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# Effects of Physical Activity on Physical Health, Cognition, and Activities of Daily Living in Persons at Risk of Alzheimer's Disease or All-cause Dementias

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# EFFECTS OF PHYSICAL ACTIVITY ON PHYSICAL HEALTH, COGNITION, AND ACTIVITIES OF DAILY LIVING IN PERSONS AT RISK OF ALZHEIMER'S DISEASE OR ALL-CAUSE DEMENTIAS

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# ABSTRACT

The purpose of this study was to summarize the effects of physical activity (PA) as a nonpharmacological preventative measure in people at risk of Alzheimer's disease (AD) or all-cause dementia. It was hypothesized that persons at risk of AD or all-cause dementia who engage in sustained and continuous PA would fare better in terms of physical health, cognition, and activities of daily living (ADLs). A systematic literature review was conducted in the Cumulative Index to Nursing and Allied Health Literature (CINAHL) using 12 keywords. Studies were included if they were randomized controlled trials with people at risk of AD or all-cause dementia reporting outcomes of PA on three domains, namely: physical health, cognition, or ADLs. Data was extracted using the Matrix Method and results were summarized using applied thematic analyses. Out of 55 records screened, eight met the inclusion criteria for data extraction. Findings indicate statistically significant improvement in four metrics of physical health such as balance, strength, stamina, and oxygenation. Findings also showed statistically significant improvement in four measures of cognition (short-term memory, lucidity, executive function, and language ability). Two studies reported statistically significant improvement in two measures of ADLs (less assistance to complete daily tasks and execution of instrumental activities). Overall, studies showed that physical health, cognition, and two measures of ADLs of people at risk of AD and all-cause dementia improve with sustained and continuous PA, although the interventions and measures were extremely heterogeneous. Future research and intervention efforts should align PA efforts with current universal recommendations to improve outcomes in the general population and in those at risk of AD and all-cause dementia.

**Keywords:** Alzheimer's Disease, Cognition, Physical Health, Activities of Daily Living, Physical Activity, All-Cause Dementia

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# Chapter 1

# INTRODUCTION

Alzheimer's disease (AD) is a form of dementia that takes a course of neurocognitive decline that is associated with age and inevitable death (Alzheimer's Association, 2019). It is also the most common cause of dementia—memory loss that is severe enough to interfere with the ability to perform activities of daily living (ADLs). Alzheimer's disease is insidious in nature and gradually increases in severity as time progresses. In the early stages of AD, there is mild memory loss, but with late-stage progression, individuals can lose the capability to hold a conversation and respond to their environment (Alzheimer's Association, 2019). The clinical diagnostic criteria for AD recognize the use of biomarkers in the preclinical stages of the disease (McKhann et al., 2011). The two indicative biomarkers in the brain are the beta amyloid peptide in plaques and hyperphosphorylated tau protein, found in neurofibrillary tangles (Lopez et al., 2019).

In 2018, it was reported that 5.7 million Americans with dementia had AD and 13 million more were predicted to have it by the year 2050 (Lane et al., 2018; Lu et al., 2020). Someone in the United States (US) develops AD every 66 seconds (Alzheimer's Association, 2019). In 2013, official death certificates recorded 84,767 deaths from AD, making it the sixth leading cause of death in the US and the fifth leading cause of death for Americans 65 years and older (Alzheimer's Association, 2019). Worldwide, the largest increase in prevalence is expected to come from low- and middle-income countries, in association with patterns of increasing cardiovascular disease, hypertension, and diabetes (Lane et al., 2018). Alzheimer's disease is the most common form of dementia, accounting for more than half of all-cause dementias, and is primarily a condition acquired later in life, doubling in prevalence every 5 years after the age of 65 (Alzheimer's Association, 2019; Lane et al., 2018).

To date, pharmacological interventions to manage, cure, or prevent dementia remain controversial. It has been demonstrated that improvements in cognitive function related to physical activity (PA) are likely

due to improvement in mood and quality of life (Bouaziz et al., 2019). Therefore, the development of nonpharmacological approaches to prevent AD, such as PA, are necessary. Within the RCT conducted with sedentary seniors between 70 and 83 years-old showed that after just 9.5 weeks of physical activity there was an improvement in both cognitive abilities (i.e., attention and mental flexibility) and physical abilities (i.e., the trail making test and the one-leg standing test) (Bouaziz et al., 2019). PA in some studies has also been shown to improve the cognitive health of those at risk of AD or dementia as well. In a RCT conducted on subjects who were at risk for AD and dementia, those assigned to the PA group saw an improvement in their cognitive health after 24 weeks of PA (Lautenschlager et al., 2008). Furthermore, there is evidence to suggest that the ability to execute ADLs can improve with added PA into the routine of those at risk of AD or dementia. For example, in a RCT the ability to complete ADL with little to no assistance was reported in subjects with AD assigned to the PA group (i.e., Barthel Index of Activities of Daily Living and Instrumental of Activities of Daily Living Scale) (Vreugdenhil et al., 2012).

Although it is known that delays in the progression of AD are linked to PA, there is still a gap in the knowledge of the extent to which PA improves three specific domains of health for those at risk of AD and dementia. Hence, this study will address the effects of PA on the health of those at risk of AD or dementia, specifically focusing on three domains of health (namely: physical health, cognition, and ADLs).

