Meeting daily physical activity recommendations can provide protection against Alzheimer´s disease

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Abstract

Objective: We studied whether being physically active can decrease Alzheimer´s disease (AD) risk with a meta-analysis of prospective observational cohort studies reporting the association between physical activity (PA) and incident AD.

Methods: Relevant papers were identified by the title and abstract in the electronic databases *Pubmed, Science Direct* and *Scopus* [keywords: "Alzheimer/'s", "Alzheimer/'s disease", "physical activity"/"sport"/"exercise", "sedentary", "fitness", and combinations thereof (until February 15, 2016 –no

language restriction)]. Inclusion criteria were: (i) division of study cohort by PA levels and sample size specification for each PA-level group; (ii) quantification (n) of subjects developing AD; (iii) PA assessment during time off-work (not just work time). We followed the recommendations for Meta-analyses Of Observational Studies in Epidemiology (MOOSE), and used the Newcastle-Ottawa scale for study quality assessment (by 2 independent reviewers).

Results: 10 (high-quality) studies were included in *Meta-analysis I* (n=23,345). The range of follow-up was approximately (3–31) years and the range of the participants' age was approximately (70–80) years. The pooled OR of developing AD if being more *vs*. less active=0.65 [95%CI: 0.56–0.74, *P*<.001; with no publication bias (*P*=.24) but with heterogeneity among studies (I^2=31.32%)]. We could identify subjects' adherence to international PA recommendations in 5 studies (*Meta-analysis II*, n=10,615): the pooled OR of developing AD if being active *vs.* inactive=0.60 [95%CI: 0.51–0.71, *P*<.001; no publication bias (*P*=.34) and no heterogeneity (I^2=5.63%)].

Conclusions: While considering the limitations of self-reported PA data, regular PA performed by elderly people might play a certain protective role against incident AD.

List of abbreviations

95%CI = 95% confidence interval

AD = Alzheimer's disease

ApoE4 = ε4 allele of the apolipoprotein

BDNF = brain derived neurotrophic factor

CVD = cardiovascular disease

METs = metabolic equivalents

MOOSE = Meta-analyses of Observational Studies in Epidemiology

MVPA = moderate-to-vigorous PA

NINCDS-ADRDA = National Institute of Neurological and Communicative disorders and Stroke–Alzheimer's Disease and Related Disorders Association

OR = odds ratio

PA = physical activity

PASE = Physical Activity Scale for the Elderly

YPAS = Yale Physical Activity Survey

Introduction

Faced with a rapidly ageing population in the developed world, the prevalence of age-associated diseases is set to rise, including notably the commonest type of dementia, Alzheimer's 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 be potentially involved in the etiology of this disease, increasing attention is paid to physical activity (PA) as an important modifiable lifestyle factor associated with AD risk.[2] PA can promote neurotrophic factors [such as the brain derived neurotrophic factor (BDNF)], hippocampal neurogenesis, synaptic plasticity or modulate 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 epidemiologic studies (published from 1990 to 2007), PA was shown to be associated with a 45% reduced risk of AD.[10] However, there is controversy in the field. For instance, Gelber *et al.* 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.[11] Comparable findings were reported by Verdelho *et al.* in European people.[6] 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 until February 15, 2016) where PA and incident AD were assessed as study outcomes. Thereafter, we included in a subsequent meta-analysis those studies that allowed determining the statistical association between levels of PA in old people and development of incident AD. We hypothesized that regular PA attenuates the risk of AD.

Methods

Systematic review

Eligibility criteria, data sources and search strategy. Relevant papers were identified by the title and abstract in the electronic databases *Pubmed*, *Science Direct* and *Scopus*, with the following keywords: "*Alzheimer"*, "A*lzheimer disease" "Alzheimer's", "Alzheimer's disease", "physical activity", "sport", "exercise", "sedentary", "fitness"*, as well as combinations thereof. There was no language restriction. Keywords were chosen taking into account the scientific literature.

The criteria for including a study in the systematic review were: (i) prospective, observational cohort study (at least for a part of the analyses); (ii) assessment of PA levels in the study cohort; (ii) subjects developed incident AD during follow-up, either before or after PA assessment; and (iv) AD diagnosis certain or at least 'probable' based on clinical data in those patients alive during the study, or on autopsy in case of death. From each study, we collected the following items if available: number of groups and number of participants within each group; subjects' characteristics (age, moment over the study period and method for determination of PA levels, categorization into PA levels, main results and conclusions).

Meta-analysis

In order to assess the statistical association between PA levels in old people and risk of incident AD, the criteria for including studies previously selected in the systematic review in a subsequent meta-analysis were: (i) the study cohort had to be divided into ≥2 groups by levels of PA and the sample size for each PA-level group had to be specified; (ii) the number of subjects who developed AD had to be quantified; and (iii) the PA level had to be assessed during time off-work, *ie,* not only during work time –in order to get the closest possible picture of *total* daily PA~~, especially among elderly people, most of whom are obviously retired.~~

Data analysis: dichotomous classification. Firstly, we used the level of PA reported by the authors of the different studies to dichotomize the cohorts of each study into the 'more active' and the 'less active' subjects, respectively (*meta-analysis I*). This was performed by dichotomizing the cohorts as follows: ~~into~~

(i) in those studies that divided subjects 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; (ii) in those studies that divided subjects by levels of activity into 4 groups, we used one ~~one arm~~ including the 2 more active groups *vs.* another arm~~,~~ including the 2 less active groups. ~~(in those studies that divided subjects by levels of activity into 4 groups) or (ii) the more active group *vs.* the less active groups (in those studies that divided subjects by levels of activity into 2 groups only).~~

