Published in final edited form as:

Alzheimers Dement. 2019 December ; 15(12): 1603–1611. doi:10.1016/j.jalz.2019.07.013.

Current and past leisure time physical activity in relation to risk of Alzheimer's disease in older adults

Erika Ogino[1], **Jennifer J. Manly, PhD**[1,2,3], **Nicole Schupf, PhD**[1,2,4], **Richard Mayeux, MD**[1,2,3,4], **Yian Gu, PhD**[1,2,3,4]

[1]The Taub Institute for Research in Alzheimer's Disease and the Aging Brain, Columbia University, New York, NY.

[2]The Department of Neurology, Columbia University, New York, NY.

[3]The Gertrude H. Sergievsky Center, Columbia University, New York, NY.

[4]The Department of Epidemiology, Joseph P. Mailman School of Public Health, Columbia University, New York, NY.

Abstract

INTRODUCTION—The associations between self-reported current and past leisure time physical activity (LTPA) and Alzheimer's disease (AD) incidence were determined using data from the multi-ethnic Washington/Hamilton Heights-Inwood Columbia Aging Project (WHICAP) study.

METHODS—The metabolic equivalent (MET) of LTPA energy expenditure was calculated for self-reported current and past LTPA for 1345 older adults. A COX proportional hazard model was conducted to estimate the association between LTPA (low, middle, and high) and incident AD risk.

RESULTS—Comparing high to low level, current and past LTPA were both associated with reduced AD risk, with HR(95%CI)=0.39 (0.20–0.75) and 0.37 (0.18–0.75), respectively. Compared with 'always low', 'increased' and 'always high' LTPA throughout life were associated with reduced AD risk, with HR(95%CI)= 0.60 (0.36–0.99) and 0.28 (0.08–0.94), respectively. Light and moderate intensity LTPA were associated with lower AD risk.

DISCUSSION—LTPA both throughout life and later in life are associated with lower risk of AD.

Keywords

dementia; Alzheimer's disease; physical activity; epidemiology; longitudinal study

Corresponding author: Yian Gu, Ph.D, yg2121@cumc.columbia.edu, 630 West 168th Street, P&S, Box 16, New York, NY 10032, Phone: 212-305-6684, Fax: 212-342-1838.

1. Introduction

Currently, there are more than 47 million individuals who are affected by dementia worldwide.[1] By 2050, this number is expected to reach 131.5 million.[1] Alzheimer's disease (AD) is the most common type of dementia, and there are no effective forms of treatment available for AD today. Therefore, it is vital that forms of prevention is found, especially by focusing on modifiable factors such as leisure time physical activity (LTPA).

Several longitudinal studies have found that regular LTPA is associated with reduced risk of dementia or AD[2–25], but others did not find a significant association between the two[26–32]. This inconsistency may be due to discrepancies in population characteristics, sample size, LTPA assessment, and dementia diagnosis. For example, the mean age of the population in the study by Broe et al was 83.4 years[26], and the results might be subject to survival bias. Some studies used weekly frequencies[21, 23, 28] or hours [22] of LTPA, rather than using recommended total metabolic equivalents (METs) to measure energy cost of LTPA [4, 6, 9, 10, 15, 24, 27, 33]. In addition, some past studies were limited in their short follow up time, and lack of diversity within participants. Some research suggests that LTPA from earlier life may influence dementia risk and cognition later in life.[20–25] However, the effect of LTPA during teenage or early adult life on dementia risk have never been studied, and few have included LTPA measures from throughout life[24, 25]. It remains unclear whether LTPA at different life stages are associated with AD risk. Consequently, change of LTPA status has also been rarely examined. Furthermore, it is unclear whether intensity of LTPA also matters in terms of protection against AD.

Previous research in the earlier recruitment cohorts of the Washington/Hamilton Heights-Inwood Columbia Aging Project (WHICAP) has shown that participating more in LTPA was associated with lower AD risk. [6] In the current study, we aimed to replicate the previous findings on current LTPA and expand the investigation to past LTPA in the newest, independent recruitment cohort of WHICAP that began in 2009.

2. Methods

2.1 Participants and Setting

WHICAP is a longitudinal study on aging and dementia of racially and socioeconomically diverse residents of the surrounding community in northern Manhattan. Community residents who were age 65 or older, fluent in English or Spanish, had no report of a dementia diagnosis or serious memory complaints were recruited primarily through a Medicare beneficiary list, supplemented by market mailing and community center visiting. To date, there have been three waves of enrollment (1992, 1999 and 2009). Participants are seen every 18–24 months. Only the 2009 cohort was included in this study as collection of self-reported past LTPA began with the 2009 cohort. Recruitment, written informed consent, and study procedures were approved by the institutional review boards of Columbia Presbyterian Medical Center, Columbia University Health Sciences, and the New York State Psychiatric Institute, and all participants provided consent.

Among 1843 enrolled participants of 2009 cohort enrolled so far, we excluded 93 (5%) participants who had prevalent dementia at baseline, 52 who died within 2 years from baseline assessment, 336 (19.7% of 1698) had no follow-up visits, 15 without LTPA information, and two participants who developed non-AD dementias. Thus, the current study included a total of 1345 subjects. Compared with 1345 included in the analysis, the 351 participants who were excluded due to lost to follow-up (N=336) or missing LTPA (N=15) had slightly less education (10.1 vs. 10.7 years, p=0.055) and were older (77.2 vs. 75.1 years, p<0.001), but were not different in sex, APOE, race/ethnicity, or LTPA level.