# Chapter 2

# LITERATURE REVIEW

## Pathophysiology of AD and other dementias

Dementia is a major neurocognitive disorder that due to its degradation of cognitive function—memory, speech, language, and other thinking abilities—and AD is the most common cause of dementia. Pathologically, AD is characterized by the presence of extracellular senile amyloid plaques, which are the product of proteolytic processing of β-amyloid proteins and intracellular neurofibrillary tangles, which are abnormal accumulations of τ proteins inside neurons (Lin et al., 2001). There is a decrease in the volume of the hippocampus—a structure important in short- and long-term memory—in people diagnosed with AD (Riedel & Micheau, 2001). Clinical impairment in AD, then, is related to synaptic dysfunctions, such as a decrease in synaptic density in the association cortices and hippocampus, as well as similar loss of pre- and post-synaptic components (Shankar & Walsh, 2009). A cascade of detrimental neuronal changes—such as increased synaptic loss, neuron dystrophy, neurofibrillary tangles, and neuronal death—follow the synaptic dysfunction (Lin & Lal, 2001).

## Physical activity and dementias

Physical activity has been demonstrated to favor brain health through attenuation of atherosclerotic cerebrovascular diseases—such as AD and vascular dementias (Ahlskog et al., 2011). The proposed mechanism for this effect is the anti-inflammatory effects of PA, increased cerebral blood flow, and reduction of oxidative stress (Ahlskog et al., 2011; Belviranli & Okudan, 2019). In a study, after 16 weeks of PA there was a 4.3% increase in serum high-density lipoprotein (HDL) cholesterol, a fat known to displace other fats associated with chronic inflammation and heart disease (Jensen, 2020). This increase in HDL cholesterol serum levels through apolipoprotein I as an effect of PA is suggested to modulate inflammation and have vasoprotective properties, with both mechanisms involved in AD pathogenesis (Jensen et al., 2020). Physical

activity can also increase the physical mobility if performed on a continuous basis. Measures of physical improvement is the functional reach (balance test) which is a measure of balance and maximal forward reach in centimeters (Vreugdenhil et al., 2012).

**Vascular dysfunction**

Recent evidence indicates that vascular risk factors—such as hypertension, diabetes, and hyperlipidemia—contribute to a higher risk for developing AD. In AD, there is a deposition of amyloid plaques in the extracellular neutrophils and the cerebral vessel walls along with neurofibrillary tangles, and with AP being particularly toxic to endothelial cells, it increases the occurrence of cerebral amyloid plaques angiopathies (Lange-Asschenfeldt & Kojda, 2008).

In turn, vascular dysfunction is associated with increased vascular oxidative stress, which is the overaccumulation to oxygen reactive species, and the lack of detoxification of these species through biological processes. The risk of AD and dementia increases in persons with vascular dysfunction, creating pathophysiological changes, such as overproduction of nitric oxide synthase, which then creates reactive oxygen species that add to the oxidative damage, neurodegeneration in the cerebral cortex, and hypercontracted blood vessels. This results in reduced cerebral blood flow as can be seen in cell cultures, plasma, and peripheral leukocytes of people living with AD (Lange-Asschenfeldt & Kojda, 2008). There is a greater overall risk of developing AD with more vascular risk factors, such as diabetes, hyperlipidemia, hypertension, and heart disease, which tend to coexist, potentiating causal pathways for the development of AD (Luchsinger et al., 2005). Such vascular conditions can affect the perfusion of oxygenated blood to the brain, which can be assessed via the Relative Cerebral Blood Flow (rCBF*)*, which uses imaging to measures the volume of blood passing through a given amount of brain tissue per minute (Thomas et al., 2013)

**Oxidative stress and vascular dementias**

Cerebrovascular small vessel diseases are causative factors for primary vascular dementia, and these same vascular risk factors—stroke, hypertension, hyperlipidemia—also contribute to the development of AD as well (Ahlskog et al., 2011; Luchsinger et al., 2005). The pathophysiology of primary vascular dementias involves neurodegenerative processes that result in cognitive changes that ultimately result in dementia signs and symptoms, in which many times it can be misdiagnosed as AD (Ahlskog et al., 2011).

**Physical activity and its role reducing oxidative stress**

Even though the parameters have not been universally accepted, consistent aerobic PA sufficient to increase heart rate and the body's need for oxygen has been demonstrated to reduce oxidative stress (Ahlskog et al., 2011). Presumably, PA must be continuous (i.e., conducted most days of the week) and sustained (e.g., for a minimum of 20-30 minutes per session) to observe oxidative stress reduction (Ahlskog et al., 2011). This reduction in oxidative stress factors ultimately translates into improved measures of cardiovascular fitness, including peak oxygen consumption per unit time ($VO_2$) and maximal oxygen intake during a given period of PA ($VO_{2max}$). In both measures, higher values indicate improved fitness (Ahlskog et al., 2011; Dustman et al., 1984).

**Physical activity and effects on the hippocampus**

The hippocampus is a core structure of the medial temporal lobe of the brain. In this region is where temporary storage of to-be-consolidated information occurs, and it is considered the center of permanent memory storage through memory traces (Riedel & Micheau, 2001). When the hippocampus is affected, memory loss occurs. Studies show that progressive hippocampal degeneration is associated with the early stages of AD and other dementias (Ahlskog et al., 2011). One specific randomized controlled trial (RCT) in a cohort study with seniors documented larger hippocampal blood volumes after just one year of aerobic PA, compared to the control group who received stretching and toning (Ahlskog et al., 2011). Another study

showed that an increase in cardiorespiratory fitness and $VO_{2max}$ in their test subjects with AD was related to change in bilateral hippocampal blood volume and improved memory performance (Morris et al., 2017).

