Leisure Activities and the Risk of Dementia: A Systematic Review and Meta-Analysis

Author(s):
Sizhen Su, MD; Le Shi, PhD; Yongbo Zheng, MD; Yankun Sun, PhD; Xiaolin Huang, MD; Anyi Zhang, MD; Jianyu Que, MD; Xinyu Sun, MD; Jie Shi, PhD; Yanping Bao, PhD; Jiahui Deng, PhD; Lin Lu, PhD

Corresponding Author: Yanping Bao, baoyp@bjmu.edu.cn

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Affiliation Information for All Authors: 1. Peking University Sixth Hospital, Peking University Institute of Mental Health, NHC Key Laboratory of Mental Health (Peking University), National Clinical Research Center for Mental Disorders (Peking University Sixth Hospital), Beijing, 100191, China; 2. Peking-Tsinghua Center for Life Sciences and PKU-IDG/McGovern Institute for Brain Research, Peking University, Beijing 100191, China; 3. National Institute on Drug Dependence and Beijing Key Laboratory of Drug Dependence, Peking University, Beijing 100191, China

Equal Author Contribution: Sizhen Su and Le Shi contributed equally to this work and should be considered co-first authors. Yanping Bao, Jiahui Deng and Lin Lu are co-senior authors.

Contributions:
Sizhen Su: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
Le Shi: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
Yongbo Zheng: Additional contributions: Literature search - Data extraction - Yankun Sun Quality assessment - Xiaolin Huang
Yankun Sun: Additional contributions: Literature search - Yongbo Zheng Data extraction - Quality assessment - Xiaolin Huang
Xiaolin Huang: Additional contributions: Literature search - Yongbo Zheng Data extraction - Yankun Sun Quality assessment
Anyi Zhang: Analysis or interpretation of data
Jianyu Que: Analysis or interpretation of data
Xinyu Sun: Drafting/revision of the manuscript for content, including medical writing for content
Jie Shi: Drafting/revision of the manuscript for content, including medical writing for content
Yanping Bao: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design
Jiahui Deng: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design
Lin Lu: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design

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ABSTRACT

Objectives: Leisure activities are major components of modifiable and healthy lifestyles and are proposed to help prevent the development of dementia. This study aimed to assess the effects of different types of leisure activities, including cognitive, physical, and social activities, on the incidence of all-cause dementia (ACD), Alzheimer’s disease (AD), and vascular dementia (VD).

Methods: We performed a systematic review and meta-analysis of the Cochrane, PubMed, Embase, and Web of Science databases to identify longitudinal studies that examined associations between leisure activities and dementia. Relative risks (RRs) and 95% confidence intervals (95% CI) were pooled using random-effects meta-analysis. Subgroup analyses were used to estimate potential effect modifiers. The study was registered with
Results: A total of 38 longitudinal studies, with 2154818 participants at baseline, 74700 ACD cases, 2848 AD cases, and 1423 VD cases during follow-up, were included in the meta-analysis. The subgroup analyses showed that physical (RR = 0.83, 95% CI: [0.78-0.88]), cognitive (RR = 0.77 [0.68-0.87]), and social (RR = 0.93 [0.87-0.99]) activities were inversely associated with incidence of ACD. In addition, physical (RR = 0.87 [0.78-0.96]) and cognitive (RR = 0.66 [0.52-0.85]) activities were related with a reduced risk of AD. Physical activity (RR = 0.67 [0.53-0.85]) was associated with a lower incidence of VD.

Conclusion: Our findings suggest that leisure activities are inversely associated with risk of ACD, AD and VD.

Keywords: dementia, Alzheimer’s disease, vascular dementia, risk, leisure activities

Introduction

Dementia is one of the most prevalent health issues. It is the fifth leading cause of death, affecting 50 million people worldwide in 2018 according to the World Health Organization (WHO). As life expectancy increases, the number of people who suffer from all-cause dementia (ACD) is expected to reach approximately 152 million by 2050, of which Alzheimer’s disease (AD) and vascular dementia (VD) are the two main subtypes. Although numerous new treatments are being investigated, no treatments can cure dementia or alter its pathological progression. The WHO recommends risk reduction to reduce the global burden of dementia. Evidence-based prevention programs are needed to decrease or delay the onset of dementia.

Leisure activities, including physical activity (PA), cognitive activity (CA), and social activity (SA), are major components of modifiable and healthy lifestyles and are beneficial to
the cognition. Previous studies showed that leisure activities were associated with various health benefits, such as a lower cancer risk, a reduction of atrial fibrillation, and subjective well-being. However, evidence of the role of leisure activities in the prevention of dementia is conflicting. Some studies indicated that engagement in leisure activities may be a potential protective factor against the risk of cognitive impairment and dementia. Other studies found no significant relationship between leisure activities and the progression of dementia or AD pathophysiology. Furthermore, AD and VD have different etiologies. Unclear are the specific subtypes of dementia that may benefit from leisure activities or the ways in which different types of leisure activities can influence the risk of incident dementia. For example, several studies found that PA was related to a reduced risk of AD but other studies showed that PA was associated with a lower risk of VD but not AD. Cognitive activity also exerted contradictory effects on incident dementia. To develop effective strategies to protect against dementia, detailed associations between different types of leisure activities and dementia and its subtypes need to be identified.

This study systematically reviewed studies of the role of leisure activities in the development of dementia and performed meta-analyses. We assessed the impact of PA, CA, and SA on the incidence of ACD, AD, and VD, and discussed the potential mechanisms of these associations and proposed strategies to prevent incident dementia.

