Review

Physical Activity and Alzheimer’s Disease: A Systematic Review

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Abstract

The current literature includes several studies investigating the association between physical activity and risk of Alzheimer’s disease (AD). The aim of this review was to systematically evaluate available evidence on this association. Medline via PubMed and CINAHL databases were searched for original English language research articles assessing the relationship between physical activity and incident AD. The review was limited to prospective observational and intervention studies. Criteria for exclusion were studies focusing on individuals with dementia, cross-sectional study design, and case reports. The quality of included studies was assessed in 5 domains of bias. Twenty-four studies met the inclusion criteria. The number of participants ranged from 176 to 5,698. Follow-up time varied from 1 to 34 years. Physical activity was inversely associated with risk of AD in most studies (n = 18). Leisure-time physical activity was particularly protective against AD, but not work-related physical activity. The risk of bias assessment showed that overall quality of evidence was moderate for 16 and low for 8 studies. Beyond all the available general recommendations for health promotion, current evidence does not allow to draw specific practical recommendations concerning the types, frequency, intensity, or duration of physical activity that may be protective against AD.

Keywords: Cognitive impairment—Dementia—Exercise

In the year 2010, 35.6 million people worldwide were diagnosed with dementia, and this number is projected to reach 1.25 billion by 2050, accounting to 22% of the world’s population (1). Growing evidence links several genetic and environmental risk factors to Alzheimer’s disease (AD) (2). It was recently estimated that about one third of AD cases worldwide may be attributable to seven modifiable risk factors: diabetes, midlife hypertension, midlife obesity, physical inactivity, depression, smoking, and low educational attainment (3). Physical activity may thus contribute to preventing and/or delaying the onset of cognitive decline and AD. Physical exercise is relatively easy to do and is most effective when done regularly. Physical activity is known to have beneficial effects on general health and can significantly reduce the risk of myocardial infarction, stroke, and diabetes (4), which may in turn contribute to reducing dementia risk. Physical activity has been reported to improve cerebral perfusion, facilitate neurogenesis and synaptogenesis, reduce neuronal loss, and preserve brain volume in regions vulnerable to AD, and also favorably influence pathological processes related to AD such as β-amyloid accumulation and tau phosphorylation (5–8). These mechanisms can explain reported links between physical activity, cognition, and dementia. Multifaceted physical activities that also involve mental and social activity may provide additional value for brain health. AD prevention in the near future may be based on multidomain strategy governing several lifestyle habits such as diet, cognitive activity, and physical activity (9).

Defining the optimal preventive strategies in terms of type, duration, and intensity of physical activity is an important practical question. This systematic review was conducted to study the role of physical activity as a potentially preventive intervention against AD. It was also aimed to investigate how much and which kind of physical activity would be protective against AD and to evaluate the quality of available evidence.
Methods

Literature Search
Medline via PubMed and CINAHL databases were searched with the same search strategies for studies published up to June 2015. The search strategy using Medical Subject Headings [mh], and keywords was: exercise OR “physical activity” AND “Alzheimer’s disease” OR “cognitive impairment” OR dementia. Combination of these terms and filters regarding study design and type (ie, randomized controlled trial, cohort study, follow-up study, and controlled clinical trial) were used to obtain the search results.

Criteria for Inclusion
Studies with longitudinal, prospective observational, or interventional designs were considered. Included were studies with populations of any age without AD at baseline; physical activity, as defined by study authors (definition without restriction was included in order to have a broad range of evidence) as exposure; and studies including only incident early-onset or late-onset AD specifically as outcome.

Study Selection
The specific search strategy retrieved 640 results in Medline and 2,940 articles in CINAHL.

Going through article titles, duplicate articles were removed. 90 articles were selected and their full texts were reviewed. 24 studies were chosen. Reference lists of studies were hand-searched to check if any potential study was not captured by the search strategy. Reviews, case reports, cross-sectional studies, uncontrolled intervention studies, and non-English language studies were excluded. Studies with dementia in general as outcome (without specifically assessing AD) were also excluded. Two authors (R.S. and E.L.) independently reviewed full texts of all articles that were considered relevant for inclusion in this review. In cases of disagreements between these two authors, a third author was consulted. The study selection process is described in Figure 1.