Assessment of cognition is imperative in the assessment of PA and its effects on AD and dementia. In a RCT conducted, cognitive and functional performance was assed using the Trail Making Test, which is a 2-part examination consisting of (1) circles numbered 1-25, and participants had to draw lines connecting numbers in ascending order (2) circles both numbered 1-13 and lettered A-L, requiring participants to connect numbers and letters in ascending order (Bouaziz et al., 2019). Another measure of cognition is the Paced Auditory Serial Addition Test (PASAT), in which participants were presented with numbers on a screen for 3 seconds and were to add each digit as it was presented (Bouaziz et al., 2019). Furthermore, a direct measure of recent memory in those at risk of AD and dementia is the Digit Span Test, which subjects were asked to repeat as many digits of a given number by memory, and in reverse as well (Dustman et al., 1984). Lastly, as language ability can be one of the many parts of cognition to be affected by AD and all-cause dementia, an assessment that measures the degree of speech impairment is the Verbal Fluency Task. Within this task there were two portions: (1) subjects were asked to produce as many words as possible beginning with the letters “F”, “A”, and “S” in 1 minute each (2) in the category fluency portion subjects were asked to evoke the greatest possible number of animals within 1 minute (Bouaziz et al. 2012).

**Brain oxygenation and aging**

Reduced cerebral oxygenation increases the risk of developing AD. One of the main factors that contributes to reduced cerebral oxygenation in old age is the increasing presence of atherosclerosis in the circulatory system (Dustman et al., 1984). Atherosclerosis decreases the ability to properly perfuse oxygen throughout the body. The main causes of atherosclerosis are genetic predisposition and, more frequently, an unfavorable lipid profile from a sedentary lifestyle (Dustman et al., 1984). Although an unfavorable lipid

profile increases the likelihood of developing AD, PA is a known nonpharmacological way to reduce plasma lipids and oxidative stress (Dustman et al., 1984; Jensen et al., 2020).

With a reduction in perfusion to the brain in aging persons there may likely be a reduction in a lucidity of an individual, specifically those at risk of AD and dementia. To evaluate the extent of lucidity following an AD or Dementia diagnosis a tool used to assess the severity of AD or dementia at a given time is the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog), within this assessment subjects are given 11 brief cognitive tests assessing memory, language, and praxis (with higher scores indicating increased severity) (Lautenschlager et al., 2008). Another tool used to examine the lucidity of those with at risk of the condition is a Mini Mental State Examination, in which orientation, memory, language, and attention (with an increased score indicating improved cognition) (Vreugdenhil et al., 2012). Similarly, an assessment that analyzes a person's mental state in greater detail is the Cambridge Cognitive Examination (CAMCOG) is used, which it is subdivided into scales that assess orientation, expressive and comprehensive language, memory, attention, praxis, calculation, abstract thinking, and perception (with a higher score indicating improvement) (Arcoverde et al., 2014).

**Physical activity and preventative health**

To date there is little knowledge connecting PA and dementia. A recent RCT demonstrated that improvement in cardiorespiratory fitness was related to improvements in functional abilities, such as memory performance, and performing ADLs (Morris et al., 2017). Before the intervention, study participants living with AD decline by 1 point per month on the Disability Assessment for Dementia Scale, while after the intervention, participants improved 1.5 points per month while the control group receiving stretching and toning declined 4.5 points per month (Morris et al., 2017).

Studies including PA as an intervention seem to improve execute ADL (i.e., eating, toileting, grooming) as well as more complex instrumental ADLs (i.e., manage medication, driving, grocery shopping).

The ability to perform ADLs in people at risk of dementia can be assessed in various ways. First, the Barthel Index of Activities of Daily Living evaluates the basic selfcare and mobility activities of an individual and is scored from 0 to 100, with a higher score indicating greater independence in ADL (Vreugdenhil et al., 2012). Second, the Analysis of Activities of Daily Living is a scale that includes 23 ADLs to complete and is scored between 0 and 78 points, with a lower score indicating more impairment in ADLs (Holthoff et al., 2015). Third, the Instrumental Activities of Daily Living is an assessment beyond the scope of basic self-care, including more complex tasks, such as driving, cooking, and shopping. This scale is scored between 0 and 14, with a higher score indication better function (Vreugdenhil et al., 2012).

Although there is literature demonstrating connections between PA and overall brain health that can improve plasticity later in life, there is a gap in the extent to which PA can improve physical health, cognition, and ADLs in persons at risk of AD and dementia. Guidelines from the American Heart Association recommend adults to perform at least 150 minutes of moderate intensity aerobic physical exercise to achieve benefits from exercise such as improved cardiovascular health, and even decreased risk of overall dementia (American Heart Association, 2021). A meta-analysis showed an effect and negative association between consistent and sustained PA and AD with a 10% to 13% decrease in risk after 10 metabolic equivalent task hours (500 kcal/week) (Xu et al., 2017). This study also found that protection against AD specifically by lowering the risk by 27% compared to all-cause dementia risk being reduced by 20% (Xu et al., 2017). An RCT recruited participants to receive three 1-hour weekly sessions of PA for four months consisting of a few minutes of warm-up exercises, followed by a routine mainly focused on aerobic exercise with a combination of fast walking with occasional slow jogging to achieve and maintain a heart rate to 70% to 80% of heart reserve, having to sustain this for longer periods of time as their conditioning improved (Dustman et al., 1984). Compared to the control group who trained with strength and flexibility exercises, the experimental group in which their regimen consisted of aerobic exercise was associated with improvement although not

statistically significant in three neuropsychological measures: critical flicker fusion threshold, culture-fair intelligence, and digit span as measurement tools (Dustman et al., 1984). Dementia decreases cognitive functions such as memory recall, attention span, response time. Improvement in critical flicker threshold, culture-fair intelligence, and digit span are indicative of improved mental flexibility—the ability to shift perceptual set—as well as memory (Dustman et al., 1984). A promising sign for all dementias is that improvement in these neuropsychological measures is indicative of the potential for aerobic exercise to improve cognitive functions that are impaired due to dementia (Dustman et al., 1984) (Lu et al., 2020). Thus, these results suggest a potential relationship between consistent and sustained PA and improved health in those at risk of AD and all-cause dementia.

