal structure involved in memory retrieval and integration, and this was also associated with improved global cognition compared to the control group. Attenuated white matter hyperintensity volume, a marker of neurovascular pathology related to cognitive decline, was also observed in those who participated in RE. Building on these findings, Broadhouse and colleagues (2020) observed that RE slowed left hippocampal atrophy and preserved subfields like the subiculum, CA1, and dentate gyrus, which are vulnerable in early stages of AD. These effects persisted even after controlling for changes in aerobic capacity, physical activity levels outside of the intervention, and strength, suggesting RE offers long-term neuroprotection independent of behavioral factors outside of the intervention. Preservation of hippocampal subfields was associated with improvements to global cognition in those that completed RE initially reported by Fiatarone Singh et al. (2014), emphasizing the potential for RE to protect brain regions relevant to AD pathology. These findings highlight RE as a promising intervention to mitigate structural brain changes associated with cognitive decline and AD risk.

Overall, the benefits of RE extend beyond domains of cognitive function; RE has also been shown to benefit brain structures implicated in AD pathology in cognitively impaired and healthy older adults based on secondary analyses of landmark clinical trials (Best et al., 2015; Bolandzadeh et al., 2015; Broadhouse et al., 2020; Oh et al., 2023; Suo et al., 2016). Meta-analytical work related to neuroimaging outcomes of RE interventions is lacking. Herold et al. (2019) conducted a systematic review on this topic and concluded that RE interventions may induce functional changes in the frontal lobe and attenuate white matter atrophy. However, as this was not a meta-analysis, no statistical synthesis was performed, limiting the ability to quantify the magnitude or consistency of these effects across studies. An important next step is to synthesize this evidence meta-analytically.

Blood-Based Biomarkers. Beyond behavioral and structural outcomes, the effect of RE on AD-related biomarkers like Aβ and p-tau remain largely unexplored in human trials. While animal research suggests that RE may influence Aβ levels (Campos et al., 2023) and p-tau pathology (Liu et al., 2020), human studies are lacking. Future research should prioritize biomarker investigations to explore more proximal mechanisms by which RE may offer cognitive and structural benefits.

3. Conclusions and future directions

Overall, there is promising evidence of the benefits of PA for the prevention of AD with emerging evidence in support of the effects of both AE and RE on putative biomarkers. Prior research supports AE as a valuable non-pharmacological approach for mitigating cognitive decline and lowering AD risk. Clinical trials consistently highlight its potential to enhance cognitive function, particularly memory and EF, in both cognitively normal individuals and those with MCI. Neuroimaging studies indicate that AE can increase brain volume, especially in memory-related regions such as the hippocampus, reinforcing its neuroprotective effects. However, its influence on blood-based biomarkers remains inconclusive. While AE appears to facilitate neuroplasticity and cognitive resilience, further research is needed to establish optimal exercise protocols and clarify its impact on neurodegenerative processes.

RE shows promise in mitigating AD risk by improving cognitive performance, particularly global cognition and executive function as well as preserving brain structures vulnerable to AD. Methodological discrepancies like the use of sham exercise sessions may inadvertently introduce confounding variables like increased socialization and albeit minimal, physiological adaptations, making the interpretation of recent findings challenging. Further, a lack of detailed reporting of differences in changes to physiological outcomes (e.g., body composition, strength) between intervention and control groups presents challenges that complicate the ability to attribute cognitive benefits solely to RE. These inconsistencies underscore the need for greater methodological clarity in future studies, particularly in delineating the unique contributions of RE-induced physical adaptations versus non-exercise factors. Moving forward, standardizing comparison groups should be a priority. One approach may be to include low dose RE (once weekly or higher frequency with low load training), moderate to high dose RE (2–3 times weekly at moderate to high intensity), and a true non-active control group. The standardization of RE protocols and adherence to the recent recommendations for "preferred reporting items for resistance exercise studies" (PRIRES) put forth by Lin and colleagues (2023) will be critical in clarifying RE's role in mitigating cognitive decline and AD risk. Addressing these methodological challenges and the lack of biomarker data will ensure future research provides robust, evidence-based insight into RE's potential to promote brain health.