In an additional analysis (*meta-analysis II*), we classified whenever this was feasible the subjects of each study into those meeting ('active') or not ('inactive'), respectively, the PA guidelines issued by the US Department of Health[13] and the World Health Organization (WHO).[14] According to these widely accepted guidelines, adults should undertake ≥150 min/week of moderate PA or ≥75 min/week of vigorous-intensity PA or an equivalent combination thereof, *ie*, ≥150 min/week of moderate-to-vigorous PA (MVPA). In contrast, 'physical inactivity' refers to those who perform insufficient amounts of MVPA (<150 min/week).[15] For older individuals (aged ≥65 years, as those participating in most studies in the meta-analysis), MVPA includes all activities with a metabolic cost of 3+ metabolic equivalents (METs),[13, 16] that is, level walking at a speed >3–4 mph or uphill walking, intense housework (*eg*, snow shoveling, intense cleaning), virtually all leisure sports activities (*eg*, hiking, bicycling, jogging, aerobics) and certainly all competitive sports. In contrast, casual walking, less intense leisure activities such as fishing, dancing slowly or playing golf (using a cart), and light yard/house work are examples of light PA. In order to include a study in the analyses based on adherence to international PA guidelines and thus to dichotomize its cohort into physically active *vs*. inactive subjects, the following data had to be reported by the authors: (i) reporting of adherence to these or some equivalent guidelines, such as those issues by the American Heart Association, *ie*, MVPA≥30 min on≥3 days/week)[17] or other recognized official institutions; or (ii) frequency/duration and intensity of PA; or (iii) total energy expenditure during PA (METs or kcal per day or week).

Quality assessment and data extraction. We followed the recommendations for Meta-analyses of Observational Studies in Epidemiology (MOOSE)[18] (see the checklist in **Supplemental file 1**) and used the New Castle Ottawa scale for assessing the quality of the papers studied.[19] Two independent reviewers (AS-

L, NG) scored the studies, and a consensus meeting was arranged to sort out differences between both of them. The articles were not blinded for authors, institution and journal, because the reviewers who performed the quality assessment were familiar with the literature.

Statistical analysis. The pooled odds ratio (OR) [95% confidence interval (CI)] of developing AD if being 'more physically active' compared with being 'less physically active' (*meta-analysis I*) or of developing AD if being physically active compared with being inactive [that is, if meeting or not international PA recommendations, respectively (*meta-analysis II*)], was estimated using a weighted random-effect model. To identify the presence of publication bias, the Egger's regression test was employed. Heterogeneity among studies was assessed using the I^2 index. The level of significance (α) was set at .05. All statistical analyses were performed using MIX Pro software version 2.0.[20]

Results

Systematic review

From the retrieved papers, 24 were included in the systematic review (**Figure 1**).[3, 6, 11, 21-41] Of these, 15 (63% of total) found a significant association between PA and AD risk, with PA having an overall protective effect against development of incident AD (see **Table 1** for details of each study).[3, 22-24, 26, 27, 30-32, 34, 36-40] In contrast, 7 studies found no significant association between PA and AD,[6, 11, 21, 29, 33, 35, 41] even if a trend was observed by some authors toward a certain protective effect of PA.[21, 29] On the other hand, 2 studies reported the results for dementia but not specifically for AD risk.[25, 28] Importantly, no study found a negative effect of PA in terms of AD risk. Also of note, there was a high degree of heterogeneity among the methods used to assess PA, with the majority of studies using different *ad hoc* questionnaires[6, 11, 21, 23, 25-28, 30, 32, 34-37, 39-41] and fewer studies reporting validated or at least previously reported questionnaires (or an adapted version of them), *ie,* the Minnesota Leisure Time Physical Activities,[3, 38] the Godin leisure time exercise,[24, 31] the Zutphen Physical Activity[29] and the Paffenbarger PA questionnaires.[33] Further, only 1 study (which showed a significant protective effect of PA on AD) used an objective method for PA evaluation, *ie,* 10-day records with accelerometry.[22] The diagnosis of AD was clinical in all the studies and based on the criteria of the National Institute of Neurological and Communicative disorders and Stroke–Alzheimer's Disease and

Related Disorders Association (NINCDS-ADRDA). An important potential confounding factor, *ApoE* genotype, was determined in all but 5 studies.[6, 27, 36, 39, 40] Two studies found the protective effect of PA to be particularly stronger in carriers of the 'unfavorable' (or 'high-risk') *ApoE* ε4 allele[30, 34] whereas 1 study found the PA benefits to be only present in ε4 non-carriers and actually absent in carriers (although numeric data were provided for all-cause dementia with no specification for AD).[38]

Meta-analysis I

Of the abovementioned 24 studies, 10 were included in *meta-analysis I*.[11, 21, 23, 27, 31, 33, 34, 36, 38, 40] Reasons for excluding studies were: study cohort not divided by levels of PA or sample size for each PA level not specified,[3, 6, 22, 24-26, 29, 30, 32, 33, 37, 39] PA level assessed only during work time,[35] or results not specifically reported for AD.[25, 28] Of a maximum 9-point score in the New Castle Ottawa scale, all 10 studies met at least 8 criteria and were considered to have high quality and in fact 2 studies reached the maximum quality-score (**Table 2**).

The duration of follow-up was ≥5 years in all but 2 studies,[23, 33] ranging from 3.9 in the study by Ravaglia *et al.*[33] to 31 years in the study by Andel *et al.*[36] The age of the studied population usually ranged between 70 and 80 years. Of the 10 studies, 7 reported a protective effect of PA against AD,[23, 27, 31, 34, 36, 38, 40] whilst 3 found no significant association between PA and AD.[11, 21, 33] In 1 of the 7 studies reporting a protective effect of PA, the benefit was especially marked for *ApoE*-ε4 allele carriers,[34] but 1 study found the opposite.[38]

Table 3 shows how subjects were divided in PA categories according to the different authors, which in turn allowed us to dichotomize each cohort in 2 categories, *ie,* 'more' *vs.* 'less active' people. When combining the data from the 10 studies (*meta-analysis I*, total n=23,345 participants), the pooled OR of developing AD if being more physically active was 0.65 (95% CI: 0.56–0.74, *P*<.001) compared to be less active (**Figure 2, upper panel**). Although there was no evidence of publication bias (*P*=.24), there was heterogeneity among the studies (I^2=31.32%).