2.2 Dementia, AD, and mild cognitive impairment diagnosis

At each assessment, participants were given standard physical and neurological examination by physicians, and medical and neurological history was collected. Information was collected during an in-person evaluation in English or Spanish including an assessment of health and function and a neuropsychological battery.[34] The neuropsychological test as well as evidence of social or occupational function deficits were used for consensus diagnosis of dementia by a group of neurologists and neuropsychologists using criteria from the *Diagnostic and Statistical Manual of Mental Disorders.* The diagnosis of probable or possible AD was based on the criteria of the National Institute of Neurological Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association.[35] The diagnosis of mild cognitive impairment (MCI) was based on standard research criteria[36] as previously described[37]. Briefly, subjects were considered having MCI if they had all the following: 1) a subjective memory complaint; 2) objective impairment in at least 1 of the four cognitive domains including memory, executive, language, and visuospatial cognition, defined based on the average neuropsychological test scores within that domain and a 1.5-SD cutoff using corrections for age, years of education, ethnicity, and sex and based on the previously established norm; 3) essentially preserved activities of daily living; and 4) no diagnosis of dementia at the consensus conference.

2.3 Leisure Time Physical activity

Information about current LTPA was collected using the Godin leisure time exercise questionnaire.[38] At baseline, participants were queried about the frequency of LTPA during the most recent 2-week period, and duration (minutes) per session, separately for 3 different intensity categories of LTPAs: vigorous (aerobic dancing, jogging, playing handball), moderate (bicycling, swimming, hiking, playing tennis), and light (walking, dancing, calisthenics, golfing, bowling, gardening, horseback riding). A MET-minutes score [4, 6, 9, 10, 15, 24, 27] in 2 weeks for each intensity category was calculated by multiplying frequency (number of sessions), duration (minutes), and standard MET (9, 5, and 3 standard METs for vigorous activities, moderate activities, and light activities, respectively[38]). We then calculated the total current LTPA level, in MET-minutes/2-week, by summing up the three category-specific MET-minutes in the past 2-week to represent each individual's total current LTPA level. Similar to other studies[24], current LTPA was further categorized into low (no LTPA), middle, or high LTPA, with the latter two levels based on dichotomized value of 1260 MET-minutes/2-week (equivalent to approximately 1.2/2.1/3.5 hours/week, or 10/18/30 minutes/day, of vigorous/moderate/light LTPA, respectively) among who reported non-zero LTPA.

At baseline, participants also self-reported yes/no and frequency (almost all time/very frequent/frequently/rarely) of any LTPA more than ten times during early life (12–25 years), early-middle life (26–50 years), and late-middle life (>50 years), separately for light, moderate, and vigorous activities. Based on the median length reported for the current LTPA for each intensity category in the study population, the durations for light, moderate, and vigorous activities were conservatively estimated to be 30, 45, and 60 minutes, respectively. The reported frequency of LTPA was converted to 14, 10, 7, 3, and 0 sessions per 2-week for 'almost all time', 'very frequent', 'frequently', 'rarely', and 'none', respectively. A total MET-minutes per 2-week was estimated for each life stage and then averaged for each participant to represent each individual's average past LTPA level. As few (n=67) subjects reported no LTPA, past LTPA was further categorized into low, middle, or high LTPA based on tertiles, with the cutoffs for 'low- mid and mid-high' being approximately '1.9 and 4.4'/ '3.5 and 7.9' / '5.8 and 13.1' hours/week of vigorous/moderate/light LTPA, respectively.

Past studies have shown that reports of LTPA using the Godin Leisure Time Exercise Questionnaire in general is reliable, with the reliability correlation coefficients ranging from 0.62 to 0.81 [38–40]. We previously reported that the LTPA level correlated well with several measures of physical performance, suggesting its validity.[6]

2.4 Covariates

Information about age, sex, education, ethnicity, body mass index (BMI, kg/m^2), smoking status, and alcohol drinking was obtained from baseline interviews. Apolipoprotein E (*APOE*) ε4 genotype was used as a dichotomous variable: absence vs presence (of either 1 or 2) of ε4 alleles. Participants were queried about comorbidities including psychiatric diseases, diabetes, insulin treatment, heart disease, hypertension, head injury, and depression, with positive answer (yes) to either having the disease or having received treatment for the disease coded as 1 and negative answer coded as 0. A comorbidity score was then calculated by summing up all these dichotomous comorbidity variables as well as smoking and drinking. Self-reported occupation was used as a categorical variable.

2.5 Statistical analysis

2.5.1 Characteristics of the subjects—LTPA levels and other characteristics of participants were compared between incident AD cases and dementia-free participants, and across the levels of LTPAs, using t-tests for continuous variables, and chi-square test for categorical variables. Spearman correlations were run between the current and past LTPA, with 95%CI from a bootstrap analysis with 1000 repeated samples.

2.5.2 Association between LTPA and risk of incident AD—Cox proportional hazards models were used to analyze the relationship between the LTPA and AD risk, adjusted for potential confounders including age, sex, ethnicity, education, and *APOE* ε4 genotype (Model 1). Additionally, we adjusted (Model 2) for occupation for past LTPA, as well as BMI, comorbidity index, and MCI status at baseline for current LTPA. All covariates were treated as time-constant. To examine the effect of change or consistency of LTPA throughout life on AD risk, we further assigned the participants into the following groups as suggested in the literature[23, 24]: "always low" defined as both average past and current

LTPA level were low; “decreased”; “increased”; “always middle”; and “always high”. We classified participants as “ever-high” (either past or current high LTPA) or “never-high”. A separate classification of “ever-low” (either past or current low LTPA) was compared with participants who were “never-low”. We also examined vigorous, moderate, light LTPA in relation to AD risk, separately for current and past LTPA.

2.5.4 Supplementary Analyses—Effect modifications by sex and APOE were tested by including an interaction term into the Cox models, followed by stratified analyses. The majority (91 of 106) of the incident AD cases were Hispanics, thus effect modification analyses on race/ethnicity was not performed.