Given the recognition that preclinical changes occur decades prior to the diagnosis of AD and the lack of effective pharmacological treatments to prevent AD, early intervention through lifestyle behaviors may be critical for preventing AD in the growing population of older adults. Prospective and RCT studies provide promising evidence, but each paradigm has strengths and weaknesses relative to advancing our understanding of the potential role of PA in the prevention of AD. One effective strategy for understanding the implications of RCT findings for AD risk is to compare benefits from RCTs to indicants of clinical meaningfulness from prospective studies. For example, if an RCT shows that 1-year of exercise results in an increase in hippocampal volume of 2% and a prospective study shows that a 2% difference in hippocampal volume has an impact on the risk of AD, this would provide a meaningful link between the shorter-term causal findings from the RCT and the longer term correlational findings from prospective studies. If PA is able to help individuals remain in a cognitively normal stage or even in the stage of MCI for longer, this would have a clear personal impact in terms of quality of life and this could also have an impact on the medical costs associated with AD as the progression of AD is linked to increased expenses (Robinson et al., 2020; Wimo et al., 2013). For example, the monthly cost for a person with MCI compared to someone with mild AD is $2,816 and $4,243, respectively (Robinson et al.). Given these personal and financial implications and the promising results observed, future researchers should continue to advance our understanding of the potential of PA for individuals younger than 65 relative to the risk of AD.

CRediT authorship contribution statement

Jennifer L. Etnier: Writing – review & editing, Writing – original draft, Conceptualization. **Chadsley M. Wessinger:** Writing – review & editing, Writing – original draft, Conceptualization. **Bryan Montero Herrera:** Writing – review & editing, Writing – original draft, Conceptualization. **Kylie C. Kayser:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

We have no competing interests to declare.

Data availability

No data was used for the research described in the article.

References

Albinet, C. T., Abou-Dest, A., André, N., & Audiffren, M. (2016). Executive functions improvement following a 5-month aquaerobics program in older adults: Role of cardiac vagal control in inhibition performance. *Biological Psychology, 115*, 69–77. https://doi.org/10.1016/j.biopsycho.2016.01.010

Alzheimer's Association. (2024). Alzheimer's disease facts and figures. https://onlinelibrary.wiley.com/doi/abs/10.1002/alz.13809.

Angevaren, M., Aufdemkampe, G., Verhaar, H. J. J., Aleman, A., & Vanhees, L. (2008). Physical activity and enhanced fitness to improve cognitive function in older people without known cognitive impairment. *Cochrane Database of Systematic Reviews, 3*, Article CD005381. https://doi.org/10.1002/14651858.CD005381.pub3

Ashton, R. E., Tew, G. A., Aning, J. J., Gilbert, S. E., Lewis, L., & Saxton, J. M. (2018). Effects of short-term, medium-term and long-term resistance exercise training on cardiometabolic health outcomes in adults: Systematic review with meta-analysis. *British Journal of Sports Medicine*. https://doi.org/10.1136/bjsports-2017-098970

Baker, L. D., Frank, L. L., Foster-Schubert, K., Green, P. S., Wilkinson, C. W., McTiernan, A., et al. (2010). Effects of aerobic exercise on mild cognitive impairment: A controlled trial. *Archives of Neurology, 67*(1), 71–79. https://doi.org/10.1001/archneurol.2009.307

Balbim, G. M., Boa Sorte Silva, N. C., ten Brinke, L., Falck, R. S., Hortobágyi, T., Granacher, U., et al. (2024). Aerobic exercise training effects on hippocampal volume in healthy older individuals: A meta-analysis of randomized controlled trials. *GeroScience, 46*(2), 2755–2764. https://doi.org/10.1007/s11357-023-00971-7

Barthélemy, N. R., Li, Y., Joseph-Mathurin, N., Gordon, B. A., Hassenstab, J., Benzinger, T. L. S., et al. (2020). A soluble phosphorylated tau signature links tau, amyloid and the evolution of stages of dominantly inherited Alzheimer's disease. *Nature Medicine, 26*(3), 398–407. https://doi.org/10.1038/s41591-020-0781-z