Methods

Search strategy

We performed a systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (PRISMA; Table e-1), and the Meta-analyses of Observational Studies in Epidemiology Checklist (MOOSE; Table e-2) guidelines. The study was registered with PROSPERO (CRD42019116857). The
Cochrane, PubMed, Embase, and Web of Science databases were searched for relevant studies up to May 8, 2021. Longitudinal studies that were published in English and assessed the role of leisure activities in incident ACD, AD, and VD were included. The following search terms (Table e-3) were used: (“leisure activities” OR “recreation” OR “cognitive activities” OR “cognitive stimulation” OR “intellectual activities” OR “mental activities” OR “exercise” OR “physical activities” OR “social activities”) AND (“dementia” OR “Alzheimer’s disease” OR “vascular dementia”) AND (“cohort studies” OR “longitudinal studies” OR “prospective studies” OR “nested case control studies”).

Selection criteria

Three authors (SS, LS, and YZ) independently screened the titles and abstracts for the eligibility of studies and reviewed the full-text articles using the Endnote X9 software. Studies were included if they met the following criteria: (1) evaluated associations between leisure activities and the incident dementia in the general population, (2) diagnosed dementia based on international diagnostic criteria, (3) employed a longitudinal design (cohort studies and nested case-control studies), (4) ascertained leisure activities via questionnaires, or interviews, and (5) provided sufficient data to calculate odds ratios (ORs), relative risks (RRs), or hazard ratios (HRs) with 95% confidence intervals (CIs) based on multivariate adjustment. The following exclusion criteria were applied: (1) case reports, commentaries, conference abstracts, reviews, and cross-sectional studies, (2) studies that presented cognitive function as a continuous variable without available ORs, RRs, or HRs, and (3) studies for which the outcome measure was not ACD, AD, or VD.

Data extraction

The data were independently extracted from eligible papers by three authors (SS, LS, and YS) who subsequently cross-checked the data, and additional information was obtained by contacting authors. Discrepancies were resolved by discussion until a consensus was
reached. The following information was extracted from each study: (1) first author, (2) publication year, (3) study design, (4) research site (country), (5) total number of participants at baseline and dementia cases during follow-up, (6) characteristics of baseline participants, such as sex ratio and age distribution, (7) follow-up time, (8) methods of ascertainment and operationalization of leisure activities, (9) type, duration, frequency, and intensity of leisure activities, (10) clinical tools used for dementia diagnosis, (11) effect estimates (ORs, RRs, or HRs) with 95% CIs, and (12) covariates that were used for adjustment.

Quality assessment

Three authors (SS, LS, and XH) assessed the quality of individual studies using the Newcastle-Ottawa Scale (NOS).\textsuperscript{23} The following items were considered: selection of the study groups, comparability of groups, and ascertainment of outcome measure for cohort studies with a sufficiently long follow-up time (≥ 5 years). A study could have a maximum quality score of 9. Studies with 7-9 points were high-quality. Studies with 4-6 points were medium-quality. Studies with 0-3 points were low-quality.

Definitions

Leisure activities, including CA, PA, and SA, were defined as activities in which individuals engaged for enjoyment or well-being.\textsuperscript{24} Cognitive activity mainly consisted of conscious and intellectual activities and included, but were not limited to, reading books, magazines, or newspapers, watching television, listening to the radio, writing for pleasure or calligraphy, playing games (e.g., cards, checkers, crossword puzzles, or other puzzles), playing musical instruments, using a computer or browsing the Internet, painting, and engaging in handicrafts. Physical activities included, but were not limited to, walking for exercise, hiking or excursions, jogging or running, swimming, stair climbing, bicycling, using exercise machines, playing ballgames or racket sports, participating in group exercises, performing Qigong or Yoga, performing calisthenics, and dancing. Social activities mainly
referred to activities that involved communication with others and included, but were not limited to, attending an interest class, joining a social center, participating in volunteer work, meeting relatives or friends, attending religious activities, and participating in organized group discussions.\textsuperscript{5, 20, 24, 25}

In this study, ACD, AD, and VD were diagnosed based on the Diagnostic and Statistical Manual of Mental Disorders, International Statistical Classification of Diseases and Related Health Problems, National Institute of Neurological Disorders and Stroke and Alzheimer’s Disease and Related Disorders Association criteria, National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria, California Alzheimer’s Disease Diagnostic and Treatment Centers criteria, Consortium to Establish a Registry for Alzheimer Disease and Pittsburgh Alzheimer Disease Research Center assessment protocols, Manchester-Lund criteria, and other recognized diagnostic criteria.

**Statistical analysis**

The statistical analyses were performed using STATA 15 software. Because the incidence of dementia was very low, ORs, RRs, and HRs were treated equally.\textsuperscript{26} The RRs and 95% CIs were used to indicate effect sizes. Heterogeneity was evaluated using the $I^2$ statistic ($I^2 = 0-60\%$ [none to moderate] and $I^2 > 60\%$ [substantial statistical heterogeneity]). If no heterogeneity was found, then a fixed-effect model was used, or the random-effect model was chosen to bolster the results. Subgroup analyses were conducted to explore the effects of PA, CA, and SA on incident ACD, AD, and VD. We used meta-regression to assess the effects of age, sex, years of follow-up, number of participants, and broad WHO regional classification (i.e., Africa, Americas, Asia, Europe, and Oceania) on study-specific effect estimates. Funnel plots were used to assess publication bias. Egger’s tests were used to estimate publication bias. Values of $p < 0.05$ were considered statistically significant. Sensitivity analyses were
conducted to evaluate the influence of each study on the overall results.