To reduce the potential recall bias of LTPA due to early-stage cognitive impairment, we limited analyses to 1187 participants who had at least 2 years of follow-up. We also performed analyses by excluding 269 participants with baseline MCI.

To examine whether change of LTPA during different life stages is associated with risk of AD, we calculated change of LTPA from early life (12–25 years) to current (longest change), change from early life (12–25 years) to late-middle life (>50 years) (early change), and change from late-middle life (>50 years) to current (late change).

To test robustness of past LTPA analyses, we analyzed past LTPA without using assumptions on frequency and duration of LTPA by coding raw reported frequency as ‘almost all time’ (coded as 3), ‘very frequent’(2), ‘frequently’(1), and ‘rarely or none (as reference)” (0), and calculated a total raw past LTPA frequency score by summing all three types of LTPA and all three age periods (ranging from 0–27, higher meaning more past LTPA).

All analyses were performed using PASW Statistics 25.0 (formerly SPSS Inc., Chicago, IL USA). Significance level was set at 0.05.

3. Results

3.1 Characteristics of the study participants

The 1345 participants included in the study were followed for an average of 4.13 (±1.92; range, 0.84–8.84) years, for a total of 5,566 person-years. Among them, 106 developed AD. About two-thirds (68%) of these participants were women, and the average age was 75.1 years. Over half of the participants were Hispanic, 20.9% were White and 23.6% were Black (Table 1).

Compared with those who remained non-demented, those who developed AD were more likely to be women, older, Hispanic, had lower education, had worse memory, had MCI, and were less likely to be physically active (Table 1).

For both current and past LTPA, those who had higher LTPA were younger, had more education, had better memory, and were less likely to have MCI. There was a higher proportion of Whites and lower proportion of Hispanics having high LTPA. Those having higher current LTPA were more likely to carry APOE ε4 allele, had fewer comorbidities,

lower BMI, and longer follow-up time. Those having higher past LTPA were more likely to be men (Tables S1 and S2).

Current LTPA was correlated with mean past LTPA (r=0.35, bootstrap 95%CI=0.36–0.45), early life LTPA (r=0.26, 95%CI=0.20–0.31), early-middle life LTPA (r=0.36, 95%CI=0.30–0.41), and late-middle life LTPA (r=0.57, 95%CI=0.52–0.61), all p<0.0001.

3.2 Cox Regression

Current and past LTPA—Current and past LTPA were associated with reduced risk of AD, with HR(95%CI)= 0.39(0.20–0.75) and 0.37(0.18–0.75) comparing the high with the low levels, respectively (Table 2, Model 1). The results remained similar in Model 2. Higher early life and late-middle life LTPA were associated with reduced AD risk.

Change of LTPA over time—Compared with “always low”, “increased” and “always high” were associated with reduced AD risk, with HR(95%CI)= 0.60 (0.36–0.99) and 0.28 (0.08–0.94), respectively (Table 3). Compared to “never-high”, “ever high” LTPA had a 60% reduction in AD risk; compared to “never-low”, “ever low” LTPA had a 63% increase in risk of AD (Table 3).

LTPA Intensity—Current light, past light, and past moderate LTPA were associated with reduced risk of AD (Table 4, Model 1).

3.3 Supplementary analyses

The interaction between sex/gender and current LTPA [HR(95%CI) for interaction=0.84 (0.42–1.65), p=0.61] or mean past LTPA [(HR(95%CI) for interaction=1.14 (0.59–2.20), p=0.71] was not significant. The interaction between *APOE* and current LTPA [(HR(95%CI) =0.92 (0.50–1.70), p=0.80] or mean past LTPA [(HR(95%CI) =1.12(0.64–1.96), p=0.70) was not significant.

Limiting analyses to 1187 participants who had at least 2 years of follow-up, both current and past LTPA were [comparing high vs. low HR(95%CI)=0.42(0.19–0.91), p=0.027; 0.41 (0.20–0.87), p=0.020, respectively, model 2] associated with reduced risk of AD.

Limiting 1076 subjects who did not have MCI at baseline (excluding 269 participants with MCI), high past LTPA had lower risk of AD than low past LTPA, HR=0.37 (95%CI=0.16–0.86, p=0.021, Model 2), and current LTPA was also associated with AD risk (comparing high with low, HR=0.46, 95%CI=0.21–0.98, p=0.044, Model 1; HR=0.49, 95%CI=0.22–1.12, p=0.09, Model 2).

Examining change of LTPA during different life stages (longest change, early change, late change), we found increased LTPA over time and always high LTPA were both associated with reduced risk of AD (supplementary Table S3).

Using total raw past LTPA frequency score, we found that higher LTPA was associated with lower risk of AD, HR=0.95 (95%CI=0.91–0.98; p=0.005 from model 1) for one unit change

in raw frequency score; and HR=0.50 (95%CI=0.28–0.91; p=0.022 from model 1) comparing high to the low tertile of the score.

4. Discussion

In the present study significant protective effect against AD was found for both current and past self-reported LTPA. In addition, increasing LTPA or always high LTPA throughout life was associated lower risk of AD compared to always low LTPA. Finally, light and moderate LTPA were associated with lower AD risk.

Our findings on current leisure-time LTPA in late-life (>65 years) are consistent with many other studies that show inverse associations between LTPA and the risk of AD among older adults [2–19]. Overall, with a few exceptions [26–32], the current evidence suggests a 40~60% reduction in AD risk by performing LTPA in older adults. Previous studies have found middle age [20–24] LTPA was associated with reduced risk of AD. We do not know the exact reason why early middle-age LTPA was not associated with risk of AD, but occupation-related PA may have confounded the LTPA-AD association during this age period when subjects were still at work. However, our results found that high LTPA in both early life and late-middle life were associated with reduced AD risk. One cross-sectional study found that, compared with those who were inactive at respective age (teenage, age 30, age 50, and old age), those who were active were less likely to be cognitively impaired [25]. Recently, a clinical trial of cognitively normal individuals aged 20–67 found improvements in both executive function and cortical thickness after 6 months of aerobic exercise, suggesting exercise may contribute to brain health in young adults [41]. From a public health point of view, it is important to promote LTPA even at young ages for protection against AD later in life.