Bateman, R. J., Xiong, C., Benzinger, T. L. S., Fagan, A. M., Goate, A., Fox, N. C., et al. (2012). Clinical and biomarker changes in dominantly inherited Alzheimer's disease. *New England Journal of Medicine, 367*(9), 795–804. https://doi.org/10.1056/NEJMoa1202753

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 Geriatrics, 15*, 9. https://doi.org/10.1186/s12877-015-0007-2

Belder, C. R. S., Boche, D., Nicoll, J. A. R., Jaunmuktane, Z., Zetterberg, H., Schott, J. M., et al. (2024). Brain volume change following anti-amyloid β immunotherapy for Alzheimer's disease: Amyloid-removal-related pseudo-atrophy. *The Lancet Neurology, 23*(10), 1025–1034. https://doi.org/10.1016/S1474-4422(24)00335-1

Best, J. R., Chiu, B. K., Liang Hsu, C., Nagamatsu, L. S., & Liu-Ambrose, T. (2015). Long-term effects of resistance exercise training on cognition and brain volume in older women: Results from a randomized controlled trial. *Journal of the International Neuropsychological Society, 21*(10), 745–756. https://doi.org/10.1017/S1355617715000673

Bolandzadeh, N., Tam, R., Handy, T. C., Nagamatsu, L. S., Hsu, C. L., Davis, J. C., et al. (2015). Resistance training and white matter lesion progression in older women: Exploratory analysis of a 12-month randomized controlled trial. *Journal of the American Geriatrics Society, 63*(10), 2052–2060. https://doi.org/10.1111/jgs.13644

Broadhouse, K. M., Singh, M. F., Suo, C., Gates, N., Wen, W., Brodaty, H., et al. (2020). Hippocampal plasticity underpins long-term cognitive gains from resistance exercise in MCI. *NeuroImage. Clinical, 25*, Article 102182. https://doi.org/10.1016/j.nicl.2020.102182

Campos, H. C., Ribeiro, D. E., Hashiguchi, D., Glaser, T., Milanis, M. da S., Gimenes, C., et al. (2023). Neuroprotective effects of resistance physical exercise on the APP/PS1 mouse model of Alzheimer's disease. *Frontiers in Neuroscience, 17*, Article 1132825. https://doi.org/10.3389/fnins.2023.1132825

Coelho-Junior, H., Marzetti, E., Calvani, R., Picca, A., Arai, H., & Uchida, M. (2022). Resistance training improves cognitive function in older adults with different cognitive status: A systematic review and meta-analysis. *Aging & Mental Health, 26*(2), 213–224a9h.

Colcombe, S. J., Erickson, K. I., Scalf, P. E., Kim, J. S., Prakash, R., McAuley, E., et al. (2006). Aerobic exercise training increases brain volume in aging humans. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 61*(11), 1166–1170. https://doi.org/10.1093/gerona/61.11.1166

Colcombe, S., & Kramer, A. F. (2003). Fitness effects on the cognitive function of older adults: A meta-analytic study. *Psychological Science, 14*(2), 125–130. https://doi.org/10.1111/1467-9280.t01-1-01430

Duong, S., Patel, T., & Chang, F. (2017). Dementia: What pharmacists need to know. *Canadian Pharmacists Journal: CPJ = Revue Des Pharmaciens Du Canada: RPC, 150*(2), 118–129. https://doi.org/10.1177/1715163517690745

Erickson, K. I., Voss, M. W., Prakash, R. S., Basak, C., Szabo, A., Chaddock, L., et al. (2011). Exercise training increases size of hippocampus and improves memory. *Proceedings of the National Academy of Sciences, 108*(7), 3017–3022. https://doi.org/10.1073/pnas.1015950108

Etnier, J. L., Salazar, W., Landers, D. M., Petruzzello, S. J., Han, M., & Nowell, P. (1997). The influence of physical fitness and exercise upon cognitive functioning: A meta-analysis. *Journal of Sport & Exercise Psychology, 19*(3), 249–277. https://doi.org/10.1123/jsep.19.3.249