Meta-analysis II

From the 10 studies included in the *meta-analysis I*, it was possible to identify whether the subjects followed or not international PA recommendations in 5 studies (total n=10,615) (**Table 3**).[21, 27, 31, 33, 38] Of note, such

dichotomization was still difficult in some studies, with the possibility of a subset of subjects overlapping between the 2 categories, *i.e.*, those assigned to the group of (i) *"weekly energy expenditure of 248-742 kcal"* in the study by Podewils *et al.*,[38] and (ii) *"0.1 h/week of vigorous PA (intensity=9 METs, ie, aerobic dancing, jogging, playing handball), 0.8 hours/day of moderate PA (5 METs, ie, bicycling, swimming, hiking, playing tennis) or 1.3 hours/week of light PA (3METs, ie, walking, dancing, calisthenics, golfing, bowling, gardening, horseback riding), or a combination thereof"* in the study by Scarmeas *et al.*.[31] Thus, in order to minimize bias, different arms were calculated in these 2 studies (**Table 3**).

In *meta-analysis II*, combining the data of the aforementioned 5 studies and using the arm 1 of Podewils *et al.*[38] and Scarmeas *et al.*[24] to discard those subjects that could be overlapping between the 2 categories (n=10,615), yielded a pooled OR of developing AD if being physically active of 0.60 (95% CI: 0.51–0.71, *P*<.001) compared to being inactive (**Figure 2, lower panel**). There was no evidence of publication bias (*P*=.34) or heterogeneity among the studies (I^2=5.63%). Similar results were obtained when combining the other arms (n=12,107) or when excluding the studies of Podewils *et al.*[38] and Scarmeas *et al.*[24] from the analyses (total n=6,854).

Discussion

The main finding of our meta-analysis was that, compared to being physically inactive, those old people (aged ~70–80 years on average) who have been physically active (*ie,* adhering to international PA guidelines, that is, engaging in ≥150 min/week of MVPA, which is the equivalent to brisk walk for ≥20–30 min in most days of the week) during the previous ~5+ years, seem to have a 40% lower chance of developing AD compared to their inactive peers. While keeping in mind the limitations of our study that are discussed below, we believe this is an overall important finding given the global, ongoing increase in AD incidence coupled with the aging of our societies and the real pandemic of physical inactivity, with ~1/3 of adults worldwide being currently inactive.[42] Thus, the bulk of the available literature suggests that overall PA is a modifiable risk factor that can modulate the risk of developing AD. It seems that the health benefits of the widely accepted PA recommendations, *ie,* adults should engage in 150+ min/week of MVPA might also include, at least partly, prevention of AD risk.

Although most data come from animal research, there is a strong biological rationale in support of the potential benefits of PA on preservation of cognitive function and modulation of AD risk, as well as on attenuation of tissue-related alterations once AD is already established.[2, 8, 43] In humans, PA has demonstrated to promote neurotrophic factors (mainly BDNF) in healthy[44] but also in AD patients,[45] hippocampal neurogenesis and synaptic plasticity,[46] and inflammatory modulation[3] which have been related with cognitive improvements.[6] On the other hand, regular PA reduces not only inflammation but also oxidative stress in the brain by inducing several antioxidant enzymes,[47-49] and modulates the production and activity of amyloid-β protein-degrading enzymes such as neprilysin and insulin degrading enzyme while reducing the amyloidogenic pathway.[50, 51] At metabolic level, PA reduces obesity, high blood pressure, as well as high levels of blood cholesterol and glucose, all of which are factors related to AD.[52] Finally, PA is often performed in group or creating social networks, which promotes healthy social interaction and leisure, with subsequent cognitive improvements.[1, 4, 34, 38, 53] On the other hand, there is epidemiological evidence coming from recent meta-analyses that PA interventions can positively influence cognitive function in patients with dementia[54] as well as in those with AD and mild cognitive improvement.[55]

There are some caveats in the present meta-analysis that preclude drawing strong conclusions. The main methodological limitation of most studies analyzed here lies on the heterogeneity of the methods reported for PA assessment, *ie,* a variety of quite different questionnaires, which frequently lacked not only objectivity but also specificity. In fact, PA was not a main outcome in some studies, which might have explained, at least partly, why this variable was not assessed more accurately. Further, recent research has shown little agreement between self-reported PA assessment through questionnaires and objective determination of PA (*i.e.*, using individually calibrated combined heart rate and movement sensing) for differentiating people adhering or not to the international PA recommendations of ≥150 min of MVPA/week.[56] In this regard, although 1 study used objective assessment with accelerometer over 10 days consecutively to show that total daily PA was negatively associated with incident AD (hazard ratio=0.48; 95% CI: 0.27–0.83) and the association remained after adjusting for several factors, including *ApoE* allele status, this study could not be included in our meta-analysis because the authors did not report the incidence of AD by PA-level groups.[22] While keeping the aforementioned limitations in mind, we believe that our study adds relevant information compared to the pioneer meta-analysis in this topic published by Hamer and

Chida.[10] Their study was based on prospective epidemiologic studies published until 2007, adding a total sample of n=13,771 whereas 6 studies have been published since then that were not included in their study and were analyzed here,[11, 23, 31, 33, 36, 40] obviously resulting in a higher total sample size, *i.e.*, n=23,345 in *Meta-analysis I*. In turn, 2 of the studies included in their meta-analysis were excluded from ours because they were not specific enough according to our criteria, *i.e.*, not allowing to dichotomizing subjects into PA-level groups.[3, 41]