Current pharmacological interventions show little to no effect preventing or treating dementias. Thus, more holistic, preventative strategies must be followed to improve cardiovascular health, reduce oxidative stress, and potentially decrease the risk of overall AD. There is a growing body of studies demonstrating the benefits of long-term regular PA on physical health, cognition, and ADLs.

Physical health in dementia is important because there seems to be a link between lack of oxygenation and the increased likelihood of developing AD and dementia and/or the severity of disease increasing at a faster rate in confirmed diagnosis. Additionally, a lack of oxygen can translate into decreased perfusion of oxygenated blood to the brain in persons with a lower maximal volume of oxygen intake. In order to measure the maximal oxygen volume intake, the measurement of Maximal Oxygen Uptake ($VO_{2max}$) is taken, which is usually measured after applied PA for a period of time, and after heart rate and respiratory rate are raised the concentration of oxygen inhaled and carbon dioxide exhaled are compared (Thomas et al., 2013). As it pertains to scoring in $VO_{2max}$ a higher percentage of oxygen compared to carbon dioxide indicates a positive maximal volume.

Cognition is important in AD and dementia because of the known decline of executive function, language ability, and motor skills. As the severity of disease increases in persons living with AD and dementia, so do these components of cognitive health. To measure executive function and language ability a tool used is the assessment of Executive Function and Language Ability, which assessed semantics and word fluency, in which that data is compared to expectation based on age and education (Holthoff et al., 2015). Another tool used to assess motor skill function is Reaction Time and Motor Skills (FETZ-test), in which subjects are asked to hold a ruler with their thumb and forefinger and release the ruler while the investigator holds it and is to catch the ruler as fast as they can once the ruler is released (Holthoff et al., 2015).

The ability to execute ADL is important in AD and dementia because as the condition progresses, the ability to complete tasks lessens and may require increased assistance. If the severity of a case is great enough, this can eventually result in the inability to complete even the simplest of tasks without the assistance of a caretaker. It has been reported that when persons living with AD and dementia engage in continuous PA, this may lessen the burden on the caretaker (Holthoff et al., 2015). When the ability to perform daily tasks is limited by the severity of disease this can require a caretaker, and the extent of those limitations will affect the caretaker to some degree. Within this RCT that was conducted, subjects that were assigned to the PA group saw a decreased NPI-caregiver score when compared to the sedentary control (Holthoff et al., 2015).

**Protective effects of sustained physical activity**

Although there is more to learn about what specific parameters of PA will cause a minimum effect, consistent and sustained PA seem to show some measurable effects. In a 2017 meta-analysis which defined PA as aerobic exercise that should be vigorous enough to burn at least 500 kcal a week, but this was measured in a unit called metabolic equivalent task-hours per week, or MET-h (Xu et al., 2017). In this research it was concluded that an increase of 10 MET-h per week there was on average 10% and 13% decrease in risk for all-cause dementia and AD (Xu et al., 2017). As a person's PA regimen continues,

physical conditioning is likely to improve in an individual as well. In a RCT conducted a measure of physical capability was a Steps Per Week and a 70k Step Goal, in which steps were measured on a weekly basis and a goal for steps achieved by the end of the intervention is 70,000 steps (Lautenschlager et al., 2008). In this experiment those that were assigned to the PA group saw a greater number of steps per week, and a greater percentage of subjects reach the 70k step goal (Lautenschlager et al., 2008). Another measure of endurance is the 6-Minute Walking Test, which evaluates the maximum distance that a person can walk in the span of 6 minutes (Roach et al., 2011). The strength of those that engage in continuous PA can increase as well when implemented. To measure the lower body strength of subjects the Sit-To-Stand test was utilized within this RCT, where subjects were asked to complete the maximum number of sit-to-stand repetitions as possible in the span of 10 seconds (Vreugdenhil et al., 2012).

Although universal recommendations for PA exists such as 150 minutes of moderate-intensity aerobic PA per week or 75 minutes per week of vigorous aerobic PA (American Heart Association, 2021). We do not know the effects of consistent and sustained PA on physical health, cognition, and ADLs of people at risk of AD or all-cause dementia. Without the knowledge of the effects of PA in these specific domains of health, it cannot be said whether PA is a viable intervention in people at risk of AD or all-cause dementia.

**Research objective**

Although there is proof of the negative association between AD and PA, what is not known is the extent to which it can affect specific components of health. Thus, this research proposes to better define the effects of PA in three health outcomes of people at risk of AD: physical health, cognition, and ADLs. To achieve this exploratory goal, I propose to search the literature for RCTs demonstrating effects of moderate and frequent PA on three health outcomes in people at risk of AD or all-cause dementia. These findings could support the standardization of PA as a nonpharmacological intervention to improve outcomes in people at risk of AD, especially given the lack of effective pharmacological interventions.

# Chapter 3

# METHODS

## Data Sources and Keyword Search

A keyword search was created for this study with the help of the UCF subject-matter Librarian (Shane Roopnarine) and search was conducted in the Cumulative Index to Nursing and Allied health Literature (CINAHL) database from its inception until February 2021 with no restriction on articles published outside of this period. The search strategy used four keywords for AD and all-cause dementia ("Alzheimer's disease" or dementia or "cognitive impairment" or "cognitive decline") and four keywords for PA ("physical activity" or exercise or fitness or "physical exercise).

## Inclusion Criteria

Only RCTs published in peer-reviewed journals that used PA interventions in populations at risk for AD or all-cause dementia to measure any of the three study outcomes (i.e., physical activity, cognition, or ADLs) were included. There were no restrictions based on date of publication, geographic area, gender, race, or analytic methods. Abstracts from the records obtained were reviewed regardless of statistical significance if (a) the article reported an RCT (i.e., there were one intervention group and at least one control group); (b) the article reported subjects who were at high risk for developing AD or dementia specifically; (c) the article reported assessment of the effects that PA had on physical health, cognition, and ADLs in groups at risk of AD, all-cause dementia, or both, regardless of statistical significance. Groups at risk included people with cognitive impairment suggestive of early-stage dementias as well as people with a clinically confirmed diagnosis of dementia.

