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Physical Activity and Alzheimer Disease: A Protective Association

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Abstract

Objective: To explore whether being physically active can decrease Alzheimer disease (AD) risk.

Participants and Methods: We conducted a meta-analysis of prospective observational cohort studies reporting the association between physical activity (PA) and incident AD. Relevant articles were identified by title and abstract in the electronic databases PubMed, ScienceDirect, and Scopus using the keywords *Alzheimer*, *Alzheimer disease*, *Alzheimer's*, *Alzheimer's disease*, *physical activity*, *sport*, *exercise*, *sedentary*, *fitness*, and combinations thereof for articles published in any language up to February 15, 2016. Criteria for consideration included division of the study cohort by PA levels and sample size specification for each PA level group, quantification (number) of persons who had development of AD, and PA assessment during time off work (not just work time). We followed the MOOSE (Meta-analyses of Observational Studies in Epidemiology) recommendations and used the Newcastle-Ottawa scale for study quality assessment.

Results: Ten high-quality studies were included in meta-analysis I (23,345 participants). Follow-up ranged from 3.9 to 31 years, and the participants' age ranged from 70 to 80 years. The pooled odds ratio for development of AD in participants who were more vs less physically active was 0.65 (95% CI, 0.56-0.74; $P<.001$; no publication bias [$P=.24$] but with heterogeneity among studies [$I^2=31.32\%$]). We could identify participants' adherence to international PA recommendations in 5 studies, which constituted meta-analysis II (10,615 participants). The pooled odds ratio for development of AD in participants who were active vs those who were inactive was 0.60 (95% CI, 0.51-0.71; $P<.001$; no publication bias [$P=.34$] and no heterogeneity [$I^2=5.63\%$]).

Conclusion: Although the limitations of self-reported PA data must be considered, regular PA performed by elderly people might play a certain protective role against AD.

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Because of rapidly aging populations in the developed world, the prevalence of age-associated diseases is set to increase, including, notably, the most common type of dementia, Alzheimer disease (AD). The burden associated with AD is also a growing problem, with an estimated 46.1% increase in AD-associated mortality from 2002 to 2006.[1] Among the numerous factors that might potentially be involved in the etiology of this disease, physical activity (PA) has received increasing attention as an important modifiable lifestyle factor associated with AD risk.[2] Physical activity can promote neurotrophic factors (such as the brain-derived neurotrophic factor), hippocampal neurogenesis, synaptic plasticity, and oxidative stress and inflammation, all contributing to cognitive improvements.[1-8] Besides the biological rationale supporting the potential preventive effects of PA on AD risk (or the modulating effects of PA once AD is already established), there is increasing epidemiological evidence from observational studies suggesting a link between regular PA and lower risk of AD or related conditions.[2,9]

In a meta-analysis of 6 prospective epidemiological studies (published from 1990 to 2007), PA was found to be associated with a 45% reduced risk of AD.[10] However, there is

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controversy in the field. For instance, Gelber et al[11] found a significant beneficial effect of PA against overall dementia risk in Japanese American men, which was also corroborated for vascular dementia but not for AD. Comparable findings were reported by Verdelho et al[6] in Europeans. An evidence report commissioned by the Agency for Healthcare Research and Quality that included publications up to October 2009 found that although globally PA (particularly high levels) was associated with decreased risk of AD, the magnitude of the relationship was rather weak and associations were not always significant after adjusting for confounding factors.[12]

The aim of this study was to determine whether being physically active could be a protective factor against the development of AD. To this end, we first conducted a systematic review of prospective observational reports published up to February 15, 2016, in which PA and AD were assessed as study outcomes. Thereafter, we included in a subsequent meta-analysis those studies that allowed determination of the statistical association between levels of PA in older people and the development of AD. We hypothesized that regular PA attenuates the risk of AD.

PARTICIPANTS AND METHODS

Systematic Review

Relevant articles were identified by title and abstract in the electronic databases PubMed, ScienceDirect, and Scopus using the keywords *Alzheimer*, *Alzheimer disease*, *Alzheimer's Alzheimer's disease*, *physical activity*, *sport*, *exercise*, *sedentary*, *fitness*, and combinations thereof for articles published in any language up to February 15, 2016.

The criteria for including a study in the systematic review were (1) prospective, observational cohort study (at least for a part of the analyses), (2) assessment of PA levels in the study cohort, (3) participants had development of AD during follow-up, either before or after PA assessment, and (4) AD diagnosis was certain or at least probable on the basis of clinical data in those patients who were alive during the study or on autopsy data in case of death. From each study, we collected the following data if available: number of groups and number of participants within each group, participants' characteristics (age, method for determination of PA levels, categorization into PA levels, main results, and conclusions).

Meta-analyses

In order to assess the statistical association between PA levels in older people and risk of AD, the criteria for including studies previously selected in the systematic review in a subsequent meta-analysis were (1) the study cohort had to be divided into 2 or more groups by levels of PA and the sample size for each PA level group had to be specified; (2) the number of participants in whom AD developed had to be quantified; and (3) the PA level had to be assessed during time off work, ie, not only during work time, in order to obtain the closest possible *total* daily PA.

Data Analysis: Dichotomous Classification. First, we used the level of PA reported by the authors of the studies to dichotomize the cohorts of each study into "more active" and "less active" participants (meta-analysis I). This categorization was performed by dichotomizing the cohorts as follows: (1) in studies that divided participants by levels of activity into 2 groups only, we used one arm corresponding to the more active group vs another arm corresponding to the less active group; (2) in studies that divided participants by levels of activity into 4 groups, we used one arm including the 2 more active groups vs another arm including the 2 less active groups.

In an additional analysis (meta-analysis II), we classified, whenever feasible, the participants of each study into those meeting ("active") or not meeting ("inactive") the PA guidelines issued by the US Department of Health[13] and the World Health Organization.[14] According to these widely accepted guidelines, adults should undertake 150 min/wk or more of moderate PA or 75 min/wk or more of vigorous PA or an equivalent combination thereof, ie 150 min/wk or more of moderate to vigorous PA (MVPA). In contrast, "physical inactivity" refers to those who perform insufficient amounts of MVPA (<150 min/wk).[15] For older individuals (aged ≥65 years, as were those participating in most studies in the

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