Systematic Evaluation
The included studies were assessed for design, setting, and study population. The definition of physical activity was evaluated systematically taking into account assessment methods, assessment period, frequency, duration, and intensity of physical activity. Adequate diagnostic evaluation and the use of appropriate diagnostic criteria for AD were checked from each of the studies. As not many validated tools are available to assess the quality of observational studies, an applicable criterion was designed by modifying the validated methods of Shamliyan and colleagues (10–12), recommendations of Agency for Healthcare Research and Quality (AHRQ) (13), GRADE (14) according to the research aims of this review. This criterion evaluated the evidence in four major domains of bias and one minor domain of bias.

Major domains of bias
Population representativeness
There were three categories “good,” “moderate,” and “low” in this domain. Good population representativeness was defined as age of participants ≤65 years and sample size >1,000. Moderate population representativeness was defined as age of the participants 65–74 years and sample size ≥1,000 and >500. Low population representativeness was defined as age of study participants ≥75 years and sample size ≤500. There are no specifically defined cutoffs for sample sizes, but a general rule is to have a sample size large enough to detect a clinically significant difference of 5% in event rates or an odds ratio or risk ratio increase of ≥1.5 or decrease of ≥0.67 between groups in at least one primary outcome measure of interest (13). Moreover, cohort studies typically require larger sample sizes to have the same power as a case–control study (15). The limitations for age were defined because the prevalence of AD is 2%–3% at age 65 and doubles every 5 years after that (16), thus increasing the likelihood of physical activity assessments being affected by undiagnosed AD. Older populations raise the question of selection bias owing to inclusion of study participants with prodromal AD or who are at highest risk for AD.

Exposure assessment
There were three categories “good,” “moderate,” and “low” in this domain. “Good” physical activity assessment was defined as the measurement being done both subjectively and objectively. “Moderate” physical activity assessment was defined as the measurement through validated questionnaires or through questionnaires based on pre-established recommendations. “Low” physical activity assessment was defined as measurement through questions such as “do you exercise regularly? yes/no”, without considering validated questionnaires or a defined standard for physical activity, using only questions but no questionnaire for physical activity assessment.

Length of follow-up
There were three categories “good,” “moderate,” and “low” in this domain. “Good” was defined as follow-up time ≥14 years. “Moderate” was defined as follow-up time between 6 and 14 years. “Low” was defined as follow-up time ≤6 years. These cutoffs were defined because the ideal follow-up would start from midlife or third decade of life and last until death. Two years was used as the minimum adequate follow-up time for AD by the AHRQ (13) systematic review, which assessed multiple exposures. In this review focusing on physical activity, a stricter minimum adequate follow-up time was preferred (6 years). AD has a long preclinical phase, and it takes time for cognitive impairment to develop into fully manifest dementia. Longer follow-up time is needed to establish a cause–effect relationship and avoid the limitations of shorter studies (which often also focus on older populations) (13).
Valid outcome assessments
This domain considered the definition of AD according to criteria of the Diagnostic and Statistical Manual of Mental Disorders (Third Edition Revised, DSM III-R) / (Fourth Edition, DSM IV) (17) for dementia diagnosis, and research criteria established by the National Institute of Neurological Disorders and Stroke and the Alzheimer’s disease and Related Disorders Association (NINCDS-ADRDA) (18).

Minor Domains of Bias
Drop-out or attrition
There were three categories “good,” “moderate,” and “low” in this domain. “Good” was defined as the loss of participants (nonresponse) ≥20%. “Moderate” was defined as the loss of participants 20% to 40%. “Low” was defined loss of participants ≤40% or up to half of the study population. 60% attrition rate over 20 years was not much, whereas 30% attrition rate over a period of 5 years was considered large (13,19).