## Measures

Studies that used PA (aerobic exercise, resistance training, flexibility training) as the intervention and assessed outcomes in physical health, cognition, and ADLs of people at risk or with a diagnosis of dementia

or AD were included. Measures of physical health included those that assessed maximum oxygen intake, blood flow, functional reach, strength, balance, and stamina. Measures of cognition included short term memory recall, executive function, verbal fluency, lucidity, and reaction time. Measures of ADL included those that assessed basic selfcare (i.e., bathing, dressing, feeding oneself), and instrumental activities (i.e., driving, cooking, and shopping).

**Data Abstraction and Analysis**

Records resulting from the literature search were screened for relevance using their title and abstract. The full text of records deemed relevant was reviewed for data extraction; outcomes were organized using Garrard's (2021) Matrix Method. Of note, articles could report one or more measures of the three outcomes of interest. From the data extraction matrix, outcomes related to physical health, cognition, and ADLs were independently reported and analyzed using a thematic analysis approach.

# Chapter 4

# RESULTS

The keyword search within CINAHL yielded 55 records. Of these, 15 were deemed relevant and kept for full-text analysis. Among the 15 studies, two were RCTs that complied with the inclusion criteria. The 13 articles excluded did not match the inclusion criteria (*n*=6), had inconsistent reporting of data and measures (*n*=7) articles. Manual search during the literature review also yielded five additional RCTs that qualified for inclusion, totaling seven RCTs for data extraction.

The seven RCTs were all published in English between 2008 and 2019. The mean number of participants was 78 and the median was 50. The selected studies contained a median of 24 participants in the experimental groups and 25 participants in the control groups. Table 1 summarizes the characteristics of the seven studies included.

Due to the lack of consistency in reporting physical activity, data was extracted and organized by themes using Garrard's (2021) Matrix Method to prepare a narrative, systematic review to approximate the research question of physical activity effects on three outcomes of AD, namely: physical health, cognition, and ADLs.

**Table 1.** Summary of Randomized Controlled Trials Analyzed

| Author(s), year | Study Location | *N* | Study objective | Intervention | Control |
|---|---|---|---|---|---|
| **Arcoverde, 2014** | Brazil | 20 | To assess the effect of aerobic exercise on the cognition & functional capacity in patients with AD. | Treadmill exercise for 30 minutes twice a week for 16 weeks at 60% $VO_{2max}$ (*n*=10):<br>1. Warm-ups for 10 minutes at 40% $VO_{2max}$<br>2. Twenty minutes of aerobic exercise at an intensity of 60% $VO_{2max}$<br>3. Five minutes of supervised stretching exercises focused on big muscle groups | Maintained clinical and pharmacological treatment for 16 weeks (*n*=10) |
| **Bouaziz et al., 2019** | France | 60 | To examine the effects of interval aerobic training program with active recovery bouts (IATP-R), | IATP-R for 9.5 weeks, consisting of 30 minutes of cycling 2 times a week (*n*=30) | Maintained sedentary lifestyle for 9.5 weeks (*n*=30) |
| **Hoffmann, 2015** | Denmark | 200 | To assess the effects of a moderate-to-high intensity aerobic exercise program in patients with mild AD. | Three weekly 1-hour sessions for 16 weeks consisting of (*n*=107):<br>1. First 4 weeks used for adaptation to exercise, building lower body strength + aerobic exercise once weekly.<br>2. The remaining 12 weeks included moderate- to high-intensity aerobic exercise (three, 10-minute intervals on: ergometer bike, cross trainer, and treadmill with 2- to 5-minute rest periods in between. | Received treatment as usual with no PA (*n*=93) |

| Author(s), year | Study Location | *N* | Study objective | Intervention | Control |
|---|---|---|---|---|---|
| **Holthoff, 2015** | Germany | 30 | To assess the effect of a home-based PA training on clinical symptoms of those at risk of AD patients, functional abilities, and caregiver burden after 12 weeks and 24 weeks. | Home-based PA program for 12 weeks with caretaker and assessment at 12 and 24 weeks consisting of (*n*=15): Lower body training on a movement trainer (ReckMOTOmed) changing between passive, motor assisted, or active resistance training of the legs as well as changes in direction (forward, reverse) every 5 minutes. | Usual care with no PA with caretaker and assessment after 12 and 24 weeks (*n*=15) |
| **Lautenschlager et. al, 2008** | Australia | 170 | To determine whether PA reduces the rate of cognitive decline amongst older adults at risk for AD or dementia. | 24-week home-based program of PA consisting of (*n*=85): 50-minute sessions 3 times a week (walking, strength training, flexibility, etc.) | 24-week-long educational program about memory loss, stress management, healthful diet, alcohol, and smoking, without PA (*n*=85) |
| **Roach, 2011** | United States of America | 82 | To determine whether an activity-specific exercise program could improve ability to perform basic mobility activities in long-term care residents with AD. | Activity-specific exercise program consisting of (*n*=28): Strength, flexibility, balance, and endurance training) for 16 weeks 5 days a week | 1. Supervised walking only with no activity specific exercise (*n*=29)<br>2. Social conversation control group with no form of PA (*n*=25) |
| **Vreugdenhil, 2012** | Australia | 40 | To assess the effectiveness of a community-based home exercise program in improving cognitive, physical function, and ADL in those at risk of AD. | In addition to usual care, a 4-month at-home exercise program consisting of (*n*=20): 10 simple exercises, each with 3 progressively challenging levels focusing on upper and lower body strength and balance, in addition to at least 30 minutes of brisk walking. | 4-months with usual care and no PA incorporated (*n*=20) |

**Abbreviations:** AD, Alzheimer's disease; ADL, activities of daily living; IATP-R, interval aerobic training program with active recovery bouts; PA, physical activity; $VO_{2max}$, maximal oxygen uptake

## Physical Health

Of the articles included (*n*=3) of the studies included reported on (*n*=4) measures of physical health, described next. Overall, interventions with a PA component seemed to improve stamina, strength, and balance.