Only a few prior studies have investigated the role of changes in LTPA habits throughout life [23, 25]. Previous studies found that maintaining a high level of LTPA[23, 24] or increasing LTPA after throughout life was associated with lower risk of dementia [23]. We confirmed such findings in the current study. Given the findings that increasing LTPA may protect against AD development, it is important to promote health education among those who did not participate in LTPA in the past. In addition, these findings also provide support for future intervention studies of LTPA in older adults regardless of past LTPA levels.

One previous study found that LTPA had a greater protective effect against AD in women than in men [3], and another study had the opposite result[23]. A recent meta-analysis concluded that there was no interaction between LTPA and sex/gender [29]. Some studies found protection of LTPA on AD among *APOE* ε4 non-carriers [23, 31]. We did not find significant interactions of LTPA with sex and APOE. Overall it remains unclear whether certain populations may benefit more from LTPA.

A key question in this research area is to determine the minimum amount of LTPA needed to have a beneficial effect on AD. Our findings suggest that at minimum, total energy expenditure should be high, but that this can be obtained from vigorous, moderate, or light intensity LTPA. We found light, but not moderate or vigorous, LTPA was associated with

reduced risk of AD. A case-control study found light exercise had reduced odds of dementia and AD when compared to those inactive[3]. It is also supported by the finding that low-intensity daily walking activity is associated with hippocampal volume in older adults.[42] A few other studies examined only vigorous LTPA, but not light or moderate LTPA, and found vigorous LTPA was associated with reduced risk of AD[14]. Nevertheless, the definition of intensity often varies across studies, and the amount of different intensity LTPAs are usually correlated or clustered within individuals, making it hard to disentangle their independent effects. Therefore, due to limited number and inconsistent results of studies examining detailed aspects of LTPA, it remains premature to determine which exact frequency, duration, and intensity are needed to reduce the risk or delay the onset of AD.

The mechanism for the LTPA benefits is unclear, but there are likely several pathways in which LTPA provides a protective effect.[43] LTPA has been found to have positive effects on synaptic plasticity and cognition.[44, 45] It has also been found to reduce rates of risk factors associate with AD such as hypertension, obesity, and diabetes, which can potentially be in the pathway from low LTPA to AD.[46] Furthermore, in animal models, LTPA has been linked to reductions in β-amyloid build up and stimulation of angiogenesis, brain perfusion and neurovascular integrity.[47–49]

There are a few limitations in our study. The study may be subjective to selection bias as participants who were less educated and older were less likely to complete follow-up evaluations. However, as these two factors were also associated with both increased AD risk and less LTPA in our study, the incomplete inclusion may have biased our results towards null. We did not have objective assessment of LTPA such as portable accelerometer at time of study initiation due to the difficulties in availability, cost, and acceptance in older adults. LTPA levels were self-reported and thus may subject to recall bias, particularly for past LTPA, even in cognitively healthy, non-demented individuals. For past LTPA, the age period “50 and above” in the questionnaire is ambiguous and may include a large range of life period. The current and past LTPA were estimated differently and may not be completely comparable. Furthermore, despite a longitudinal study design, lower LTPA may be a result of preclinical AD or other health and medical confounds existing at baseline [32]. To reduce the likelihood of reverse causation in the current study, we adjusted for multiple comorbidities, excluded prevalent MCI participants, and limited the analyses to those with two or more years of follow-up, and found the association of LTPA with lower AD risk remained consistent. While we adjusted for many potential confounders, residual confounding from unavailable variables such as diet may remain, although it seems they may act independently [6]. Another limitation of the study is the relatively short follow-up time and small number of incident AD cases (for example, only 3 subjects developed AD in the “always high” group), thus the effect modification analyses by sex/gender, APOE, and race/ethnicity were underpowered. We did not examine types of LTPA but a previous study showed amount of activity (energy expenditure), rather than the type of activity, was more important.[50]

There are many strengths of this study. We examined change of LTPA status over the life course and the intensity of LTPA on AD risk. The participants are from a multiethnic community-based population, thus increasing the generalizability to the increasingly diverse

U.S. population. The consensus diagnosis of AD was based on comprehensive assessments and standard research criteria. Furthermore, the study controlled for many potential confounders.

Conclusion

Our results provide support that higher LTPA throughout life is protective against AD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Data collection and sharing for this project was supported by the Washington Heights-Inwood Columbia Aging Project (WHICAP, PO1AG007232, R01AG037212, RF1AG054023, R00AG042483, R01AG059013) funded by the National Institute on Aging (NIA) and by the National Center for Advancing Translational Sciences, National Institutes of Health, through Grant Number UL1TR001873. This manuscript has been reviewed by WHICAP investigators for scientific content and consistency of data interpretation with previous WHICAP Study publications. We acknowledge the WHICAP study participants and the WHICAP research and support staff for their contributions to this study.