Results

Figure 1 presents a flow chart of the identification of eligible studies. A total of 16126 articles were retrieved. After excluding duplicate publications, there were 13307 articles, of which 12571 were irrelevant studies, reviews, commentaries, guidelines, case reports, perspectives, meeting abstracts, animal, cellular/molecular studies, and non-English studies. Of the remaining 736 studies, a total of 38 longitudinal studies were included in the meta-analysis after reviewing the full texts.

Characteristics of eligible studies

The characteristics of the 38 eligible longitudinal studies (37 cohort studies and one nested case-control study) are presented in Table 1. These studies had a total of 2154818 participants (mean age: 45.00-93.00 years old) at baseline, 74700 ACD cases, 2848 AD cases, and 1423 VD cases during follow-up (2.90-44.00 years). Among these studies, 12 were conducted in North America, 22 were conducted in Europe, three were conducted in Asia, and one was conducted in Oceania. According to the NOS (Table e-4), 32 studies were of high quality, and six studies were of medium quality. The measurement of leisure activities was based on self-report questionnaires in 24 studies and interviews in 14 studies. Detailed information about the methods that were used to reflect features of leisure activities, such as frequency, intensity, or duration, in the original studies is shown in Table e-5. All studies provided RRs (HRs or ORs) and 95% CIs based on adjustment for multiple potential covariates, including age, sex, education, and apolipoprotein E (Table e-5).
Leisure activities and all-cause dementia

Thirty-six studies investigated the relationship between leisure activities and ACD, including 2152163 participants (mean age: 45.00-93.00 years old) at baseline and 74700 ACD cases during follow-up (2.90-44.00 years). Five studies of these studies only showed the relationship of leisure activities and incident dementia. Others investigated the role of different types of leisure activities, including PA (29 studies), CA (eight studies), and SA (four studies), on the incidence of ACD. The meta-analysis showed that individuals who engaged in leisure activities were associated with a 0.83-fold lower risk of developing ACD compared with individuals who did not engage in leisure activities (RR = 0.83, 95% CI: 0.80-0.87, \( I^2 = 79.9\% \), \( p < 0.001 \); Figure 2). The subgroup analyses showed that PA, CA, and SA were inversely associated with incidence of ACD (PA: RR = 0.83, 95% CI: 0.78-0.88, \( I^2 = 73.8\% \), \( p < 0.001 \); CA: RR = 0.77, 95% CI: 0.68-0.87, \( I^2 = 83.6\% \), \( p < 0.001 \); SA: RR = 0.93, 95% CI: 0.87-0.99, \( I^2 = 12.7\% \), \( p = 0.329 \); Figure 5; Figure e-1). The meta-regression showed that types of leisure activities, number of participants, sex, age at baseline, follow up duration, and WHO regional classification were not significantly associated with development of ACD (Table e-6).

Leisure activities and Alzheimer’s disease

Fifteen articles assessed the role of leisure activities in incident AD. These studies included a total of 60666 participants (mean age: 47.20-81.10 years old) at baseline and 2848 AD patients during follow-up (3.90-44.00 years). Compared with participants who did not engage in leisure activities at baseline, participants who engaged in leisure activities were associated with a 18% lower risk of developing AD (RR = 0.82, 95% CI: 0.74-0.90, \( I^2 = 72.7\% \), \( p < 0.001 \); Figure 3). The subgroup analysis, including PA (14 studies), CA (four studies), and SA (one study), showed that the tendency was the same when examining the roles of PA and CA in the occurrence of AD (PA: RR = 0.87, 95% CI: 0.78-
Leisure activities and vascular dementia

The overall weighted RRs for associations between leisure activities and VD are shown in Figure 4. Nine articles that included 40600 participants (mean age: 47.20-74.80 years old) at baseline and 1423 VD patients during follow-up (3.00-44.00 years) evaluated the role of leisure activities in incident VD. We found that participants who engaged in leisure activities were associated with a 0.68-fold lower risk of VD compared with participants who did not engage in leisure activities (RR = 0.68, 95% CI: 0.54-0.86, $I^2 = 61.8\%$, $p = 0.007$; Figure 4). The subgroup analyses of PA (nine studies) showed that participants who engaged in PA were associated with a lower risk of VD compared with participants who did not engage in PA (RR = 0.67, 95% CI: 0.53-0.85, $I^2 = 61.5\%$, $p = 0.008$; Figure 5; Figure e-3). With regard to the relationship between CA and VD risk, only one study found that CA was not significantly associated with development of VD (RR = 0.98, 95% CI: 0.44-2.18; Figure 5; Figure e-3). No study evaluated the relationship between SA and incident VD. The meta-regression showed that types of leisure activities, number of participants, sex, age at baseline, follow up duration, and WHO regional classification were not significantly associated with incidence of VD (Table e-6).

Publication bias and sensitivity analysis

The Figure e-4 presented funnel plots of the meta-analyses of the roles of leisure activities in incident ACD, AD, and VD. Publication bias assessed by using Egger’s tests
was found when evaluating the relationships between leisure activities and incident ACD and AD, indicating that there was a selective publication, and some negative results might be underreported (Figure e-5). To investigate the impact of any one study on the overall results, sensitivity analysis was performed. No change in the direction of the results was found after excluding any single study (Figure e-6; Figure e-7).

Discussion

The present meta-analysis comprehensively and quantitatively assessed the association between different types of leisure activities and the risk of ACD and its two major subtypes, AD and VD, based on studies with large sample sizes. We found that leisure activities were significantly associated with a lower risk of incident ACD, AD, and VD, even after adjusting for confounding factors. Physical activity was inversely associated with risk of ACD, AD, and VD. Cognitive activity was in relation with a reduced risk of ACD and AD. Social activity was associated with a reduced incidence of ACD. These findings indicate the potential relationship between various types of leisure activities and different subtypes of dementia risk, with implications for future strategies that seek to prevent the incident dementia.