*Steps per week and 70k step goal*

In a study by Lautenschlager et al. (2008), participants were placed in the experimental group received a 24-week home-based PA program that were 50-minute sessions 3 times per week. Subjects who received the intervention were able to choose exercises that focused on walking, strength, and flexibility—though it was recommended that the regimen consist of mostly walking. Most subjects in the PA group did in fact choose walking as the focus of their PA program. The control group received usual care in their respective facilities and received education material about memory loss, stress management, healthful diet, alcohol consumption, and smoking. Each week there were three, 50-minute sessions for both groups and, after 6 months, the intervention group achieved 9,000 more steps per week than the control group. Included in the experiment for both groups was a step goal of 70,000 steps per week, a significant 25% of the experimental group was able to achieve this goal compared to only 17.6% in the control group ($p$=0.009) (Lautenschlager et al., 2008).

*Functional Reach (Balance test)*

In a RCT conducted by Vreugdenhil et al. (2012) improvement was seen after four months of PA in community-dwelling patients diagnosed living with AD. During this time-period the PA consisted of ten simple exercises, each with three progressively challenging levels focusing on upper and lower body strength, in addition to 30 minutes of brisk walking. Although, there was no assigned frequency of exercise per week, subjects along with their caretakers were recommended to exercise daily if possible. The control group was not given any exercise regimen but received their usual care. There was a significant increase of 4.2 cm in

functional reach in the PA group compared to the control's decrease of 1.9 cm ($p$=0.032) (Vreugdenhil et al., 2012).

*Sit-to-Stand Test (mobility and lower body strength)*

In the RCT by Vreugdenhil et al. (2012), improvement in mobility and lower body strength were observed after four months of PA. Subjects performed the sit-to-stand test in 10 seconds as a measure of lower body strength. The maximum number of repetitions in this allotted time were counted and a mean score was calculated for the intervention and control groups. After the 4-month program, the PA group had a significant improvement in the mean number of repetitions (+1.7) compared to the control group's decline of (-1.0) ($p$=<0.001) (Vreugdenhil et al., 2012).

*6-minute walking distance*

Participants in a RCT conducted by Roach et al. (2011) assigned to the intervention group were given selective activity specific PA five days per week for 16 weeks, focusing on strength, flexibility, balance, and endurance. Subjects were also assigned to two control groups: one consisted of supervised walking with no activity specific PA and one consisting of social conversation group with no form of PA. Strength and flexibility training consisted of exercises that were designed to strengthen the trunk and lower extremities. The second strength exercise consisted of the intervener and subject facing each other, and the subject had to push or pull against the resistance provided by the intervener, this was to increase trunk strength and hip mobility. The balance and weight shifting exercise included the subject standing in front of the intervener and wearing a gait belt. The intervener would hold on to the gait belt as the subject stepped in all directions (left, right, backward, forward). Assistance would be decreased, and repetitions would increase as the trial proceeded. The final portion of exercises consisted of a supervised walk where the subjects could use assistive devices and/or physical assistance if needed. The duration of the walks started at 10 minutes, and as the conditioning improved it would increase to 20 min. Subjects' intensity and duration of the selected

exercises increased, starting with 2 to 3 repetitions, progressing to 7 to 9 repetitions, and duration starting at 15 minutes and being increased to 30-minute sessions. The intervention group's 6-minute walking distance had a nonsignificant increase of 11.4% compared to the control's increase by 9.5% ($p$= >0.050) (Roach et al., 2011).

**Cognition**

Of the included studies there were ($n$=6) studies that included ($n$=8) measures of cognition, described next. Overall, the interventions with a PA component seemed to improve short term memory, lucidity, executive function, and language ability.

*Trail making Test*

In a study by Bouaziz et al. (2019) RCT participants who completed 30 minutes of cycling twice a week over the span of 9.5 weeks saw improvement. In each of the sessions for the PA group there would be six 5-minute periods of PA combining 4-minutes of cycling within the sessions. Each session would also begin with a 3-minute warm up period and finished with a 3-minute recovery. For each decrease of 10 beats/min in HR, there would be a 10% increase in the "BASE" with the "RECOVERY" value remaining constant. The control group was to maintain a sedentary lifestyle throughout the 9.5-week trial.

At the end of the trial there was a significant difference in the executive functions of those in the exercise group as measured by the trail making test (TMT-A; TMT-B). In TMT-A where 25 circles were numbered (1-25), subjects were asked to trace a line to each number in ascending order. The PA group saw a (-12.3%) reduction in the time it took to complete the task, compared to the control's increase of +1.5% to their time. In TMT-B there were circles numbered (1-13) and lettered (A-L). Subjects had to alternate between the letters and numbers without lifting the pencil. The PA group also outperformed with a significant decrease in the time it took to complete the task (-13.3%) compared to the controls increase of (+0.9%) ($p$= <0.050) (Bouaziz et al., 2019).

*Paced auditory serial addition test (PASAT)*

In the previously mentioned RCT, as a cognitive measuring tool subjects were presented with numbers on a screen for 3 seconds and would have to add each new digit to the one presented before. The PA group saw significant improvement from baseline with a significant +14.8% average improvement in their score, compared to the control groups decrease of -1.4% ($p$= <0.050) (Bouaziz et al., 2019).