Fiatarone Singh, M. A., Gates, N., Saigal, N., Wilson, G. C., Meiklejohn, J., Brodaty, H., et al. (2014). The study of mental and resistance training (SMART) study—resistance training and/or cognitive training in mild cognitive impairment: A randomized, double-blind, double-sham controlled trial. *Journal of the American Medical Directors Association, 15*(12), 873–880. https://doi.org/10.1016/j.jamda.2014.09.010

Firth, J., Stubbs, B., Vancampfort, D., Schuch, F., Lagopoulos, J., Rosenbaum, S., et al. (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

Fox, N. C., Black, R. S., Gilman, S., Rossor, M. N., Griffith, S. G., Jenkins, L., et al., AN1792(QS-21)-201 Study. (2005). Effects of Abeta immunization (AN1792) on MRI measures of cerebral volume in Alzheimer disease. *Neurology, 64*(9), 1563–1572. https://doi.org/10.1212/01.WNL.0000159743.08996.99

Geng, Q., Zhai, H., Wang, L., Wei, H., & Hou, S. (2023). The efficacy of different interventions in the treatment of sarcopenia in middle-aged and elderly people: A network meta-analysis. *Medicine, 102*(27), Article e34254. https://doi.org/10.1097/MD.0000000000034254

Gordon, B. A., Blazey, T. M., Su, Y., Hari-Raj, A., Dincer, A., Flores, S., et al. (2018). Spatial patterns of neuroimaging biomarker change in individuals from families with autosomal dominant Alzheimer's disease: A longitudinal study. *The Lancet Neurology, 17*(3), 241–250. https://doi.org/10.1016/S1474-4422(18)30028-0

Hamer, M., & Chida, Y. (2009). Physical activity and risk of neurodegenerative disease: A systematic review of prospective evidence. *Psychological Medicine, 39*(1), 3–11. https://doi.org/10.1017/S0033291708003681

Herold, F., Törpel, A., Schega, L., & Müller, N. G. (2019). Functional and/or structural brain changes in response to resistance exercises and resistance training lead to cognitive improvements – a systematic review. *European Reviews of Aging & Physical Activity, 16*(1). N.PAG-N.PAG. sph.

Iso-Markku, P., Kujala, U. M., Knittle, K., Polet, J., Vuoksimaa, E., & Waller, K. (2022). Physical activity as a protective factor for dementia and Alzheimer's disease: Systematic review, meta-analysis and quality assessment of cohort and case–control studies. *British Journal of Sports Medicine, 56*(12), 701–709. https://doi.org/10.1136/bjsports-2021-104981

Kivimäki, M., Singh-Manoux, A., Pentti, J., Sabia, S., Nyberg, S. T., Alfredsson, L., et al. (2019). Physical inactivity, cardiometabolic disease, and risk of dementia: An individual-participant meta-analysis. *BMJ.* , Article l1495. https://doi.org/10.1136/bmj.l1495

Langlois, F., Vu, T. T. M., Chassé, K., Dupuis, G., Kergoat, M.-J., & Bherer, L. (2013). Benefits of physical exercise training on cognition and quality of life in frail older adults. *The Journals of Gerontology: Serie Bibliographique, 68*(3), 400–404. https://doi.org/10.1093/geronb/gbs069

ACSM. (2022). In G. Liguori, Y. Feito, C. Fountaine, & B. Roy (Eds.), *ACSM's guidelines for exercise testing and prescription*. WorldCat: Wolters Kluwer. Eleventh edition.