After pooling 2154818 participants at baseline and 74700 ACD patients during follow-up from 38 articles, we found that participants who engaged in leisure activities were associated with a 0.83-fold lower risk of incident ACD. Leisure activities were in relation with decreased risk of AD and VD. Leisure activities are generally modifiable factors. Based on the findings, some measures may be considered to decrease the incident dementia. Our results are consistent with previous meta-analyses, but these previous studies did not consider the relationship between different types of leisure activities and dementia risk. Because different types of leisure activities may have distinct influences, we classify leisure
activities into PA, CA, and SA, and discussed the unique possible influence of each activity on dementia. Furthermore, we focus on the two most prevalent dementia subtypes to determine the associations between different types of leisure activities and AD and VD. This study provides a comprehensive synthesis of three types of leisure activities and ACD and its two subtypes, AD and VD, for the development of early and effective management strategies and policies for the prevention of dementia. In addition, this study not only provides an update to previous meta-analyses in this field but also uses a unified selection criteria and quality assessment for different types of leisure activities to reduce heterogeneity and ensure the robustness of epidemiological evidence and quantitative estimation.

Many studies have assessed the association between PA and the risk of developing dementia. Our results are consistent with previous studies and provide further evidence of the inverse correlation between PA and ACD and its two subtypes, AD and VD. Fibronectin type III domain-containing protein 5 (FNDC5)/irisin was found to be reduced in AD patients and in AD experimental models, and physical activity might rescue synaptic plasticity and memory deficits, important factors in the dementia process, by the mediation of FNDC5/irisin. A previous meta-analysis showed that PA was associated with lower risk of AD compared with ACD and VD. Evidence from animal and human studies suggests that PA is related to lower levels of brain amyloid-β plaques and tau proteins, which have been implicated in the progression of AD. Physical activity is also beneficial for attenuating amyloid-β-related gray matter volume loss in the brain, ameliorating impairments in hippocampal neurogenesis and plasticity, and lowering oxidative stress. Long-term PA was reported to be associated with improvement on cognitive function with increased hippocampal brain-derived neurotrophic factor (BDNF) and synaptophysin. With regard to VD, the association between PA and the lower risk of VD is consistent with previous studies.
dementia was related to physically inactive individuals with cardiometabolic disease.\textsuperscript{14} Moreover, previous studies found that PA decreased the risk of vascular and metabolic adverse events, enhanced insulin sensitivity, increased BDNF levels, and increased hippocampus volume.\textsuperscript{e68-e71} A recent study showed that PA benefited the brain by increasing clusterin and decreasing neuroinflammation in patients with cognitive impairment.\textsuperscript{e72} However, detailed relationships between PA and the incidence of AD and VD and the associated mechanisms need further exploration.

Cognitive activity is different from PA, although it was still shown to be related to decreased incidence of ACD and AD. Cognitive activity helps maintain and improve cognitive skills, such as memory, processing speed, thinking, and reasoning skills. Many studies have confirmed the beneficial role of CA in preventing dementia, even after controlling for vascular risk factors, depressive symptoms, and physical functioning.\textsuperscript{5, 6, 20, e53} A large-sample cohort study that included 15582 participants (71-77 years of age) and a 5.0 year median follow-up time showed that CA was linked to a 29% lower risk of dementia.\textsuperscript{20} Cognitive activity has been found to modulate disease progression and increase hippocampal neurogenesis by upregulating neurotrophins and BDNF in mutant mice with AD-like pathology.\textsuperscript{e73} A systematic review of diffusion tensor imaging in middle-aged adults showed that cognitive training was effective against age-related frontal and medial white matter microstructural decline.\textsuperscript{e74} Moreover, previous studies have shown that CA is more related to mental stimulation than PA and SA and may enhance the survival of hippocampal neurons and lead to better cognitive performance.\textsuperscript{e75-e77} However, because of the limited number of studies that were included in the present meta-analysis, we cannot exclude the possible role of CA in the development of VD. Furthermore, watching television was defined as a cognitive activity in three out of nine studies that investigated the correlation between cognitive activity and dementia included in this meta-analysis.\textsuperscript{6, 20, 48} This broad definition
may contribute to a bias because watching television may be insufficiently stimulating to promote cognitive performance, and the effect of watching television needs to be further investigated by strictly designed large-scale clinical trials. A more stringent definition needs to be used in further studies when investigating the association between cognitive activity and dementia.

Social activity was also associated with a decreased incidence of ACD, although this finding was based on only four studies. However, this finding was inconsistent with the results of two cohort studies. This discrepancy may be attributable to the relatively low number of studies. The protective effect of SA on cognitive function may be associated with the enhancement of social contact and emotional support and reduction of depression and stress. However, socially active people tend to engage in more CA and PA, which are associated with a lower risk of ACD. As the inter-correlation and complexity among different types of leisure activities were not clearly reported in most studies, we were unable to investigate the extent to which people engage in all three activities. Thus, ascertaining the real impact of SA on ACD may be difficult. Future studies should determine whether specifically SA plays a role in preventing ACD. Moreover, the association between SA and incident AD and VD is still unclear. Only one such study was included in the present meta-analysis, and no significant relationship was found between SA and AD. To our knowledge, this is the first systematic assessment of the effect of SA on dementia. This finding prompts the importance of implementation of SA for public health of the elderly especially in the context of COVID-19 pandemic and quarantine strategy. Further studies should investigate the relationship between SA, especially social communication, and the development of AD and VD.