*Verbal Fluency Task*

Within the same study another measure of executive function was the verbal fluency task, composed by letter fluency and category fluency tests. In letter fluency, subjects were asked to produce as many words as possible beginning with the letters "F", "A", and "S" in 1 minute each (p= <0.050) (Bouaziz et al., 2019). In the category fluency portion subjects were asked to evoke the greatest possible number of animals within 1 minute. In the PA group benefits were measured in the category fluency task there was a significant increase in their score (+11.7%), compared to the control with a decrease of (-1.1%). In the letter fluency task, there was no significant difference between the PA group and the control ($p$= <0.050) (Bouaziz et al., 2019).

*Alzheimer's disease assessment scale-cognitive subscale (ADAS-Cog)*

In a study by Lautenschlager et al. (2008), one of the primary assessments to measure cognition was the ADAS-Cog scale. This scale had scores ranging from (0-70) and consisted of 11 brief cognitive tests assessing memory, language, and praxis. After the 24-week program that has been described, the PA group saw a significant average decrease in their score of (-0.26) while the control saw an average increase in score of (+1.04) points ($p$= 0.040) (Lautenschlager et al., 2008).

In the RCT conducted by Vreugdenhil et al. (2012) the PA group saw a decrease in their score after the described 4-month home exercise program. Subjects in the PA group saw a significant average decrease in ADAS-Cog score of (-4.9) while the control group saw an increase in their score of 2.1 ($p$=0.001).

In a RCT conducted by Hoffmann et al. (2015) while subjects who were in the PA group did not see an increase or decrease in score, a maintenance of ADAS-Cog score was seen. In the experiment, subjects in the PA group were to complete three weekly 1-hour sessions for 16-weeks. In the first 4 weeks, the time was used for subject adaptation to exercise, building up lower body strength and conditioning them for aerobic exercise. This time-period was followed by 12 weeks that included moderate to high intensity aerobic exercise (in total 3 x 10 min intervals on ergometer bike, cross trainer, and treadmill) with 2- to 5-minute rest periods between exercises. The control group was to receive treatment as usual with no PA involved. As mentioned, the PA group saw no change in their score over 16 weeks, while the control group experienced an increase in score that was not statistically significant ($p$= 0.0406).

*Mini mental state examination*

In the RCT conducted by Vreugdenhil et al. (2012) those who participated in the PA group also saw better scores in their mini mental state examination. This examination was used to assess the cognitive health of the subjects including tests on orientation, attention, memory, and language. The examination is set at a range of 10-28 (Vreugdenhil et al., 2012). After the trial those in the PA group saw a significant increase in their score by (+2.6) points while those in the control group saw a decrease in their score of (-1.6) points ($p$= 0.001).

*Executive Function and Language Ability*

In a RCT conducted by Holthoff et al. (2015) subjects witnessed improvement in their condition after completing the 24-week home-based PA program. In the PA program the exercises were to be completed with a caretaker, and assessment of subject's condition would be taken at 12-weeks then 24 weeks. Within the trial period the exercises consisted of lower body training on a movement trainer (ReckMOTOmed) changing intensity between passive, motor assisted, or active resistance training. In addition to this there would be a change in direction (forward and reverse) every 5 minutes. The sessions were to be 30 minutes,

three times per week, for 24 weeks. Subjects were administered semantic and phonemic word fluency tests. Those in the PA group saw significant improvement with a (+0.55) point increase in their score compared to the control who saw a (-1.87) point decrease ($p$= <0.050) (Holthoff et al., 2015).

*Reaction Time and Motor Skills (FETZ test)*

In an assessment of reaction time, hand-eye quickness, in attention were measured using the reaction time ruler or FETZ test, which measures the time a subject takes to respond to the dropping of a 0.50-meter ruler (Holthoff et al., 2015). The subject is to hold the ruler with their thumb and forefinger then release the ruler while the investigator continues to hold it and is to catch the ruler as fast as they can once it is released. There was a significant change in the PA group with a decrease of (-0.03) decrease in time compared to the control who saw no change from baseline assessment ($p$= <0.050) (Holthoff et al., 2015).

*Cambridge cognitive examination (CAMCOG)*

In a RCT conducted by Arcoverde et al. (2014) those in the PA group saw improvement in CAMCOG scores after the 16-week PA program. Within the 16-week period PA consisted of two 30-min treadmill sessions twice a week. During these sessions there would be a warm-up period for 10 minutes at 40% $VO_{2max}$. The next portion of the PA sessions consisted of 20-minutes of exercise at 60% $VO_{2max}$, followed by 5-minutes of supervised stretching exercises focusing on big muscle groups. The CAMCOG examination was used as measure of cognitive function with an increased score indicating better cognition. While the PA group experienced a significant 6-point improvement, the control group saw a 6-point decrease in their score ($p$=0.001).

**Activities of Daily Living**

Of the studies included ($n$=2) of the studies included reported ($n$=3) measures of ADLs, described next. Overall, interventions with a PA component seemed to improve ability to complete ADL with lessened assistance and improved execution of instrumental ADLs.

*Barthel Index of Activities of Daily Living*

In the conducted by Vreugdenhil et al. (2012) subjects in the PA group saw improvement in their Barthel Index scores. After the 4-month at home PA program described, the PA group saw a significant average (+2.6) point increase in their score, while the control was not reported to see any change in score ($p$= 0.047) (Vreugdenhil et al., 2012).

*Analysis of Activities of Daily Living Scale*

In the RCT conducted by Holthoff et al. (2015) subjects in the PA group showed significant change with an increase of (+2.6) points compared to the control who saw no change in their score compared to baseline ($p$= <0.050) (Holthoff et al., 2015).

*Instrumental Activities of Daily Living*

In the RCT conducted by Vreugdenhil et al. (2012) it was reported that subjects in the PA group saw an improvement in Instrumental Activities of Daily living as well. Subjects in the PA group reported a significant average increase of (+1.6) points, while the control group saw a decrease of (-1.4) points in their Instrumental ADLs score ($p$= 0.007) (Vreugdenhil et al., 2012).