Several important questions remain unanswered and should be the subject of future research. First, the methods for quantifying PA must be improved in future research. While recognizing that implementation of objective methods for PA assessment (notably, accelerometry) can be problematic in large cohorts as opposed to questionnaires, future research should use validated questionnaires for old people, *eg*, the Physical Activity Scale for the Elderly (PASE)[57] or the Yale Physical Activity Survey (YPAS),[58] instead of questionnaires developed *ad hoc*. However, these questionnaires are often lengthy and some individuals, especially those with cognitive impairment, might experience difficulties in completing them. For this reason, future studies should also consider the use of objective physical function tests for seniors, such as a gait speed assessment or the 6-minute walk test. In addition, adherence to international PA recommendations MVPA should be ideally reported. On the other hand, although the data from *meta-analysis II* support the benefits of following international PA guidelines to prevent AD, which is in line with the bulk of evidence for 2 other major conditions, which are largely age-related, cardiovascular disease (CVD) and several types of cancer (mainly breast and colorectal),[59] more research is needed to determine to what extent the protective effects of PA on AD risk are dose-dependent. Future research might also determine the specific effects on AD risk of a special type of exercise that should be an integral part of the regular PA routine of the elderly for its benefits in prevention of aging muscle atrophy (sarcopenia) and frailty: resistance (weight lifting) exercise.[16] It also remains to be determined if the protective effects of PA are not only confined to people aged ≤80 years but also to the 'oldest old' (that is, people aged 85–90 years and above), who represent the most rapidly population segment and are obviously at highest risk for neurodegeneration. Another question of interest is the potential effects of PA not only on risk of AD, but also on the burden associated with this condition once it has started. In this regard, 2 studies included in the present systematic review showed that the co-presence of *ApoE* ε4 with low PA was particularly associated with shorter AD-

free survival time[23] or that higher PA levels were associated with prolonged survival in AD.[24] Other studies have reported that PA interventions increase the functional capacity of AD patients,[60, 61] which is an important finding because 'functional decline' and loss of muscle mass are prevalent among patients with AD and major contributors to poor healthcare outcome.[62]

Conclusion

Regular PA performed by elderly people might have a certain protective effect against the development of AD. ~~Because there is growing evidence that the endemic of physical inactivity starts before adulthood,[42] future long-term follow-up studies are needed to determine the effects of PA levels across the human lifespan on AD risk.~~ Monitoring PA (such as recently recommended by the American Heart Association for adult populations (**PMID: 24126387**)) along with indicators of physical function would provide the information needed for healthcare professionals to consider using a more proactive approach regarding PA in older people and favor the implementation of effective PA interventions.

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Figure Legends

Figure 1. Flow chart of literature search.

Figure 2. Results of *meta-analysis I* (upper panel) and *II* (lower panel). Abbreviations: AD, Alzheimer's disease; CI, confidence interval; OR, odds ratio.

Table 1. Main characteristics of the studies included in the Systematic Review.

Author (year)	Follow-up, mean± SD	Design	Study groups	Group characteristics	Sample size (% women) for analyses	Age, mean± SD (or range)	AD diagnosis	*ApoE* genotyping	PA assessment (time, method)	Main results	Authors' conclusions
Abbott et al. (2004)[21]	7 years	Prospective, observational cohort study	Total cohort included in analyses	Physically capable old men (Honolulu-Asia Aging Study)	n=2,257 (0%)	71–93 years (at baseline)	Clinical (NINCDS-ADRDA criteria)	Yes	Baseline Self-reports of walk distance (mile/day)	RH for AD=1.81 [95% CI: 0.97–3.40] if walking ≤ 2 miles/day *vs.* ≥2 miles/day	Walking is associated with a non-significant trend toward a reduction in AD risk
			Incident AD	Developed AD over the follow-up	n=101 (0%)						
Andel et al. (2008)[36]	31 years	Case-control (within a prospective, observational cohort study of the Swedish Twin Registry assessed on average 31 years prior to dementia assessment)	Control (dementia-free)		n=3,134 (60%)	79.1±4.7 years (at cognitive screening follow-up)	Clinical (NINCDS-ADRDA criteria)	No	Baseline (25–50 years of age) Questionnaire, PA level measured on a 4-point scale: 0 (hardly any PA); 1 (light PA, *eg*, walking); 2 (regular sports); 3 (hard physical training)	Adjusted OR for AD risk =0.64 (95%CI: 0.41–1.00) for light PA; =0.34 (95%CI: 0.14–0.86) for regular PA; and =0.65 (95%CI: 0.33–1.29) for hard PA. In co-twin control analyses, significance was not reached	Participants who engaged in light/ regular PA had reduced odds of AD ~31 years later
			Cases	Developed AD over the follow-up	n=197 (76%)	83.8±5.5 years (at cognitive screening follow-up)					
Brasky et al. (2014)[3]	9 years	Case-control (within a prospective, observational cohort study of n=82 US people aged ≥65 years and cognitively intact at baseline)	Controls	Remained cognitively intact over the follow-up	n=43 (51%)	79.3±4.8 years (at follow-up)	Clinical (not actually detailed)	Yes	Baseline Minnesota Leisure Time Physical Activities questionnaire	Those who developed AD had lower PA intensity reported at baseline [score of 1.9±0.9 (on a 0–3 range) in the Minnesota questionnaire[l] compared with those who did not (1.5±0.7; *P*=.03)]	Lower PA intensity at baseline was significantly associated with developing AD 9 years later
			Cases	Developed AD over the follow-up	n=39 (62%)	81.9±5.1 years (at follow-up)					
Buch	4 years	Prospecti	Total	US old	n=716	81.6±7.1	Clinical	Yes	Baseline	Total	High level