The present meta-analysis benefited from a large sample size and comprehensive examinations of the correlation between three types of leisure activities and ACD and its
subtypes. However, our study has several limitations. Firstly, self-reports via questionnaires and interviews were mostly used to assess leisure activities, which may lead to misestimation of the effects of leisure activities on dementia. Secondly, we did not analyze the effects of different levels (strenuous or frequent) of leisure activities on the risk of dementia because of the limited number of studies that met the selection criteria. Specifically defining different levels of PA, CA, and SA using uniform standards is difficult, as the methods used to assess leisure activities were quite different among the original studies. Thirdly, publication bias exists when evaluating the relationship between leisure activities and incident ACD and AD. This paper was limited to longitudinal studies that were published in English, and research in other languages and grey literatures were not captured, which may result in publication bias, meaning that the correlative inference is limited. Fourthly, this paper as over a third of the included studies had a follow-up of less than 6 years, many of the participants with dementia were likely to have undiagnosed early-stage disease at the time of enrollment. Therefore, a longer follow-up period is needed to confirm the correlation between leisure activities and dementia in the future. Finally, leisure activities were divided into three different categories including PA, CA and SA, and each of which also included different kinds of activities. Our analysis did not provide evidence of the association between each specific activity and dementia due to the limited number of studies.

In conclusion, the present meta-analysis found that leisure activities were significantly associated with a lower risk of incident dementia. Physical, cognitive, and social activities were inversely associated with incidence of ACD. The lower incidence of AD was significantly related to PA and CA, and individuals who engaged in PA were correlated to a relatively low risk of VD. Future studies should include large sample sizes and long follow-up time to objectively assess leisure activities based on standard methods to reveal further associations between leisure activities and incident dementia.
References


Additional references e51–e79 available at supplementary appendix.
Figure Legends

Figure 1. Flow chart of the identification of eligible studies.
Figure 2. Forest plot of the protective role of leisure activities in the risk of all-cause dementia. The results are expressed as relative risks (RRs) and 95% confidence intervals (95% CIs).

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<th>Weight (%)</th>
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<td>3.39</td>
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<tr>
<td>Ref. #53</td>
<td>0.84 (0.72, 0.98)</td>
<td>3.21</td>
</tr>
<tr>
<td>Ref. #54</td>
<td>0.61 (0.38, 0.98)</td>
<td>0.73</td>
</tr>
<tr>
<td>Ref. #55</td>
<td>0.76 (0.60, 0.97)</td>
<td>2.04</td>
</tr>
<tr>
<td>e-Ref. #51</td>
<td>0.62 (0.44, 0.89)</td>
<td>1.19</td>
</tr>
<tr>
<td>e-Ref. #52</td>
<td>0.81 (0.63, 1.06)</td>
<td>1.77</td>
</tr>
<tr>
<td>Overall (I² = 79.9%, p = 0.000)</td>
<td>0.83 (0.80, 0.87)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Note: Weights are from random-effects analysis.
Figure 3. Forest plot of the protective role of leisure activities in the risk of Alzheimer’s disease. The results are expressed as relative risks (RRs) and 95% confidence intervals (95% CIs).

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ref. #6</td>
<td>0.79 (0.66, 0.95)</td>
<td>8.05</td>
</tr>
<tr>
<td>Ref. #28</td>
<td>0.98 (0.89, 1.08)</td>
<td>9.85</td>
</tr>
<tr>
<td>Ref. #31</td>
<td>0.69 (0.45, 1.06)</td>
<td>3.73</td>
</tr>
<tr>
<td>Ref. #18</td>
<td>1.01 (0.89, 1.14)</td>
<td>9.33</td>
</tr>
<tr>
<td>Ref. #34</td>
<td>0.59 (0.41, 0.84)</td>
<td>4.64</td>
</tr>
<tr>
<td>Ref. #50</td>
<td>0.69 (0.45, 1.05)</td>
<td>3.79</td>
</tr>
<tr>
<td>Ref. #36</td>
<td>0.63 (0.48, 0.83)</td>
<td>6.09</td>
</tr>
<tr>
<td>Ref. #38</td>
<td>0.84 (0.75, 0.94)</td>
<td>9.54</td>
</tr>
<tr>
<td>Ref. #16</td>
<td>0.66 (0.47, 0.82)</td>
<td>6.00</td>
</tr>
<tr>
<td>Ref. #43</td>
<td>0.94 (0.77, 1.16)</td>
<td>7.54</td>
</tr>
<tr>
<td>Ref. #46</td>
<td>0.91 (0.72, 1.16)</td>
<td>6.81</td>
</tr>
<tr>
<td>Ref. #17</td>
<td>1.04 (0.64, 1.70)</td>
<td>3.12</td>
</tr>
<tr>
<td>Ref. #15</td>
<td>0.67 (0.53, 0.85)</td>
<td>6.85</td>
</tr>
<tr>
<td>Ref. #50</td>
<td>1.10 (0.95, 1.29)</td>
<td>8.70</td>
</tr>
<tr>
<td>eRef. #53</td>
<td>0.58 (0.44, 0.77)</td>
<td>5.97</td>
</tr>
</tbody>
</table>

Overall ($I^2 = 72.7\%, p = 0.000$)

0.82 (0.74, 0.90) 100.00

Note: Weights are from random effects analysis

Figure 4. Forest plot of the protective role of leisure activities in the risk of vascular dementia. The results are expressed as relative risks (RRs) and 95% confidence intervals (95% CIs).