# DISCUSSION

In this study I aimed to describe the effects of PA on physical health, cognition, and ability to complete ADLs in people at risk for AD or all-cause dementia who participated in RCTs. The seven RCTs included demonstrated promising effects in the three study outcomes, with all the measures of physical health, cognition, and ADLs reaching levels of significance. It is important to note, all studies that included significant change it was the various forms of aerobic PA that seemed to cause this effect. This can mean that PA given the right intervals may be a viable intervention method that can be to lower the risk of developing AD and all-cause dementia. With only 7 RCTs meeting the inclusion criteria, there seems to be a paucity of studies quantifying consistent and sustained PA that can cause not only statistically significant, but clinically meaningful effects. As a starting point, studies can follow recommendations for the general population of 120-150 minutes of moderate aerobic exercise (i.e., walking, swimming, cycling) per week much like the universal recommendation that is recommended and accepted by many (American Heart Association, 2021). Specific PA interventions targeting people at risk of AD or all-cause dementia can be adapted from these universal guidelines.

We expected to observe improvement in physical health after implementing sustained PA interventions. Statistically significant improvements were observed in most physical health measures, namely: functional reach (balance test), sit-to-stand test, and steps per week (with the 6-minute walking test not reaching significance). This can be due to the contribution of PA to the improvement in vascular health, as well as mobility. Though, assessment of physical health at more than just baseline to completion of the program could better illustrate the progression of physical health in the subjects who adapt PA as part of their lifestyle. Also, not all the interventions progressed PA in duration or intensity, which should prompt to considering a plateau effect. There were also inconsistencies in the application of PA for subjects, with

allowance of a minimum and maximum requirement of activity per week. Thus, allowing heterogeneity in the amount of PA completed by subjects throughout the trial.

There were also statistically significant improvements reported for cognition in the subjects who completed PA interventions. Cognition is one of the domains of health most affected by the progression of AD or dementia. Thus, improvement in cognition may be due to the preventative effects of PA on oxidative stress and vascular risk factors, which can negatively impact cognition. With all studies including some form of aerobic PA (walking, cycling, swimming, etc.), it can be assumed that the improvement in vascular health, which therefore may have improved the flow of oxygenated blood to the brain (Lange-Asschenfeldt & Kojda, 2008). This improvement in vascular health can be the contributing factor to the improved cognition that was reported in the studies. With the application of sustained and continuous PA and improvement in physical health this can possibly translate to the improvement seen in of the assessments of cognition (namely: Trail making test, PASAT, Verbal Fluency Task, Executive Function and Language Ability, FETZ test, Digit-Span, ADAS-Cog, mini mental state examination, and CAMCOG). All these assessments were objective, reducing the possibility of bias in scoring. Although, those living with AD or all-cause dementia can experience lapses in cognition, and in the case of mental examinations this can greatly affect a score. In future studies assessing subjects at more than just the baseline and end of the intervention may help to give a true value given that the subjects may not be in a lucid state of mind at the time of examination.

Activities of daily living are likely to be affected by change in physical health, cognition, or both but it was the least common outcome that was measured across all experiments. Out of the seven studies that were included, only two analyzed ADLs. In the assessment of daily living significant improvement was seen in all the measures used (namely, Barthel Index of ADL, Analysis of Activities of daily living scale, and instrumental activities of daily living). Improvements were likely due to improvement in physical health and cognition, making it easier for subjects to execute tasks. With so little focus on the effects of PA on ADL in

concurrence with physical health and cognition it limits the knowledge of the extent of PA efficacy as an intervention.

This study is not void of limitations. First, there is a scarcity of data from RCTs. This may be due to sustained and continuous PA not yet being recognized as a mitigation strategy for AD and dementia. Publication bias may also play a limiting role, where only studies with statistically significant findings tend to be published. Second, there is wide heterogeneity in the outcomes and their measures, as evidenced by several approaches to measure physical health, cognition, and ADLs. Third, with the lack of a standardized PA regimen for people at risk of AD or all-cause dementia, there is great heterogeneity in the way these studies are reported. For example, in the RCT conducted by Roach et al. (2011), there was a minimum and maximum amount of PA that subjects had to maintain, which leaves ambiguity to assess the specific profile of PA that was effective to observe these results.

Limitations aside, this study also presents important strengths. First, the Systematic Literature Review approach captured publications in peer-reviewed, indexed journals. Thus, providing trusted sources of information from which data was extracted. Furthermore, the use of the Gerrard's (2021) Matrix Method is an efficient way to organize data, making comparison of that extracted data less tasking. Also, this study further advances the research available for the application of PA as an intervention method for those at risk of AD and all-cause dementia. Additionally, in my findings, although limited, has shown the need for more research to add to the argument that PA is indeed a viable intervention in persons at risk of AD and all-cause dementia. Moreover, it has also highlighted the need for more consistent PA regimen, because without a defined parameter of PA it is hard to say what quantity of PA causes an effect. For example, instead of a minimum and maximum amount of PA in each period, set a standard amount of PA that must be completed. Furthermore, this study also highlights the necessity for there to be assessment of subjects at multiple periods throughout the trial, rather than just at baseline and post-intervention.

In conclusion, there seems to be positive effect on physical health, cognition, and ADL with the introduction of PA as an intervention method. The application of PA as an intervention has shown a significant difference in physical health, cognition, and ADLs. This significant change that was witnessed in most experiments is critical for the future application of PA in those at risk of AD and all-cause dementia. It was also seen that PA caused statistically significant changes in measures of cognition. The statistically significant changes described in RCTs suggest that PA may indeed be an effective intervention to improve physical health, cognition, and ADLs in those at risk of AD and all-cause dementia.

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