The quality of evidence of the included studies was assessed based on the categories described earlier. Quality of evidence was defined as “good” (ie, low risk of bias) if the study was rated as “good” in all major domains, and “good” or “moderate” in the minor domain. Quality of evidence was defined as “moderate” (ie, moderate risk of bias) if the study did not meet the above-mentioned requirements for good quality of evidence, but was rated as “good” or “moderate” in <4 domains. Representativeness of sample, method of exposure assessment, and length of follow-up taken into consideration may affect more significantly the reliability of a study in the context of the current review than, for example, drop out. Therefore, the domains were placed into two hierarchical groups to assess the overall quality of evidence.

Results
Design, Setting, and Study Population
Supplementary Table 1 presents a summary of the 24 longitudinal observational studies included in the systematic review. Of these, 22 studies (20–41) included participants from the general population, and only two focused on patients (memory clinic patients with mild cognitive impairment) (42), or patients evaluated for cognitive, neurological, or mood-related complaints (43). Twenty-one studies (21–28,30–33,35–43) included both women and men. Two studies (29,34) were conducted only among men and one cohort (20) consisted only of women. The sample size of the included studies varied from 176 to 5,698 study participants. Power calculations were reported only for two studies (21,22).

Definition of Physical Activity
Four groups of studies were identified based on the overall definition of physical activity (Supplementary Table 1). The first group focused specifically on leisure-time physical activities, and all seven studies reported significant associations with AD (20–25,42). The second group assessed various combinations of leisure-time and household physical activities, with five (26–30) out of seven studies (26–32) reporting significant associations with AD. The third group had various assessments of exercise in general (without further specifications), and five (33–36,43) out of six (33–37,43) studies linked physical activity to reduced AD risk. The fourth and smallest group focused on occupational physical activity, either alone or in combination with leisure-time or household activities, with mixed results (38–41). Only one study investigated commuting physical activity separately (40).

Assessment Methods of Physical Activity
The included studies had varied methods of physical activity assessment. Only one study assessed physical activity both objectively and subjectively (27). Fifteen studies used validated questionnaires (20,21,26,27,29–32,34–36,38,41–43). Four studies developed questionnaires based on different established recommendations for physical activity (22,24,28,40). Four studies developed their own questionnaires without using established recommendations or validated questionnaires (23,25,33,37).

Physical Activity Assessment Period
Assessment period of physical activity varied among the included studies. Five studies (20,22,24,40,41) assessed physical activity as hours per week (20,24), and one as hours per day (41), general level over a period of 31 years (22), and one tried to capture minutes spent in physical activities daily (40) at midlife. Nineteen studies assessed the level of physical activity in the past year (23,39) one day in the past year (33,37) over a month or less than a month (21,25–32,34–36,38,42,43) at late life. Two studies aimed to measure 24-hour activity (27,29).

Type of Physical Activities
A wide variety of sports activities were recorded tennis (20,21), golf (21,30–32), bicycling (20,23,26,27,30–32), bowling (21,30–32), playing handball (21), horseback riding (21), other sports (20,22,42), walking (20–23,25,26,28,31,32,42), jogging or running (20,30,32), aerobics or calisthenics (21,23,27,30,32), water aerobics or water exercise (23,27,30,32), swimming (21,23,27,30–32), weight training or stretching (23), physical conditioning (25), hard physical training (20,22), any type of leisure-time physical activity (24), and exercise (31), including the following descriptions of group-based exercises: general exercise (27,30,32), regular exercise (22,35,36), light exercise (22,33,37), moderate to vigorous exercise (33,37), and other exercise (23,33,37). In addition, a variety of other activities were captured, defined as hobbies (25,26), dancing (21,30–32,39), traveling (42), hiking (21,23,30), and gardening (20–22,26,28,29,42). Several household activities were recorded, including yard work (27,30,32), climbing more than two flights of stairs (31), housework (31), babysitting (31), carpentry (29), lifting or shoveling (29), and odd jobs (28). Work-related activities were classified according to type of commuting to work, intensity, and duration (38,40).