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ref. #31</td>
<td>0.56 (0.33, 0.93)</td>
<td>10.10</td>
</tr>
<tr>
<td>Ref. #18</td>
<td>0.76 (0.64, 0.93)</td>
<td>18.33</td>
</tr>
<tr>
<td>Ref. #34</td>
<td>0.74 (0.47, 1.16)</td>
<td>11.53</td>
</tr>
<tr>
<td>Ref. #36</td>
<td>0.64 (0.41, 1.01)</td>
<td>11.55</td>
</tr>
<tr>
<td>Ref. #16</td>
<td>0.87 (0.47, 1.61)</td>
<td>8.33</td>
</tr>
<tr>
<td>Ref. #43</td>
<td>0.47 (0.29, 0.79)</td>
<td>10.45</td>
</tr>
<tr>
<td>Ref. #46</td>
<td>1.13 (0.88, 1.45)</td>
<td>16.73</td>
</tr>
<tr>
<td>Ref. #17</td>
<td>0.38 (0.14, 0.81)</td>
<td>5.14</td>
</tr>
<tr>
<td>eRef. #52</td>
<td>0.42 (0.22, 0.80)</td>
<td>7.86</td>
</tr>
</tbody>
</table>

Overall ($I^2 = 61.80\%, p = 0.007$)