man et al. (2012)[22]		ve, observational cohort study	cohort included in analyses	people without dementia ≥2 annual cognitive assessments and valid baseline accelerometer recordings	(76%)	years (at baseline)	(NINCDS-ADRDA criteria)		Objective assessment with accelerometer over 10 days consecutively	daily PA was associated with incident AD (HR= 0.48; 95%CI: 0.27–0.83) The association remained after adjusting for several factors including *ApoE* allele status	of PA is associated with a reduced risk of developing AD
			Incident AD	Developed AD over the follow-up	n=71						
De Bruijn et al. (2013)[29]	8.8 years	Prospective, observational cohort study	Total cohort included in analyses	Elderly Dutch persons (age range 61–97 years)	n=4,406 (59%)	72.7±7.2 years (at baseline)	Clinical (similar to NINCDS-ADRDA criteria)	Yes	Adapted version of the Zutphen Physical Activity Questionnaire[74] (hours/week spent in walking, cycling, gardening, diverse sports, hobbies, and housekeeping activities)	Non-significant trend [HR=0.89 (95%CI: 0.76–1.03)] towards an association between PA lower risk of AD, and only in follow-up ≤4 years	If existing, the potential protective effect of PA against AD is short-term (≤4 years)
			Incident AD	Developed AD over the follow-up	n=490						
Ferrari et al. (2013)[30]	9 years	Prospective, observational cohort study	Total cohort included in analyses	Cognitively intact people from Sweden	n=932	≥75 years (at baseline)	Clinical (similar to NINCDS-ADRDA criteria)	Yes	Baseline Questionnaire on leisure PA	High leisure PA associated with lower AD (HR=0.60; 95%CI: 0.43–0.84), especially in people with 1+ ε4 allele [HR=0.51 (95%CI: 0.28–0.95)]	Leisure PA reduces the risk AD, and the association is stronger in people with the *ApoE* ε4 allele
			Incident AD	Developed AD over the follow-up	n=247						

Gelber et al. (2012)[11]	25 years	Prospective, observational cohort study	Total cohort included in analyses	Japanese American men (born in 1965–1968) examined for dementia after 25 years	n=3,468	71–93 years (at follow-up)	Clinical (NINCDS-ADRDA criteria)	Yes	Midlife PA questionnaire: hours/day in no activity (sleeping, lying), sedentary behavior (sitting, standing), or light (*eg*, walking), moderate (*eg*, gardening, carpentry), and heavy (*eg*, shoveling, digging) PA	OR for AD risk in people with low PA at midlife=1.44 (95%CI: 0.94–2.21)	No association between PA habits in middle age and risk of AD
			Incident AD	Developed AD over the follow-up	n=117						
Norton et al. (2012)[28]	6.3±5.3 years	Prospective, observational cohort study	Total cohort included in analyses	Non-demented participants from the US	n=2,491 (49%)	73.0±5.7 years (at follow-up)	Clinical (NINCDS-ADRDA criteria)	Yes	Baseline Questionnaire on frequency and average time spent in past 12 months in walking for exercise, heavy housework, garden/yard work, use of an exercise machine, calisthenics/ weight-lifting, or any moderate to vigorous exercise	No results were independently and separately reported for the association between PA and AD	-
			Incident AD	Developed AD over the follow-up	n=200						
Kishimoto et al. (2016)[40]	17 years	Prospective, observational cohort study	Total cohort included in analyses	Community-dwelling elderly Japanese individuals without dementia aged ≥65 years	n=803 (61%)		Clinical (NINCDS-ADRDA criteria)	No	Baseline Questionnaire on leisure-time PA: frequency per week and time spent in each session during the past month in: light/bris	The incidence of AD was significantly lower in the active group compared with the inactive group (age- and sex-adjusted HR 0.59;	PA has a potentially protective factor against AD in the elderly Japanese population, and this protective influence may continue for more than 10 years

									k walking, calisthenics, gateball, golf, dancing, jogging, hiking, bowling, cycling, hunting, gardening, Japanese traditional dance (Nihon Buyo), and other types of exercise. 'Physically active' was defined as engaging in the aforementioned types of PA ≥1 times per week during leisure time	95%CI: 0.42–0.85; *P*=.004).
			Incident AD	Developed AD over the follow-up	n=165					
Laurin et al. (2001)[27]	5 years	Prospective, observational cohort study	Total cohort included in analyses	Randomly selected people aged ≥65 years, who were evaluated in the 1991-1992 Canadian Study of Health and Aging	n=3,848 (60%)	≥65 years (at baseline)	Clinical (NINCDS-ADRDA criteria)	No	Baseline Questionnaire on frequency and intensity of PA	High levels of PA (≥3 times/week at an intensity >walking) were associated with reduced risks of AD (OR=0.50; 95%CI: 0.28–0.90)	Regular PA could represent an important and potent protective factor for AD in elderly persons
			Incident AD	Developed AD over the follow-up	n=169					
Larson et al. (2006)[26]	6.2±2.0 years	Prospective, observational cohort study	Total cohort included in analyses	People aged ≥65 years without cognitive impairment	n=1,740 (60%)	≥70 years (at baseline)	Clinical (NINCDS-ADRDA criteria)	Yes	Baseline Questionnaire about times/week doing ≥15 min of walking, hiking, bicycling, aerobics/calisthenics, swimming, water aerobics,	The age- and sex-adjusted HR of dementia AD for the regular PA group (≥3 times/week) was 0.64 (95%CI: 0.43–0.96)	Regular PA (≥3 times/week) is associated with a delay in the onset of AD