Non-standard abbreviations

AD	Alzheimer's Disease
LTPA	leisure time physical activity
MCI	mild cognitive impairment
MET	metabolic equivalent
WHICAP	Washington/Hamilton Heights-Inwood Columbia Aging Project

References

1. World Alzheimer Report. Alzheimer's Disease International; 2016.
2. Fabrigoule C, Letenneur L, Dartigues JF, Zarrouk M, Commenges D, Barberger-Gateau P. Social and leisure activities and risk of dementia: a prospective longitudinal study. J Am Geriatr Soc. 1995;43(5):485–90. [PubMed: 7730528]
3. Laurin D, Verreault R, Lindsay J, MacPherson K, Rockwood K. Physical activity and risk of cognitive impairment and dementia in elderly persons. Archives of neurology. 2001;58(3):498–504. [PubMed: 11255456]
4. Podewils LJ, Guallar E, Kuller LH, Fried LP, Lopez OL, Carlson M, et al. Physical activity, APOE genotype, and dementia risk: findings from the Cardiovascular Health Cognition Study. American journal of epidemiology. 2005;161(7):639–51. [PubMed: 15781953]
5. Larson EB, Wang L, Bowen JD, McCormick WC, Teri L, Crane P, et al. Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. Annals of internal medicine. 2006;144(2):73–81. [PubMed: 16418406]
6. Scarmeas N, Luchsinger JA, Schupf N, Brickman AM, Cosentino S, Tang MX, et al. Physical activity, diet, and risk of Alzheimer disease. Jama. 2009;302(6):627–37. [PubMed: 19671904]
7. Abbott RD, White LR, Ross GW, Masaki KH, Curb JD, Petrovitch H. Walking and dementia in physically capable elderly men. Jama. 2004;292(12):1447–53. [PubMed: 15383515]

8. Taaffe DR, Irie F, Masaki KH, Abbott RD, Petrovitch H, Ross GW, et al. Physical activity, physical function, and incident dementia in elderly men: the Honolulu-Asia Aging Study. The journals of gerontology Series A, Biological sciences and medical sciences. 2008;63(5):529–35.

9. Ravaglia G, Forti P, Lucicesare A, Pisacane N, Rietti E, Bianchin M, et al. Physical activity and dementia risk in the elderly: Findings from a prospective Italian study. Neurology. 2008;70(19_Part_2):1786–94. [PubMed: 18094335]

10. Kim KW, Park JH, Kim MH, Kim MD, Kim BJ, Kim SK, et al. A nationwide survey on the prevalence of dementia and mild cognitive impairment in South Korea. Journal of Alzheimer's disease : JAD. 2011;23(2):281–91. [PubMed: 21178286]

11. Gureje O, Oladeji B, Abiona T. Incidence and risk factors for late-life depression in the Ibadan Study of Ageing. Psychological medicine. 2011;41(9):1897–906. [PubMed: 21275087]

12. Buchman AS, Boyle PA, Yu L, Shah RC, Wilson RS, Bennett DA. Total daily physical activity and the risk of AD and cognitive decline in older adults. Neurology. 2012;78(17):1323–9. [PubMed: 22517108]

13. Verdelho A, Madureira S, Ferro JM, Baezner H, Blahak C, Poggesi A, et al. Physical activity prevents progression for cognitive impairment and vascular dementia: results from the LADIS (Leukoaraiosis and Disability) study. Stroke; a journal of cerebral circulation. 2012;43(12):3331–5.

14. Bowen ME. A prospective examination of the relationship between physical activity and dementia risk in later life. American journal of health promotion : AJHP. 2012;26(6):333–40. [PubMed: 22747314]

15. de Bruijn RF, Schrijvers EM, de Groot KA, Witteman JC, Hofman A, Franco OH, et al. The association between physical activity and dementia in an elderly population: the Rotterdam Study. European journal of epidemiology. 2013;28(3):277–83. [PubMed: 23385659]

16. Wang S, Luo X, Barnes D, Sano M, Yaffe K. Physical activity and risk of cognitive impairment among oldest-old women. The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry. 2014;22(11):1149–57. [PubMed: 23831179]

17. Kishimoto H, Ohara T, Hata J, Ninomiya T, Yoshida D, Mukai N, et al. The long-term association between physical activity and risk of dementia in the community: the Hisayama Study. European journal of epidemiology. 2016;31(3):267–74. [PubMed: 26857126]

18. Zhou Z, Fu J, Hong YA, Wang P, Fang Y. Association between exercise and the risk of dementia: results from a nationwide longitudinal study in China. BMJ Open. 2017;7(12):e017497.

19. Llamas-Velasco S, Contador I, Villarejo-Galende A, Lora-Pablos D, Bermejo-Pareja F. Physical Activity as Protective Factor against Dementia: A Prospective Population-Based Study (NEDICES). Journal of the International Neuropsychological Society : JINS. 2015;21(10):861–7. [PubMed: 26581797]

20. Andel R, Crowe M, Pedersen NL, Fratiglioni L, Johansson B, Gatz M. Physical exercise at midlife and risk of dementia three decades later: a population-based study of Swedish twins. The journals of gerontology Series A, Biological sciences and medical sciences. 2008;63(1):62–6.

21. Etgen T, Sander D, Huntgeburth U, Poppert H, Forstl H, Bickel H. Physical activity and incident cognitive impairment in elderly persons: the INVADE study. Arch Intern Med. 2010;170(2):186–93. [PubMed: 20101014]

22. Mehlig K, Skoog I, Waern M, Miao Jonasson J, Lapidus L, Bjorkelund C, et al. Physical activity, weight status, diabetes and dementia: a 34-year follow-up of the population study of women in Gothenburg. Neuroepidemiology. 2014;42(4):252–9. [PubMed: 24923622]

23. Tolppanen AM, Solomon A, Kulmala J, Kareholt I, Ngandu T, Rusanen M, et al. Leisure-time physical activity from mid- to late life, body mass index, and risk of dementia. Alzheimer's & dementia : the journal of the Alzheimer's Association. 2015;11(4):434–43 e6.