Lin, T.-Y., Chueh, T.-Y., & Hung, T.-M. (2023). Preferred reporting items for resistance exercise studies (PRIRES): A checklist developed using an umbrella review of systematic reviews. *Sports Medicine - Open, 9*, 114. https://doi.org/10.1186/s40798-023-00640-1

Liu, Y., Chu, J. M. T., Yan, T., Zhang, Y., Chen, Y., Chang, R. C. C., et al. (2020). Short-term resistance exercise inhibits neuroinflammation and attenuates neuropathological changes in 3xTg Alzheimer's disease mice. *Journal of Neuroinflammation, 17*(1), 4. https://doi.org/10.1186/s12974-019-1653-7

Liu-Ambrose, T. (2010). Resistance training and executive functions: A 12-month randomized controlled trial. *Archives of Internal Medicine, 170*(2), 170. https://doi.org/10.1001/archinternmed.2009.494

Livingston, G., Huntley, J., Liu, K. Y., Costafreda, S. G., Selbæk, G., Alladi, S., et al. (2024). Dementia prevention, intervention, and care: 2024 report of the Lancet standing commission. *The Lancet, 404*(10452), 572–628. https://doi.org/10.1016/S0140-6736(24)01296-0

Mavros, Y., Gates, N., Wilson, G. C., Jain, N., Meiklejohn, J., Brodaty, H., et al. (2017). Mediation of cognitive function improvements by strength gains after resistance training in older adults with mild cognitive impairment: Outcomes of the study of mental and resistance training. *Journal of the American Geriatrics Society, 65*(3), 550–559. https://doi.org/10.1111/jgs.14542

Morris, J. K., Vidoni, E. D., Johnson, D. K., Van Sciver, A., Mahnken, J. D., Honea, R. A., et al. (2017). Aerobic exercise for Alzheimer's disease: A randomized controlled pilot trial. *PLoS One, 12*(2), Article e0170547. https://doi.org/10.1371/journal.pone.0170547

Nichols, E., Steinmetz, J. D., Vollset, S. E., Fukutaki, K., Chalek, J., Abd-Allah, F., et al. (2022). Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: An analysis for the Global Burden of Disease Study 2019. *The Lancet Public Health, 7*(2), e105–e125.

Oh, J., Crockett, R. A., Hsu, C.-L., Dao, E., Tam, R., & Liu-Ambrose, T. (2023). Resistance training maintains white matter and physical function in older women with cerebral small vessel disease: An exploratory analysis of a randomized controlled trial. *Journal of Alzheimer's Disease Reports, 7*(1), 627–639. https://doi.org/10.3233/ADR-220113

Quiroz, Y. T., Zetterberg, H., Reiman, E. M., Chen, Y., Su, Y., Fox-Fuller, J. T., et al. (2020). Plasma neurofilament light chain in the presenilin 1 E280A autosomal dominant Alzheimer's disease kindred: A cross-sectional and longitudinal cohort study. *The Lancet Neurology, 19*(6), 513–521. https://doi.org/10.1016/S1474-4422(20)30137-X

Robinson, R. L., Rentz, D. M., Andrews, J. S., Zagar, A., Kim, Y., Bruemmer, V., et al. (2020). Costs of early stage Alzheimer's disease in the United States: Cross-sectional analysis of a prospective cohort study (GERAS-US)1. *Journal of Alzheimer's Disease, 75*(2), 437–450. https://doi.org/10.3233/JAD-191212

Ryman, D. C., Acosta-Baena, N., Aisen, P. S., Bird, T., Danek, A., Fox, N. C., & Dominantly Inherited Alzheimer Network. (2014). Symptom onset in autosomal dominant

alzheimer disease: A systematic review and meta-analysis. *Neurology, 83*(3), 253–260. https://doi.org/10.1212/WNL.0000000000000596. et-al.

Sabia, S., Dugravot, A., Dartigues, J.-F., Abell, J., Elbaz, A., Kivimäki, M., et al. (2017). Physical activity, cognitive decline, and risk of dementia: 28 year follow-up of whitehall II cohort study. *BMJ, 357*, Article j2709. https://doi.org/10.1136/bmj.j2709

Sato, K., Kondo, N., Hanazato, M., Tsuji, T., & Kondo, K. (2021). Potential causal effect of physical activity on reducing the risk of dementia: A 6-year cohort study from the Japan gerontological evaluation study. *International Journal of Behavioral Nutrition and Physical Activity, 18*(1), 140. https://doi.org/10.1186/s12966-021-01212-w