0.68 (0.54, 0.86) 100.00

Note: Weights are from random effects analysis
Figure 5. Subgroup analysis of the protective role of different types of leisure activities in the risk of all-cause dementia, Alzheimer’s disease, and vascular dementia.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Studies (n)</th>
<th>Number of participants</th>
<th>RR (95% CI)</th>
<th>Heterogeneity</th>
<th>p value for subgroup difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause dementia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical activity</td>
<td>29</td>
<td>1,285,115</td>
<td>0.83 (0.78, 0.88)</td>
<td>73.80</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cognitive activity</td>
<td>8</td>
<td>27,857</td>
<td>0.77 (0.68, 0.86)</td>
<td>85.60</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Social activity</td>
<td>4</td>
<td>25,609</td>
<td>0.93 (0.87, 0.99)</td>
<td>12.70</td>
<td>0.329</td>
</tr>
<tr>
<td>Alzheimer disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical activity</td>
<td>14</td>
<td>59,891</td>
<td>0.87 (0.78, 0.96)</td>
<td>64.40</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cognitive activity</td>
<td>4</td>
<td>9,765</td>
<td>0.66 (0.52, 0.85)</td>
<td>70.30</td>
<td>0.018</td>
</tr>
<tr>
<td>Social activity</td>
<td>1</td>
<td>5,698</td>
<td>0.89 (0.63, 1.26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular dementia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical activity</td>
<td>9</td>
<td>40,600</td>
<td>0.67 (0.53, 0.85)</td>
<td>61.50</td>
<td>0.008</td>
</tr>
<tr>
<td>Cognitive activity</td>
<td>1</td>
<td>800</td>
<td>0.98 (0.44, 2.18)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 1. Summary of longitudinal studies included in the meta-analysis.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Country</th>
<th>Total sample</th>
<th>Female (%)</th>
<th>Age at baseline (y)</th>
<th>Method of leisure activities</th>
<th>Leisure activity types</th>
<th>Follow up duration (y)</th>
<th>Diagnosis of dementia</th>
<th>Participants with dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akbaraly, 2009⁶</td>
<td>cohort study</td>
<td>France</td>
<td>5698</td>
<td>60.87%</td>
<td>73.7±5.4</td>
<td>questionnaire</td>
<td>cognitive, physical, social</td>
<td>4</td>
<td>ACD: DSM-4, AD: NINCDS-ADRDHA AD: NINCDS-ADRDHA, VD: NINDS-AIREN, Frontotemporal lobe dementia: the Manchester-Lund criteria; dementia with Lewy bodies: the revised Criteria of Consortium for Dementia with Lewy bodies</td>
<td>ACD: 161 (AD: 105)</td>
</tr>
<tr>
<td>Blasko, 2014⁷</td>
<td>cohort study</td>
<td>Austria</td>
<td>399</td>
<td>61.14%</td>
<td>75.8±0.5</td>
<td>interview</td>
<td>cognitive, physical</td>
<td>5</td>
<td>AD: NINCDS-ADRDA, VD: NINDS-AIREN, Frontotemporal lobe dementia: the Manchester-Lund criteria; dementia with Lewy bodies: the revised Criteria of Consortium for Dementia with Lewy bodies</td>
<td>ACD: 117</td>
</tr>
<tr>
<td>Chang, 2010⁸</td>
<td>cohort study</td>
<td>Iceland</td>
<td>4945</td>
<td>57.67%</td>
<td>51.1±5.7</td>
<td>interview</td>
<td>physical</td>
<td>25.8</td>
<td>DSM-4</td>
<td>ACD: 184</td>
</tr>
<tr>
<td>de Bruijn, 2013²⁸</td>
<td>cohort study</td>
<td>Netherlands</td>
<td>4406</td>
<td>59.00%</td>
<td>72.7±5.2</td>
<td>questionnaire</td>
<td>physical</td>
<td>8.8</td>
<td>ACD: DSM-3R, AD: NINCDS-ADRDHA</td>
<td>ACD: 583 (AD: 490)</td>
</tr>
<tr>
<td>Floud, 2020²⁹</td>
<td>cohort study</td>
<td>UK</td>
<td>1136846</td>
<td>100.00%</td>
<td>56±5</td>
<td>interview</td>
<td>physical</td>
<td>18</td>
<td>ICD-10</td>
<td>ACD: 30957</td>
</tr>
<tr>
<td>Floud, 2021³⁰</td>
<td>cohort study</td>
<td>UK</td>
<td>851307</td>
<td>100.00%</td>
<td>60±5</td>
<td>interview</td>
<td>leisure</td>
<td>16</td>
<td>ICD-10</td>
<td>ACD: 31187</td>
</tr>
<tr>
<td>Gelber, 2012³¹</td>
<td>case–control study nested in a prospective cohort</td>
<td>USA</td>
<td>3468</td>
<td>0.00%</td>
<td>Mean 52</td>
<td>interview</td>
<td>physical</td>
<td>25</td>
<td>ACD: DSM-3R, AD: NINCDS-ADRDHA, VD: criteria of California Alzheimer’s Disease Diagnostic and Treatment Centers</td>
<td>ACD: 223 (AD: 117, VD: 78)</td>
</tr>
<tr>
<td>Study (year)</td>
<td>Cohort/Country</td>
<td>Sample size</td>
<td>Percentage</td>
<td>Age (mean ± SD)</td>
<td>Methodology</td>
<td>Diagnostic Criteria</td>
<td>ACD (Subjects)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grasset, 2017</td>
<td>Cohort Study, France</td>
<td>3670</td>
<td>58.01%</td>
<td>75.3±6.8</td>
<td>Questionnaire, Physical</td>
<td>DSM-3R</td>
<td>11.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hansson, 2019</td>
<td>Cohort Study, Sweden</td>
<td>20639</td>
<td>60.00%</td>
<td>57.5 (51.0-63.8)</td>
<td>Questionnaire, Physical</td>
<td>DSM-5</td>
<td>15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hughes, 2010</td>
<td>Cohort Study, USA</td>
<td>942</td>
<td>66.45%</td>
<td>75.8±5.1</td>
<td>Interview, Cognitive</td>
<td>Modified CERAD and Pittsburgh Alzheimer Disease Research Center assessment protocols</td>
<td>ACD: 111</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kishimoto, 2016</td>
<td>Cohort Study, Japan</td>
<td>803</td>
<td>61.30%</td>
<td>74±6.8</td>
<td>Questionnaire, Physical</td>
<td>DSM-3R, AD: NINCDS-ADRDA, VD: NINDS-AIREN</td>
<td>ACD: 291</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laros, 2006</td>
<td>Cohort Study, USA</td>
<td>1740</td>
<td>60.34%</td>
<td>74.4±5.7</td>
<td>Questionnaire, Physical</td>
<td>DSM-4, AD: NINCDS-ADRDA</td>
<td>ACD: 158</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laurin, 2001</td>
<td>Cohort Study, Canada</td>
<td>4615</td>
<td>60.33%</td>
<td>≥65</td>
<td>Questionnaire, Physical</td>
<td>DSM-4</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lee, 2018</td>
<td>Cohort Study, China</td>
<td>15582</td>
<td>63.90%</td>
<td>74 (71-77)</td>
<td>Questionnaire, Cognitive, Social, Physical</td>
<td>ICD-10R</td>
<td>ACD: 1349</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Llamas-Velasco, 2015</td>