24. Palta P, Sharrett AR, Deal JA, Evenson KR, Gabriel KP, Folsom AR, et al. Leisure-time physical activity sustained since midlife and preservation of cognitive function: The Atherosclerosis Risk in Communities Study. Alzheimer's & dementia : the journal of the Alzheimer's Association. 2019;15(2):273–81.

25. Middleton LE, Barnes DE, Lui LY, Yaffe K. Physical activity over the life course and its association with cognitive performance and impairment in old age. J Am Geriatr Soc. 2010;58(7): 1322–6. [PubMed: 20609030]
26. Broe GA, Creasey H, Jorm AF, Bennett HP, Casey B, Waite LM, et al. Health habits and risk of cognitive impairment and dementia in old age: a prospective study on the effects of exercise, smoking and alcohol consumption. Australian and New Zealand journal of public health. 1998;22(5):621–3. [PubMed: 9744220]
27. Bae JB, Kim YJ, Han JW, Kim TH, Park JH, Lee SB, et al. Incidence of and risk factors for Alzheimer's disease and mild cognitive impairment in Korean elderly. Dement Geriatr Cogn Disord. 2015;39(1–2): 105–15. [PubMed: 25401488]
28. Verghese J, Lipton RB, Katz MJ, Hall CB, Derby CA, Kuslansky G, et al. Leisure activities and the risk of dementia in the elderly. The New England journal of medicine. 2003;348(25):2508–16. [PubMed: 12815136]
29. Morgan GS, Gallacher J, Bayer A, Fish M, Ebrahim S, Ben-Shlomo Y. Physical activity in middle-age and dementia in later life: findings from a prospective cohort of men in Caerphilly, South Wales and a meta-analysis. Journal of Alzheimer's disease : JAD. 2012;31(3):569–80. [PubMed: 22647258]
30. Wilson RS, Mendes De Leon CF, Barnes LL, Schneider JA, Bienias JL, Evans DA, et al. Participation in cognitively stimulating activities and risk of incident Alzheimer disease. Jama. 2002;287(6):742–8. [PubMed: 11851541]
31. Akbaraly TN, Portet F, Fustinoni S, Dartigues JF, Artero S, Rouaud O, et al. Leisure activities and the risk of dementia in the elderly: results from the Three-City Study. Neurology. 2009;73(11): 854–61. [PubMed: 19752452]
32. Sabia S, Dugravot A, Dartigues JF, Abell J, Elbaz A, Kivimaki M, et al. Physical activity, cognitive decline, and risk of dementia: 28 year follow-up of Whitehall II cohort study. Bmj. 2017;357:j2709. [PubMed: 28642251]
33. Taylor HL, Jacobs DR Jr., Schucker B, Knudsen J, Leon AS, Debacker G. A questionnaire for the assessment of leisure time physical activities. Journal of chronic diseases. 1978;31(12):741–55. [PubMed: 748370]
34. Stern Y, Andrews H, Pittman J, Sano M, Tatemichi T, Lantigua R, et al. Diagnosis of dementia in a heterogeneous population. Development of a neuropsychological paradigm-based diagnosis of dementia and quantified correction for the effects of education. Archives of neurology. 1992;49(5): 453–60. [PubMed: 1580806]
35. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology. 1984;34(7):939–44. [PubMed: 6610841]
36. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. Archives of neurology. 1999;56(3):303–8. [PubMed: 10190820]
37. Manly JJ, Tang MX, Schupf N, Stern Y, Vonsattel JP, Mayeux R. Frequency and course of mild cognitive impairment in a multiethnic community. Annals of neurology. 2008;63(4):494–506. [PubMed: 18300306]
38. Godin G, Shephard RJ. A simple method to assess exercise behavior in the community. Can J Appl Sport Sci. 1985;10(3):141–6. [PubMed: 4053261]
39. Sallis JF, Buono MJ, Roby JJ, Micale FG, Nelson JA. Seven-day recall and other physical activity self-reports in children and adolescents. Med Sci Sports Exerc. 1993;25(1):99–108. [PubMed: 8423762]
40. Jacobs DR Jr., Ainsworth BE, Hartman TJ, Leon AS. A simultaneous evaluation of 10 commonly used physical activity questionnaires. Med Sci Sports Exerc. 1993;25(1):81–91. [PubMed: 8423759]
41. Stern Y, MacKay-Brandt A, Lee S, McKinley P, McIntyre K, Razlighi Q, et al. Effect of aerobic exercise on cognition in younger adults: A randomized clinical trial. Neurology. 2019.

42. Varma VR, Chuang YF, Harris GC, Tan EJ, Carlson MC. Low-intensity daily walking activity is associated with hippocampal volume in older adults. Hippocampus. 2015;25(5):605–15. [PubMed: 25483019]

43. Phillips C, Baktir MA, Das D, Lin B, Salehi A. The Link Between Physical Activity and Cognitive Dysfunction in Alzheimer Disease. Phys Ther. 2015;95(7):1046–60. [PubMed: 25573757]

44. Gomez-Pinilla F, Vaynman S, Ying Z. Brain-derived neurotrophic factor functions as a metabotrophin to mediate the effects of exercise on cognition. The European journal of neuroscience. 2008;28(11):2278–87. [PubMed: 19046371]

45. Vaynman S, Ying Z, Gomez-Pinilla F. Hippocampal BDNF mediates the efficacy of exercise on synaptic plasticity and cognition. The European journal of neuroscience. 2004;20(10):2580–90. [PubMed: 15548201]

46. Kesaniemi YK, Danforth E Jr., Jensen MD, Kopelman PG, Lefebvre P, Reeder BA. Dose-response issues concerning physical activity and health: an evidence-based symposium. Med Sci Sports Exerc. 2001;33(6 Suppl):S351–8. [PubMed: 11427759]