									weight training, or stretching and other exercise		
			Incident AD	Developed AD over the follow-up	n=107						
Lindsay et al. (2002)[37]	5 years	Case-control (within a prospective, observational cohort study of 4,088 Canadian people aged ≥65 years who were cognitively normal in 1991)	Controls	Remained dementia-free over the follow-up	n=4,008 (57.5%)	78 years (70–100) (at follow-up)	Clinical (NINCDS-ADRDA criteria)	Yes	Baseline Interview: participants were simply asked whether they engaged in regular exercise (yes/no), but "regular" was not explicitly defined	OR of AD risk in physically active *vs.* non-active people=0.69 (95%CI: 0.50–0.96)	The beneficial effect of regular PA on AD risk is strong and significant
			Cases	Developed AD over the follow-up	n=194 (67.5%)	87 years (69–105) (at follow-up)					
Luck et al. (2014)[23]	4.5 years	Prospective, observational cohort study	Total cohort included in analyses	German people aged ≥75 years without any type of dementia	n=2,582 (64.7%)	81.1±3.5 years (at follow-up)	Clinical (NINCDS-ADRDA criteria)	Yes	Baseline Questionnaire (those who participated all or several days/week in an activity (long walks, swimming, gymnastics, housework, gardening, babysitting, other activities such as bowling or playing golf) were classified as 'active'	The presence of the *ApoE* ε4 allele significantly increased [HR=2.13 (95%CI: 1.56–2.92)] and higher PA significantly decreased risk for AD [HR=0.81 (95%CI: 0.69–0.94], respectively The co-presence of *ApoE* ε4 with low PA was associated with a particularly higher risk for AD [HR=3.73 (95%CI: 2.40–	PA in late life reduces the risk of AD

										5.80)]	
			Incident AD	Developed AD over the follow-up	n=184						
Podewils et al. (2005)[38]	Mean of 5.4 years	Prospective, observational cohort study	Total cohort included in analyses	US men and women aged ≥65 years, free of dementia at baseline	n=3,373 (41%)	74.8±4.9 years (at baseline)	Clinical (NINCDS-ADRDA criteria)	Yes	Baseline Modified Minnesota Leisure Time Activity questionnaire (activities over 2 weeks)	HR for incident AD in those engaging in ≥4 sessions PA/week =0.55 (95%CI: 0.34–0.88). However, such association was actually absent in *ApoE* ε4 carriers (of note, specific numeric data of HR for AD in ε4 carriers *vs.* non-carriers were reported by the authors for all-cause dementia but not for AD	Engaging in a number of different PA protects against AD risk over a ~5-year follow-up, although the potential exercise benefits may be limited to *ApoE* ε4 non-carriers.
			Incident AD	Developed AD over the follow-up	n=245						
Ravaglia et al. (2008)[33]	3.9±0.7 years	Prospective, observational cohort study	Total cohort included in analyses	Italian subjects aged ≥65 years and cognitively normal at baseline	n=749 (54%)	73.2±6.0 years (at baseline)	Clinical (NINCDS-ADRDA criteria)	Yes	Baseline Paffenbarger PA questionnaire (stairs climbed, blocks walked, strenuous sports played, and a composite PA index [74]	After adjustment for socio-demographic and genetic confounders, AD risk was not associated with PA, *ie*, HR=0.87 (95%CI: 0.49–1.60) for those performing 30+ min of MVPA on 4+ days per week *vs.* those not doing so	PA was not associated with a lower risk of AD
			Incident AD	Developed AD over the follow-up	n=86						
Rovio	21±4.9	Prospecti	Total	Old	n=1,449	71.6±4.1	Clinical	Yes	Baseline	No	Having an

et al. (2007)[35]	years	ve, observational cohort study	cohort included in analyses Incident AD	Finnish people aged 65–79 years	(62%) n=48	years (at follow-up)	(NINCDS-ADRDA criteria)		[*ie*, midlife (range 39–64 years)] Questionnaire on work-related PA (sedentary *vs*. active work)	significant association between occupational PA and AD risk [HR=1.90 (95%CI: 0.73–4.95) for active vs. sedentary work]	active work is not enough to protect against AD
Rovio et al. (2005)[34]	Same as above	Same as above	Total cohort included in analyses Incident AD	Same as above Developed AD over the follow-up	n=1,251 (61%) n=41	Same as above	Same as above	Yes	Baseline (same as above) Questionnaires on leisure-time PA: 'active' (>2 times/week), sedentary (<2 times/week)	Leisure-time PA at midlife≥ 2 times/week was associated with a reduced risk of AD [OR=0.35 (95%CI: 0.16–0.80)], and the association was particularly stronger in *ApoE* ε4 carriers [HR=0·24 (95%CI: 0·07–0·79)] than in non-carriers [HR=0·61 (95%CI: 0.21–1·80)]	PA during leisure time at midlife is associated with a lower risk of AD, especially in *ApoE* ε4 carriers
Scarmeas et al. (2009)[31]	5.4±3.3 years	Prospective, observational cohort study	Total cohort included in analyses Incident AD	US community-dwelling elders without dementia Developed AD over the follow-up	n=1,880 (69%) n=282 (68%)	76.4±6.3 years (at follow-up) 82±6.8 years (at follow-up)	Clinical (NINCDS-ADRDA criteria)	Yes	Questionnaire on frequency, duration and intensity of PA; data analyzed in tertiles ('no', 'some' or 'much PA').	Compared with no PA, HR for some PA=0.75 (95%CI: 0.54–1.04) and HR for much PA=0.67 (95%CI: 0.47–0.95)	Increased PA is associated with reduced risk of AD
Scar	5.2±4.4	Prospecti	Total	US	n=357	78.8±6.7	Clinical	Yes	Once	Compare	PA may