Duration, Frequency, and Intensity
The studies had different measures of physical activities. Three studies assessed duration, frequency, and intensity (20,21,39). Frequency and duration were measured by six studies (23,24,30,32,34,43). Frequency and intensity were measured by three studies (22,36,38). Duration and intensity were measured by five studies (26,29,33,34,41). Intensity was taken into account by 12 studies (20–22,28–30,33,34,36,37,39,41) directly or through measures of frequency, duration or type of activity. Six studies evaluated the intensity of physical activity in terms of Metabolic Equivalent of Task (METS) (21,26,30,33,37,39). Two studies measured frequency only (31,42) and two used no measures for physical activity in terms of duration, frequency, or intensity (25,35).
Physical Activity Measures in Statistical Analyses
Five studies classified responses regarding intensity (29,30,36,37,39) of physical activity. Seven studies (20,23,24,33,35,37,43) dichotomized responses as “active” or “sedentary”, “yes” or “no”, “frequent” or “not frequent” based on number of times per week or duration of physical activity or both, or by intensity in METS. Three studies grouped the responses in three categories (21,27,42). Other studies divded the information on physical activity into four categories based on the distance walked or frequency/intensity of physical activity (22,38,39).

Quality Assessment
The overall quality of evidence was moderate for 16 studies (20–26,29–32,34,38,40,41,43) and low for 8 (27,28,33,35–37,39,42) studies. Supplementary Table 2 presents a summary of quality assessment of the included studies based on the following domains.

Population representativeness
Five studies (20,22,24,40,41) were assessed as having “good” representative sample. Sixteen studies (21,23,25–30,32–36,38,39,43) had “moderately” representative sample whereas three had “low” representative sample (31,37,42).

Assessment of exposure
Only one study (27) was assessed to have “good” exposure measurement because it used both subjective and objective measures. Nineteen studies (20–26,29–32,34,36,38–43) had “moderate” measures to assess physical activity. They used validated questionnaires or based their questionnaires on established recommendations. Four studies (28,33,35,37) had “low” quality exposure assessment measures because they employed self-report only at rough level such as “do you exercise regularly” with answer options yes or no.

Length of follow-up
Six studies (20,22,24,31,40,41) were considered as having “good” follow-up time; five studies (23,25,26,34,38) had “moderate” follow-up and thirteen studies (21,27–30,32,33,35–37,39,42,43) had a “low” follow-up time.

Outcome assessment
All studies had valid outcome assessments because they used criteria of the DSM III-R/DSM IV (17) for dementia diagnosis, and research criteria established by the National Institute of Neurological Disorders and Stroke and the Alzheimer’s disease and Related Disorders Association (NINCDS-ADRDA) (18) for the diagnosis of AD.

Loss of follow-up/ Drop out
In their final analyses, nine studies (21,24,25,28,30,31,38,42,43) had “20%” loss of participants and were considered as “good” in this regard. Ten studies (20,22,26,29,32–34,37,40,41) having an attrition rate 20% to 40% were considered “moderate” and five studies (23,27,35,36,39) had ‘40%’ loss of study population and were considered “low” quality in the current domain.

Discussion
Of the 24 studies included in the systematic review, 16 provided moderate quality of evidence. A majority of studies (18 out of 24) reported beneficial effects of physical activity on the risk of AD. Leisure-time physical activity had a clear association with reduced risk of AD. However, the risk reduction was less clear for occupational and commuting physical activity. The only study separating occupational from commuting activities, and distinguishing them from leisure-time activities, did not find a relation to AD risk (40), suggesting that work-related physical activity may not be enough to protect against AD.

Our findings are consistent with previous meta-analyses reporting beneficial effects of physical activity on the risk of AD and dementia in general (3,44–47). However, meta-analyses have been limited to smaller groups of studies with comparable measures of physical activity and have not discussed leisure-time versus other activities. In this review including a larger number of studies, the six studies that found no associations with AD included work-related physical activity, or leisure-time and household activities together, or just “exercise in general” without further specification. The lack of association may be due to methodological weaknesses of the studies. The quality of evidence was low in majority of the six studies. The assessed household activities and chores varied substantially between studies and vague exposure definitions such as “exercise in general” were used. It may also suggest a different significance for AD risk related to different types of physical activity.