47. Adiará PA, Perreau VM, Pop V, Cotman CW. Voluntary exercise decreases amyloid load in a transgenic model of Alzheimer's disease. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2005;25(17):4217–21. [PubMed: 15858047]

48. Swain RA, Harris AB, Wiener EC, Dutka MV, Morris HD, Theien BE, et al. Prolonged exercise induces angiogenesis and increases cerebral blood volume in primary motor cortex of the rat. Neuroscience. 2003;117(4):1037–46. [PubMed: 12654355]

49. Brown BM, Peiffer JJ, Taddei K, Lui JK, Laws SM, Gupta VB, et al. Physical activity and amyloid-beta plasma and brain levels: results from the Australian Imaging, Biomarkers and Lifestyle Study of Ageing. Molecular psychiatry. 2013;18(8):875–81. [PubMed: 22889922]

50. Thompson PD, Buchner D, Pina IL, Balady GJ, Williams MA, Marcus BH, et al. Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease: a statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity). Circulation. 2003;107(24):3109–16. [PubMed: 12821592]

Research in Context

Systematic review: The author reviewed previously published findings on leisure time physical activity and Alzheimer's disease or dementia. Previous findings have suggested the protective effect of physical activity, but few studies have examined past and current physical activity at the same time.

Interpretation: Our study showed significant protective effects of leisure time physical activity on Alzheimer's disease risk, suggesting the importance of leisure time physical activity throughout life.

Future Directions: Future longitudinal or interventional studies can help to further our understanding of the role of current leisure time physical activity in dementia prevention in older adults. Longitudinal studies with the leisure time physical activity information collected during early and mid-life are needed to verify our findings on past physical activity. Additionally, follow-up studies are needed to confirm the desirable frequency, duration, and intensity of physical activity for reducing dementia risk.

Highlights

- Both current and earlier life physical activity were independently associated with reduced risk of Alzheimer's disease (AD), with more leisure time physical activity (LTPA) leading to greater protective effects.
- Compared with always having low LTPA, increasing LTPA or maintaining a high LTPA throughout life was associated with lower risk of AD.
- While having a high amount of leisure time physical activity at some point in life was particularly beneficial, avoiding being physically inactive throughout life was also important for prevention of AD.
- There was health benefit in AD prevention by performing light and moderate LTPA.

Table 1.

Characteristics of study participants according to the Alzheimer's Disease status.

	No dementia	Incident AD‖	All	P- value
Number	1239	106	1345	/
Women, N(%)*	826 (67)	86 (81)	912 (68)	0.002
Age at baseline (years), mean (SD)	74.6 (5.99)	80.9 (6.85)	75.1 (6.30)	<0.0001
Race/Ethnicity, N(%)*				<0.0001
White	277(22.4)	4 (3.8)	281 (20.9)	
Black	307 (24.8)	10 (9.4)	317 (23.6)	
Hispanic	633 (51.1)	91 (85.8)	724 (53.8)	
Others	22 (1.8)	1 (10)	23 (1.7)	
Education (years), mean (SD)	11.06 (5.17)	6.44 (4.24)	10.70 (5.25)	<0.0001
≥1 Apolipoprotein E ε4, N(%)*	319 (25.8)	35 (33.0)	354 (26.3)	0.104
MCI, N(%)	234 (18.9)	35 (33.0)	269 (20.0)	<0.0001
Memory z-score, mean(SD)	0.42 (0.68)	−0.43 (0.64)	0.35 (0.71)	<0.0001
Body mass index (kg/m^2), mean (SD) †	29.51 (6.32)	29.75 (5.64)	29.53 (6.27)	0.719
Comorbidity score, mean (SD)	3.00 (1.64)	3.29 (1.60)	3.03 (1.64)	0.082
Current LTPA (MET- minutes/2wks), mean (SD)	1788 (3214)	514 (751)	1689 (3111)	<0.0001
Mean past LTPA (MET- minutes/2wks), mean (SD)	3945 (2859)	2034(1964)	3795(2846)	<0.0001
Past LTPA at age 12–25 (MET- minutes/2wks), mean (SD)	6080 (4101)	3678 (3675)	5890(4119)	<0.0001
Past LTPA at age 26–50 (MET- minutes/2wks), mean (SD)	3375 (3424)	1457(1810)	3224 (3366)	<0.0001
Past LTPA at age 50+ (MET- minutes/2wks), mean (SD)	2397 (2827)	968 (1585)	2285 (2776)	<0.0001
Duration of follow-up (years), mean(SD)	4.20 (1.92)	3.41 (1.69)	4.13 (1.92)	<0.0001

‖Two participants who developed other types of dementia were excluded from the analyses.

*N(%) indicate number (percentage) of subjects. Percentages may not equal 100% due to rounding. 1 subject missing APOE e4. 58 subjects missed information on BMI.

†Calculated as weight in kilograms divided by height in meters squared.

Table 2.

Cox Proportional Hazard Ratios for incident Alzheimer's Disease (AD) by Current and Past Leisure Time Physical Activity (LTPA) Levels