measet al. (2011)[24]	years	ve, observational cohort study	cohort included in analyses Incident AD	individuals aged >65 years and non-demented who developed incident AD thereafter. They were prospectively followed with standard neurological and neuropsychological evaluations every ~1.5 years Developed AD over the follow-up	(69%) n=276	years (at follow-up)	(NINCDS-ADRDA criteria)		every ~1.5–year period Modified Godin leisure time exercise questionnaire[75] and score data analyzed in 3 levels of PA (like in the above study by the same group)	d to physically inactive AD subjects, those reporting some PA had a HR of 0.43 (95%CI: 0.28–0.67; *P*<.001) and those reporting much PA had a HR of 0.25 (0.15–0.40; *P*<.001)	decrease risk for AD
Taaffe et al. (2008)[32]	Mean of 6.1 years	Prospective, observational cohort study	Total cohort included in analyses	Dementia-free elderly men participating in the Honolulu–Asia Aging Study	n=2,263 (0%)	76.4±3.8 years (at baseline)	Clinical (NINCDS-ADRDA criteria)	Yes	Baseline Questionnaire on average number of hours/day in each of the 5 following PA levels: basal (sleeping or lying down); sedentary (*eg*, sitting or standing, reading, eating), and slight (*eg*, walking on level ground), moderate (*eg*, gardening or carpentry), and heavy PA (*eg*, lifting or shoveling). Subjects were categorized by tertiles of: (i) PA levels (*ie*,	There was a significantly reduced risk of AD with increasing levels of PA in men with poor physical function [HR=0.57 (95%CI: 0.32–0.99) for moderate levels and HR=0.50 (95%CI: 0.28–0.89) for high levels] but not in men with moderate or high physical function	There is a protective effect of PA on AD risk, but only in men with poor physical function

									low, moderate, high) and (ii) physical function (using a test developed *ad hoc* with 4 performance tasks: 3-meter timed walk, time to rise from a chair 5 times, grip strength of the dominant hand and a balance test)		
			Incident AD	Developed AD during the follow-up	n=83						
Verdelho et al. (2012)[6]	3 years	Prospective, observational multi-national cohort study	Total cohort included in analyses	Independent European elderly people aged 65-84 years	n=639 (55%)	74±5 years (at baseline)	Clinical (NINCDS-ADRDA criteria)	No	Baseline and yearly during follow-up Interview on PA assessed and defined according to the AHA ('physically active' if PA≥30 min on≥3 days/week)[PMID: 8772712]	PA did not significantly influence evolution to AD [HR=1.09 (95%CI: 0.50–2.37)	PA reduced the risk of cognitive impairment (mainly vascular dementia) but not of AD, in older people living independently
			Incident AD	Developed AD over the follow-up	n=34						
Wang et al. (2006)[25]	5.9 years	Prospective, observational cohort study	Total cohort included in analyses	US people aged ≥65 years without dementia	n=2,288 (60%)		Clinical (NINCDS-ADRDA criteria)	Yes	Baseline Assessment of PA (during the last year) with questionnaire (days/week doing ≥15 min of walking, hiking, bicycling, aerobics/calistheni	% of subjects with PA levels ≥3 days/week was higher (76%) in those who remained dementia-free at follow-up *vs.* those who developed dementia	Low levels of PA (<3 days/week) were associated with an increased risk of dementia (data not specified for AD)

									cs, swimming, water aerobics, weight training, or stretching and other exercise	(66%) – although data not specified for AD–	
			Incident AD	Developed AD over the follow-up	n=221						
Wilson et al. (2002)[41]	4.1 years	Prospective, observational cohort study	Total cohort included in analyses Incident AD	US people aged ≥65 years	n=842 (59%) n=139	76±6 years (at baseline)	Clinical (NINCDS-ADRDA criteria)	Yes	Baseline Questionnaire: participation in the following activities in the past 2 weeks: walking for exercise, jogging/ running, gardening/ yard work, dancing, calisthenics/general exercise, golf, bowling, bicycle riding and swimming/water exercises. PA was expressed as hours/week.	PA was unrelated to risk of AD (OR=1.04; 95%CI: 1.04 (0.98–1.10)	Weekly hours of PA was not related to disease risk
Yoshitake et al. (1995)[39]	7 years	Prospective, observational cohort study	Total cohort included in analyses Incident AD	Japanese non-demented residents, aged ≥65 years Developed AD over the follow-up	826 (60%) n=42	73.5 years (at follow-up)	Clinical (NINCDS-ADRDA criteria)	No	Baseline Interview (4 categories not specified, each for leisure and for work)	The RR for AD=0.20 (95%CI: 0.06–0.68) in physically active subjects	Moderate PA has a significant preventive effect against AD

Abbreviations: AD, Alzheimer's disease; AHA, American Heart Association; *ApoE*, apolipoprotein E gene; CI; confidence interval; CRF, cardiorespiratory fitness; HR, hazard ratio; ICD-10, International Classification of Diseases and Related Health Problems, 10th revision; MVPA, moderate-to-vigorous PA; NINCDS-ADRDA, National Institute of Neurological and Communicative disorders and Stroke–Alzheimer's Disease and Related Disorders Association; OR, odds ratio; PA, physical activity; RH, relative hazard; RR, relative risk.

Table 2. Quality of the studies included in the meta-analyses.

	SCORE			
	SELECTION	COMPARABILITY	OUTCOME	TOTAL
Abbott et al. (2004)[21]	****	**	**	8
Andel et al. (2008)[36]	***	**	***	8
Gelber et al. (2012)[11]	****	**	***	9
Kishimoto et al. (2016)[40]	****	**	***	9
Laurin et al. (2001)[27]	****	**	**	8
Luck et al. (2014)[23]	****	**	**	8
Podewils et al. (2005)[38]	****	**	**	8
Ravaglia et al. (2008)[33]	****	**	**	8
Rovio et al. (2005)[34]	***	**	***	8
Scarmeas et al. (2009)[31]	****	**	**	8

Quality was assessed using the Newcastle-Ottawa Scale (NOS):[19] a study can be given a maximum score of 4 stars for selection, 2 stars for comparability and 3 stars for outcome; thus, 9 stars is the maximum possible total score.

Table 3. Main data on levels and categories of physical activity (PA) in the studies included in the meta-analysis.