Sewell, K. R., Rainey-Smith, S. R., Pedrini, S., Peiffer, J. J., Sohrabi, H. R., Taddei, K., et al. (2024). The impact of exercise on blood-based biomarkers of Alzheimer's disease in cognitively unimpaired older adults. *GeroScience, 46*(6), 5911. https://doi.org/10.1007/s11357-024-01130-2

Sofi, F., Valecchi, D., Bacci, D., Abbate, R., Gensini, G. F., Casini, A., et al. (2011). Physical activity and risk of cognitive decline: A meta-analysis of prospective studies. *Journal of Internal Medicine, 269*(1), 107–117. https://doi.org/10.1111/j.1365-2796.2010.02281.x

Stephen, R., Hongisto, K., Solomon, A., & Lönnroos, E. (2017). Physical activity and Alzheimer's disease: A systematic review. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*. https://doi.org/10.1093/gerona/glw251. glw251.

Suo, C., Singh, M. F., Gates, N., Wen, W., Sachdev, P., Brodaty, H., et al. (2016). Therapeutically relevant structural and functional mechanisms triggered by physical and cognitive exercise. *Molecular Psychiatry, 21*(11), 1633–1642. https://doi.org/10.1038/mp.2016.19

WHO. (2020). Recommendations. In *WHO guidelines on physical activity and sedentary behaviour*. World Health Organization. https://www.ncbi.nlm.nih.gov/books/NBK566046/.

Wimo, A., Reed, C. C., Dodel, R., Belger, M., Jones, R. W., Happich, M., et al. (2013). The geras study: A prospective observational study of costs and resource use in community dwellers with Alzheimer's disease in three European countries–study design and baseline findings. *Journal of Alzheimer's Disease: JAD, 36*(2), 385–399. https://doi.org/10.3233/JAD-122392

World Health Organization. (2023). Dementia. https://www.who.int/news-room/fact-sheets/detail/dementia.

Xu, L., Gu, H., Cai, X., Zhang, Y., Hou, X., Yu, J., et al. (2023). The effects of exercise for cognitive function in older adults: A systematic review and meta-analysis of randomized controlled trials. *International Journal of Environmental Research and Public Health, 20*(2). https://doi.org/10.3390/ijerph20021088. Article 2.

Yaffe, K., Barnes, D., Nevitt, M., Lui, L.-Y., & Covinsky, K. (2001). A prospective study of physical activity and cognitive decline in elderly women: Women who walk. *Archives of Internal Medicine, 161*(14), 1703–1708. https://doi.org/10.1001/archinte.161.14.1703

Yu, J.-T., Xu, W., Tan, C.-C., Andrieu, S., Suckling, J., Evangelou, E., et al. (2020). Evidence-based prevention of Alzheimer's disease: Systematic review and meta-analysis of 243 observational prospective studies and 153 randomised controlled trials. *Journal of Neurology, Neurosurgery & Psychiatry, 91*(11), 1201–1209. https://doi.org/10.1136/jnnp-2019-321913

Zhang, M., Jia, J., Yang, Y., Zhang, L., & Wang, X. (2023). Effects of exercise interventions on cognitive functions in healthy populations: A systematic review and meta-analysis. *Ageing Research Reviews, 92*. N.PAG-N.PAG. a9h.

Zhang, X., Li, Q., Cong, W., Mu, S., Zhan, R., Zhong, S., et al. (2023). Effect of physical activity on risk of Alzheimer's disease: A systematic review and meta-analysis of twenty-nine prospective cohort studies. *Ageing Research Reviews, 92*, Article 102127. https://doi.org/10.1016/j.arr.2023.102127

Zhao, R. R., Mavros, Y., Meiklejohn, J., Anderberg, K. A., Singh, N., Kay, S., et al. (2022). Effect of high-intensity power training on cognitive function in older adults with Type 2 diabetes: Secondary outcomes of the GREAT2DO study. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 77*(10), 1975–1985. https://doi.org/10.1093/gerona/glac090