			Model 1		Model 2	
		AD/Total	**HR (95%CI)**	**P**	**HR (95%CI)**	**P**
Current LTPA	Low	49/331	Reference		Reference	
	Middle	43/536	0.69 (0.45–1.07)	0.101	0.71 (0.44–1.15)	0.169
	High	12/463	**0.39 (0.20–0.75)**	**0.005**	**0.42 (0.21–0.86)**	**0.017**
	p-trend			**0.003**		**0.014**
Mean past LTPA	Low	64/449	Reference			
	Middle	32/448	0.94 (0.6–1.48)	0.794	0.99 (0.63–1.57)	0.985
	High	10/448	**0.37 (0.18–0.75)**	**0.005**	**0.40 (0.20–0.80)**	**0.017**
	p-trend			**0.011**		**0.022**
Past LTPA at age 12–25 (early life)	Low	59/441	Reference		Reference	
	Middle	32/457	0.92 (0.58–1.44)	0.705	0.93 (0.59–1.47)	0.744
	High	15/447	**0.49 (0.27–0.89)**	**0.019**	**0.52 (0.28–0.95)**	**0.032**
	p-trend			**0.028**		**0.046**
Past LTPA at age 26–50 (early-middle life)	Low	60/470	Reference		Reference	
	Middle	34/441	0.90 (0.57–1.41)	0.647	0.94 (0.59–1.49)	0.784
	High	12/434	0.59 (0.30–1.14)	0.116	0.62 (0.32–1.20)	0.156
	p-trend			0.140		0.198
Past LTPA at age 50 above (late-middle life)	Low	72/472	Reference		Reference	
	Middle	24/439	**0.51 (0.31–0.84)**	**0.008**	**0.55 (0.33–0.90)**	**0.017**
	High	10/434	**0.32 (0.16–0.64)**	**0.001**	**0.34 (0.17–0.70)**	**0.003**
	p-trend			**<0.0001**		**0.001**

Abbreviation: CI, confidence interval; HR, hazard ratio.

*Model 1 was adjusted for age at baseline, sex, ethnicity, education, apolipoprotein E ε4 allele, and Model 2 was additionally adjusted for occupation (for all four past LTPA variables), as well as MCI status at baseline, body mass index, and comorbidities including psychiatric diseases, diabetes, insulin treatment, heart disease, hypertension, head injury, depression, smoking, heavy alcohol drinking (for current LTPA).

All statistical significance ($p \leq 0.05$) results are shown in bold.

Table 3.

Cox proportional hazard ratios for incident Alzheimer's disease (AD) by change of leisure time physical activity (LTPA) throughout life.

Change of LTPA from average past to current	AD/Total	Model 1		Model 2	
		HR (95%CI)	P	HR (95%CI)	P
Always low	37/185	Reference		Reference	
Decreased	19/312	0.64 (0.36–1.14)	0.126	0.58 (0.30–1.13)	0.109
Increased	32/400	**0.60 (0.36–0.99)**	**0.046**	**0.56 (0.32–0.98)**	**0.043**
Always moderate	13/201	0.67 (0.34–1.29)	0.229	0.74 (0.37–1.47)	0.390
Always high	3/232	**0.28 (0.08–0.94)**	**0.04**	0.31 (0.09–1.06)	0.062
Never High	85/659	Reference		Reference	
Ever High	19/671	**0.40 (0.24–0.68)**	**0.001**	**0.46 (0.27–0.80)**	**0.006**
Never Low	28/736	Reference		Reference	
Ever Low	76/594	**1.63 (1.03–2.59)**	**0.037**	1.33 (0.81–2.17)	0.254

Abbreviation: CI, confidence interval; HR, hazard ratio.

*Model 1 was adjusted for age at baseline, sex, ethnicity, education, apolipoprotein E ε4 allele, and Model 2 was additionally adjusted for occupation, MCI status at baseline, body mass index (calculated as weight in kilograms divided by height in meters squared), and comorbidities including psychiatric diseases, diabetes, insulin treatment, heart disease, hypertension, head injury, depression, smoking, heavy alcohol drinking).

†Statistical significant ($p \leq 0.05$) results are shown in bold.

Table 4.

Cox proportional hazard ratios for incident Alzheimer's Disease (AD) by intensity of leisure time physical activity levels.

LTPA	Level	AD/total	HR (95%CI)	p	HR (95%CI)	p
Current vigorous	No	101/1179	Reference		Reference	
	Yes	3/148	0.84 (0.26–2.73)	0.77	1.01 (0.31–3.28)	0.99
Current moderate	No	98/1093	Reference		Reference	
	Yes	6/230	0.64 (0.28–1.49)	0.30	0.74 (0.32–1.75)	0.50
Current light	Low	50/362	Reference		Reference	
	Middle	36/521	0.72 (0.45–1.05)	0.08	0.69 (0.42–1.14)	0.15
	High	**17/437**	**0.46 (0.26–0.81)**	**0.008**	**0.47 (0.25–0.88)**	**0.018**
	p-trend			**0.005**		**0.015**
Past vigorous	Low	70/551	Reference		Reference	
	Middle	21/358	0.81 (0.49–1.36)	0.43	0.81 (0.48–1.36)	0.43
	High	15/436	0.59 (0.33–1.05)	0.07	0.63 (0.35–1.11)	0.11
	p-trend			0.07		0.10
Past moderate	Low	55/415	Reference		Reference	
	Middle	39/488	0.93 (0.61–1.43)	0.75	0.95 (0.61–1.47)	0.81
	High	12/441	**0.42 (0.22–0.80)**	**0.008**	**0.43 (0.23–0.83)**	**0.01**
	p-trend			**0.02**		**0.02**
Past light	Low	50/395	Reference		Reference	
	Middle	36/485	0.72 (0.46–1.11)	0.14	0.76 (0.49–1.19)	0.23
	High	20/465	**0.53 (0.30–0.95)**	**0.03**	0.59 (0.33–1.07)	0.08
	p-trend			**0.02**		0.07

Abbreviation: CI, confidence interval; HR, hazard ratio.

*Model 1 was adjusted for age at baseline, sex, ethnicity, education, apolipoprotein E ε4 allele, and Model 2 was additionally adjusted for occupation (for all four LTPA variables), as well as MCI status at baseline, body mass index, and comorbidities including psychiatric diseases, diabetes, insulin treatment, heart disease, hypertension, head injury, depression, smoking, heavy alcohol drinking (for current LTPA variables).

†Statistical significant (p≤0.05) results are shown in bold.