Author (year)	Criteria used in the different studies to define PA categories	Age, mean±SD	Total sample size (% women)	Sample size with AD	Sample size 'less active' *vs.* 'more active' within each study for *meta-analysis I**	Sample size 'inactive' *vs.* 'active' according to international PA guidelines for *meta-analysis II***
Abbott et al. (2004)[21]	<0.25 mile walked per day	77.4 ±4.4 years	n=600	n=30	n=1,369 less active	n=1,369 inactive
	0.25–1 mile walked per day	77.3±4.2 years	n=769	n=39		
	>1–2 mile walked per day	76.7±3.8 years	n=433	n=21	n=888 more active	n=888 active
	>2 mile walked per day	76.0±3.6 years	n=455	n=11		
Andel et al. (2008)[36]	Almost no exercise when aged 25–50 years	79.6±5.2 years	n=352 (67%)	n=35	n=2,583 less active	--
	Light exercise such as walking or light gardening when aged 25–50 years	79.6±4.9 years	n=2,231 (66%)	n=138		
	Regular exercise involving sports when aged from aged 25–50 years	78.2±4.4 years	n=296 (39%)	n=6	n=551 more active	--
	Hard physical training when aged 25–50 years	80.1±5.4 years	n=255 (36%)	n=18		
Gelber et al. (2012)[11]	No highest quartile of time spent in slight (*eg*, walking) or moderate activities (*eg*, gardening), =7.2±3.2 and 4.4.±3.0 hours/day, respectively	-	n=1,994	n=69	n=1,994 less active	--
	Highest quartile of time spent in slight (*eg*, walking) or moderate activities (*eg*, gardening), =7.2±3.2 and 4.4.±3.0 hours/day, respectively	-	n=1,474	n=48	n=1,474 more active	--
Laurin et al. (2001)[27]	Not reporting regular exercise	-	n=1,183	n=80	n=1,689 less active	n=1,689 inactive
	<3 times/week	-	n=506	n=21		
	>3 times/week at intensity=walking	-	n=1,412	n=52	n=2,159 more active	n=2,159 active
	>3 times/week at intensity>walking	-	n=747	n=16		
Luck et al. (2014)[23]	Not participating all or several days/week in a PA ([long walks, swimming, gymnastics, housework, gardening, babysitting, others (*eg*, bowling, golf)]	- -	n=1,050	n=104	n=1,050 less active	--
	Participating all or several days/week in a PA ([long walks, swimming, gymnastics, housework, gardening, babysitting, others (*eg*, bowling, golf)]	-	n=1,532	n=80	n=1,532 more active	--
Kishimoto et al. (2016)[40]	Not engaging in exercise (see below), *ie*, 0 times/week)		n=539 (64%)	n=123	n=539 less active	--
	Engaging in exercise (*eg*, light/brisk walking, calisthenics, gateball, golf, dancing, jogging, hiking, bowling, cycling, hunting, gardening, Japanese traditional dance (Nihon Buyo)) ≥1 times/week during leisure time		n=264 (51%)	n=42	n=264 more active	--
Podewils et al.	Weekly energy expenditure <248	75.2±5.1	n=844	n=69	n=1,686 less	Arm 1, n=844

(2005)[38]	kcal	years	(75.7%)		**active**	**inactive** **Arm 2, n=844 inactive** **Arm 3, n=1,686 inactive**
	Weekly energy expenditure 248–742 kcal	74.9±5.1 years	n=842 (68.3%)	n=70		
	Weekly energy expenditure 743–1657 kcal	74.7±4.9 years	n=844 (55.7%)	n=58	**n=1,687 more active**	**Arm 1, n=1,687 active** **Arm 2, n= 2,529 active** **Arm 3, n= 1,687 active**
	Weekly energy expenditure ≥1,657 kcal	74.4±4.4 years	n=843 (36.8%)	n=48		
Ravaglia et al. (2008)[33]	No adhering to CDCP/ACSM recommendations		n=290	n=44	**n=290 less active**	**n=290 inactive**
	Adhering to CDCP/ACSM recommendations		n=459	n=42	**n=459 more active**	**n=459 active**
Rovio et al. (2005)[34]	No participating in leisure-time PA ≥2 times/week (*ie*, <2 times/week)	70.9±3.9 years	n=736 (64%)	n=31	**n=736 less active**	-
	Participating in leisure-time PA ≥2 times/week	71.5±4.0 years	n=515 (55.7%)	n=10	**n=515 more active**	-
Scarmeas et al. (2009)[31]	0 hours/week of PA	-	n=520	n=102	**n=1,170 less active**	**Arm 1, n=520 inactive** **Arm 2, n=1,170 inactive** **Arm 3, n=520 inactive**
	0.1 h/week of vigorous PA (intensity=9 METs, *ie*, aerobic dancing, jogging, playing handball), 0.8 hours/day of moderate PA (5 METs, *ie*, bicycling, swimming, hiking, playing tennis) or 1.3 hours/week of light PA (3METs, *ie*, walking, dancing, calisthenics, golfing, bowling, gardening, horseback riding), or a combination thereof	-	n=650	n=99		
	1.3 hours/week of vigorous PA, 2.3 hours/week of moderate PA, or 3.8 hours/week of light PA, or a combination thereof	-	n=710	n=81	**n=710 more active**	**Arm 1, n=710 active** **Arm 2, n=710 active** **Arm 3, n=1,360 active**

Abbreviations: ACSM, American College of Sports Medicine; AD, Alzheimer's disease; CDCP, Centers for Disease Control and Prevention; MET, metabolic equivalent (=3.5 mL O_2/kg/min).

*For *Meta-analysis I*, we dichotomized the study cohorts into (i) one arm including the 2 more active groups *vs*. another arm, including the 2 less active groups (in those studies that divided subjects by levels of activity into 4 groups) or (ii) the more active group *vs*. the less active groups (in those studies that divided subjects by levels of activity into 2 groups only).

** For *Meta-analysis II*, we dichotomized the study cohorts, whenever it was possible, into physically 'active' or 'inactive' subjects, *ie*, doing or not ≥150 min/week of moderate-to-vigorous PA (MVPA), respectively.

*** Three different arms were calculated for the study of Podewils et al.[38] and Scarmeas et al.[31] because the authors there could be 'overlapping' of active and inactive people (see text for more details).