Interestingly, the benefit of physical activity, for example, cardiovascular prevention has been related to the amount of activity per day (energy expenditure), rather than to the type and modality of activity (48). However, manual or physical work per se, or occupational physical demands have been associated with increased risk of AD (40). Higher work-related physical activity level has been linked to lower education and socioeconomic status, and less cognitive stimulation (40). These are all risk factors for AD and dementia (2). Work-related and leisure-time physical activity also seem to be inversely related, that is, individuals who are physically active at work tend to be more sedentary during leisure time (40). Leisure-time physical activities have been indicated also as important sources of social and cognitive stimulation (31). These multifactorial effects (social, cognitive, and physical activation) on brain function, cognitive performance, and the prevention of AD appear to have common and overlapping pathways (38,49).

Life-course Perspective on Physical Activity and AD
According to the cognitive reserve hypothesis, physical activity performed across the whole life span may contribute to maintenance of cognitive function in old age (49). All studies of midlife leisure-time physical activity in the present review emphasized beneficial effects on lowering AD risk. However, it may not be too late to become physically active later in life, considering that most included studies had participants aged 65 and older, and a majority indicated beneficial effects of leisure-time physical activity. Changes in physical activity during the life span have been less investigated in relation to AD, but one population-based study found protective effects against dementia in people who either maintained a high level of leisure-time physical activity from midlife to late life, or increased their physical activity level later in life (50).

Leisure-time and work-related physical activity can have very different patterns across the life span, as retirement potentially leaves more room for leisure-time physical activity. However, retirement from physically demanding occupations was reported to lead to a decline in overall physical activity, particularly in individuals with lower socioeconomic status (51). In contrast, retirement from...
sedentary occupations led to an increase in overall physical activity, particularly in individuals with higher socioeconomic status (51). Such changes over time may explain why work-related physical activity alone was not associated with AD risk (40,50,51).

Other factors (eg, genetic susceptibility and gender) may also affect the relation between physical activity and AD across the life span. It is not fully clear whether genetically susceptible people (eg, APOE4 carriers) may benefit more from healthy lifestyle changes including physical activity, or whether the APOE4 allele counteracts the protective effects of physical activity. Midlife leisure-time physical activity was reported to reduce the risk of AD and dementia two decades later particularly in APOE4 carriers (24), whereas late-life physical activity had shorter-term beneficial effects particularly in APOE4 noncarriers (28). The impact of apolipoprotein E allele on AD and dementia seems to become weaker at older ages (52) and also the impact of physical inactivity may be lower among APOE4 carriers who survive to old age (50). Interactions between physical activity and hormones have been suggested to relate to cognitive functioning in women (53–55). Although some studies found that physical activity had a greater protective effect against AD and dementia in women than in men (36), no effect modification by gender was reported in a meta-analysis (56).

The predementia phase of AD is long and the association between physical activity and AD needs to be considered across the course of AD (16). Ongoing pathologic processes leading to subsequent dementia may also lead to declining physical activity (50). The three population-based studies focusing on leisure-time physical activity or exercise in general which did not find associations with AD had older populations with late-life assessments (31,32,37), could have potentially included more individuals with preclinical or undiagnosed AD. However, the two studies (42,43) of patients with mild cognitive impairment or neurological symptoms included in the present review suggested that physical activity may still have some benefits in prodromal or early AD.

How Much Physical Activity Is Enough?
It is difficult to formulate recommendations based on studies that are so different concerning physical activity definitions, assessment periods and methods, types, duration, and intensity. Some studies have based their physical activity categorizations on available recommendations for health promotion, thus suggesting that such recommendations may also apply to AD prevention (43). However, from a practical perspective, it remains unclear which types or combination(s) of leisure-time physical activities in which intensity, frequency, and duration are needed to reduce the risk or delay the onset of AD.

Among the studies included in this review, only one assessed physical activity both subjectively and objectively (27), whereas the rest relied on subjective assessment via questionnaires or self-reports. Subjective measures may be affected by social desirability bias (57) and recall bias, and self-perception of physical activity may vary across countries and cultures (57).

As all included studies were observational, conclusions on causality must be drawn with restraint. No randomized controlled trials (RCTs) of physical activity have yet reported clear beneficial effects on dementia incidence. Importantly, if the benefits of physical activity are small and amass over many years, they may be difficult to capture in RCTs which are often relatively short in duration.