<td>Cohort Study, Spain</td>
<td>3105</td>
<td>56.60%</td>
<td>73.2±6.3</td>
<td>Interview, Physical</td>
<td>DSM-4</td>
<td>ACD: 134</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Luck, 2014</td>
<td>Cohort Study, Germany</td>
<td>2492</td>
<td>64.70%</td>
<td>81.1±3.5</td>
<td>Interview, Cognitive, Physical</td>
<td>DSM-4, AD: NINCDS-ADRDA</td>
<td>ACD: 278</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marioni, 2015</td>
<td>Cohort Study, France</td>
<td>2854</td>
<td>59.00%</td>
<td>77.0±6.8</td>
<td>Interview, Social</td>
<td>DSM-3R</td>
<td>ACD: 783</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marsiglio, 2019</td>
<td>Cohort Study, Sweden</td>
<td>2648</td>
<td>62.95%</td>
<td>73.6±10.5</td>
<td>Interview, Leisure</td>
<td>DSM-4</td>
<td>ACD: 246</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morgan, 2012</td>
<td>Cohort Study, UK</td>
<td>1005</td>
<td>0.00%</td>
<td>56</td>
<td>Questionnaire, Physical</td>
<td>NINDS-AIREN</td>
<td>ACD: 72</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nabe-Nielsen, 2021</td>
<td>Cohort Study, Denmark</td>
<td>4721</td>
<td>0.00%</td>
<td>49.0±5.3</td>
<td>Interview, Physical</td>
<td>ICD-10</td>
<td>ACD: 697</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Country</td>
<td>Sample Size</td>
<td>Percent</td>
<td>Mean ± SD</td>
<td>Methodology</td>
<td>Domain</td>
<td>ACD Criteria</td>
<td>AD Criteria</td>
<td>VD Criteria</td>
</tr>
<tr>
<td>------------------------------</td>
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</tr>
<tr>
<td>Najar, 2019</td>
<td>cohort study</td>
<td>Sweden</td>
<td>800</td>
<td>100.00%</td>
<td>47.2±4.5</td>
<td>interview</td>
<td>cognitive, physical</td>
<td>DSM-3R, AD: NINCDS-ADRDA, VD: NINDS-AIREN</td>
<td>44</td>
<td>AD: 194 (AD: 102, VD: 27)</td>
</tr>
<tr>
<td>Neergaard, 2016</td>
<td>cohort study</td>
<td>Denmark</td>
<td>5512</td>
<td>100.00%</td>
<td>70.6±6.5</td>
<td>questionnaire</td>
<td>physical</td>
<td>ICD-10</td>
<td>ACD: 268</td>
<td>ACD: 1063</td>
</tr>
<tr>
<td>Paganini-Hill, 2016</td>
<td>cohort study</td>
<td>USA</td>
<td>587</td>
<td>not reported</td>
<td>93±2.6</td>
<td>questionnaire</td>
<td>leisure</td>
<td>AD: NINCDS-ADRDA, VD: NINDS-AIREN</td>
<td>3</td>
<td>AD: 479 (AD: 245, VD: 213)</td>
</tr>
<tr>
<td>Palta, 2019</td>
<td>cohort study</td>
<td>USA</td>
<td>10705</td>
<td>55.95%</td>
<td>59.9±5.67</td>
<td>questionnaire</td>
<td>physical</td>
<td>DSM-5</td>
<td>ACD: 1063</td>
<td></td>
</tr>
<tr>
<td>Neergaard, 2016</td>
<td>cohort study</td>
<td>Denmark</td>
<td>5512</td>
<td>100.00%</td>
<td>70.6±6.5</td>
<td>questionnaire</td>
<td>physical</td>
<td>ICD-10</td>
<td>ACD: 268</td>
<td>ACD: 1063</td>
</tr>
<tr>
<td>Podewils, 2005</td>
<td>cohort study</td>
<td>USA</td>
<td>3375</td>
<td>59.10%</td>
<td>74.8±4.9</td>
<td>questionnaire</td>
<td>physical</td>
<td>DSM-5</td>
<td>ACD: 1063</td>
<td></td>
</tr>
<tr>
<td>Ravaglia, 2008</td>
<td>cohort study</td>
<td>Italy</td>
<td>749</td>
<td>53.50%</td>
<td>73.2±6.0</td>
<td>questionnaire</td>
<td>physical</td>
<td>ACD: DSM-4, AD: NINCDS-ADRDA, VD: NINDS-AIREN</td>
<td>3.9</td>
<td>ACD: 86 (AD: 54, VD: 27)</td>
</tr>
<tr>
<td>Sabia, 2017</td>
<td>cohort study</td>
<td>UK</td>
<td>10308</td>
<td>33.11%</td>
<td>45.0±6.0</td>
<td>questionnaire</td>
<td>physical</td>
<td>ICD-10</td>
<td>ACD: 329</td>
<td>ACD: 207</td>
</tr>
<tr>
<td>Scarmeas, 2001</td>
<td>cohort study</td>
<td>USA</td>
<td>1772</td>
<td>68.12%</td>
<td>75.6±6.30</td>
<td>interview</td>
<td>leisure</td>
<td>DSM-3R</td>
<td>ACD: 329</td>
<td>ACD: 207</td>
</tr>
<tr>
<td>Scarmeas, 2009</td>
<td>cohort study</td>
<td>USA</td>
<td>1880</td>
<td>69.00%</td>
<td>77.2±6.6</td>
<td>questionnaire</td>
<td>physical</td>
<td>NINCDS-ADRDA</td>
<td>AD: 282</td>
<td></td>
</tr>
<tr>
<td>Sommerlad, 2020</td>
<td>cohort study</td>
<td>UK</td>
<td>6050</td>
<td>30.70%</td>
<td>55.9±6.0</td>
<td>questionnaire</td>
<td>leisure</td>
<td>ICD-10</td>
<td>ACD: 247</td>
<td>ACD: 247</td>
</tr>
<tr>
<td>Sorman, 2014</td>
<td>cohort study</td>
<td>Sweden</td>
<td>1475</td>
<td>56.67%</td>
<td>73.7±6.9</td>
<td>questionnaire</td>
<td>cognitive, social</td>
<td>DSM-4</td>
<td>AD: 357</td>
<td>ACD: 236 (AD: 188)</td>
</tr>
<tr>
<td>Tan, 2017</td>
<td>cohort study</td>
<td>USA</td>
<td>3714</td>
<td>54.44%</td>
<td>70.5±7.0</td>
<td>questionnaire</td>
<td>physical</td>
<td>DSM-4</td>
<td>ACD: 544</td>
<td></td>
</tr>
<tr>
<td>Tolppanen, 2015</td>
<td>cohort study</td>
<td>Finland</td>
<td>3559</td>
<td>56.50%</td>
<td>51.2±6.0</td>
<td>questionnaire</td>
<td>physical</td>
<td>DSM-4</td>
<td>ACD: 544</td>
<td></td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Study</th>
<th>Country</th>
<th>Age at Baseline (y): mean±standard deviation/median (interquartile range)</th>
<th>Source of Diagnosis</th>
<th>AD:</th>
<th>ACD:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verdelho, 2012</td>
<td>cohort study</td>
<td>not reported</td>
<td>639 55.00% 74.1±5 interview physical</td>
<td>AD: NINCDS-ADRDA, VD: NINDS-AIREN</td>
<td>3</td>
<td>90</td>
</tr>
<tr>
<td>Verghese, 2003</td>
<td>cohort study</td>
<td>Canada</td>
<td>469 64.06% 79.1±3.1 questionnaire cognitive, physical</td>
<td>DSM-3R/DSM-3</td>
<td>5.1</td>
<td>124</td>
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<tr>
<td>Wilson, 2007</td>
<td>cohort study</td>
<td>USA</td>
<td>775 75.36% 80.4±7.4 questionnaire cognitive, physical</td>
<td>NINCDS-ADRDA</td>
<td>3.5</td>
<td>124</td>
</tr>
<tr>
<td>Wu, 2020</td>
<td>cohort study</td>
<td>China</td>
<td>1648 54.50% 71.5±7.4 questionnaire cognitive, physical</td>
<td>DSM-4</td>
<td>5.3</td>
<td>166</td>
</tr>
<tr>
<td>Zotcheva, 2018</td>
<td>cohort study</td>
<td>Norway</td>
<td>28916 50.20% 53.4 questionnaire cognitive, physical</td>
<td>ICD-10</td>
<td>15.2</td>
<td>359</td>
</tr>
</tbody>
</table>

Age at baseline (y): mean±standard deviation/median (interquartile range) years.

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