Single- or Multidomain Approach?
Physical activity is one component of a healthy lifestyle. Cognitive impairment, AD, and dementia are known to have a multifactorial etiology (9,58), and focusing on physical activity alone may not be enough for effective prevention. Previous prevention trials with single-domain lifestyle interventions involving physical activity (59–61), diet (62), or management of vascular factors (63,64) have yielded disappointing or modest results. The LIFE trial for example did not show any improvement in cognition for a moderate-intensity physical activity program compared with a health education program (61). The focus of prevention trials has now shifted toward longer-term interventions (eg, 2–6 years) targeting multiple risk factors simultaneously. Preventive multidomain lifestyle interventions, including physical activity as one of the domains, were shown to have beneficial effects on cognition in populations at increased risk of AD and dementia, but not in unselected populations (9,58). Adequately targeted multidomain strategies instead of focusing on physical activity alone may thus be essential for effective dementia prevention (9,58).

Strengths, Limitations, and Future Directions
The main strengths of this review are the focus on the effects of leisure-time versus work-related physical activity on the risk of AD specifically and the assessment of the quality of evidence and risk of bias of the included studies. However, the review was limited to an English language search strategy and comprehensive databases. Hence, studies published in other languages were not captured. The included studies were conducted in developed countries, and it remains unclear whether the findings also apply to developing countries. Though being a strength, the quality assessment may also have limitations. It does not take into account all the measures concerning the internal validity of studies, and misjudgments cannot be fully excluded.

Future research on physical activity and AD needs to consider several key aspects: study design and size, physical activity assessment, and AD diagnosis. Although the new-generation multidomain, larger, and longer-term prevention trials are promising, observational studies are still needed to elucidate the details of how leisure-time and work-related physical activity are linked to each other in relation to the development of AD. Also their dynamic interactions with genetic and other lifestyle factors across the life span need further elucidation. International collaborations and joint development of large longitudinal datasets may also facilitate in-depth investigation in the field, for example, in regard to ethnic/race, regional or cultural aspects.

The use of standardized physical activity assessments comparable across studies would greatly facilitate recommendations for AD prevention. Standardized assessments would also be needed to specify which dimensions of physical activity are most important to monitor temporal trends within populations and to design and monitor personalized preventive interventions. Validation studies of exposure measures, that is, interviews, questionnaires, and self-reports of physical activity, are needed to find out if and to what extent recall bias occurs (57,63). Objective, real-time recordings of biomechanical or physiological effects of performing physical activity have been suggested to avoid self-report or recall bias (66).

Combining subjective and objective measures of physical activity would be preferable, although demanding. The structured interviews or questionnaires assessing physical activity should be more detailed with regard to the type, intensity (eg, the level of perceived physical strain), frequency, and duration of physical activity. This would enable the conversion of the total output of physical activity into energy expenditure units (eg, MET-minutes or kcal) and increase the comparability of the findings across different studies. This would also allow to draw physical activity recommendations for cognitive health (57).
The standard diagnostic criteria used for AD (eg, DSM and NINCDS-ADRDA) are primarily clinical and have well-known limitations (67). The shift from primarily clinical criteria to diagnostic criteria, including AD biomarkers, with staging of AD into preclinical, prodromal, and dementia stages (67), is a relatively recent development only starting to be used in research.

Conclusion
There seems to be an inverse association between physical activity and the risk of AD, though the overall quality of evidence is moderate. Leisure-time physical activity is particularly protective against AD. The window of opportunity for beneficial effects of physical activity seems to be broad and may extend to people who become active later in life. However, beyond already available general recommendations for health promotion, it is very challenging to draw specific practical recommendations from the current evidence regarding the type, frequency, intensity, and duration of physical activity that could protect against AD. It is likely that physical activities that have additional social and cognitive stimulation components may be most effective. The multidomain approach to AD and dementia prevention also seems more promising compared with the traditional, single-domain approach.

Supplementary Material
Supplementary data are available at The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences online.

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Conflict of Interest
The authors have nothing to disclose.

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