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Dose-response relationship between late-life physical activity and incident dementia: a pooled analysis of 10 cohort studies of memory in an international consortium

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AUTHOR CONTRIBUTION

DD, PSS, MG, MNH, MFLC, TPN, OG, SS, NS, HB, RBL were responsible for study conceptualization and design. WW, ZX, EJ, TPN, XG, QG, OG, AFML, NFMR, NS, CAA, MY, RBL, MJK were responsible for data collection. WW, ZX, TPN, XG, QG, NS, JDC, MJK, DML were responsible for data curation. WW and DD were responsible for data validation. WW, TPN, XG, QG, SS, MJK, DML were responsible for project administration. DD, QZ, TPN, OG, NS, PSS were responsible for funding acquisition. WW, DD, JL were responsible for data analysis. WW and DD were responsible for original draft. All authors contributed to data interpretation, reviewed, and approved the final draft of the paper. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Abstract

INTRODUCTION: Though consistent evidence suggests that physical activity may delay dementia onset, the duration and amount of activity required remains unclear.

METHODS: We harmonized longitudinal data of 11988 participants from 10 cohorts in 8 countries to examine the dose-response relationship between late-life physical activity and incident dementia among older adults.

RESULTS: Using no physical activity as a reference, dementia risk decreased with duration of physical activity up to 3.1–6.0 hours/week (HR 0.88, 95% CI 0.67–1.15 for 0.1–3.0 hours/week; HR 0.68, 95% CI 0.52–0.89 for 3.1–6.0 hours/week), but plateaued with higher duration. For the amount of physical activity, a similar pattern of dose-response curve was observed, with an inflection point of 9.1–18.0 metabolic equivalent value (MET)-hours/week (HR 0.92, 95% CI 0.70–1.22 for 0.1–9.0 MET-hours/week; HR 0.70, 95% CI 0.53–0.93 for 9.1–18.0 MET-hours/week).

DISCUSSION: This cross-national analysis suggests that performing 3.1–6.0 hours of physical activity and expending 9.1–18.0/MET-hours of energy per week may reduce dementia risk.

Keywords

physical activity; dementia; cohort; population-based; dose-response; pooled analysis

1. INTRODUCTION

Dementia is one of the major causes of disability and dependency among older people because it affects memory, thinking, behavior, and ability to perform everyday activities.[1] Currently over 50 million people are living with dementia worldwide, and the number is estimated to approach 152 million by 2050.[2] Besides the development of effective medications, several modifiable risk factors could be targetted as potential means to mitigate the growing disease burden as the population ages.

Physical activity is defined as any bodily movement produced by skeletal muscles that requires energy expenditure.[3] Physical inactivity, together with 11 other modifiable risk factors, accounts for around 40% of worldwide dementias, which consequently could theoretically be prevented or delayed, according to the 2020 report of the Lancet

Commission on dementia prevention, intervention, and care.[4] Both the World Health Organization (WHO) guideline and the Lancet Commission report 2020 suggest that older adults keep physically active to prevent dementia.[4,5] However, there is no recommended dose of physical activity.

Understanding the dose-response association between physical activity and dementia is essential to both the design of intervention studies and the development of evidence-based guidelines for physical activity. A few previous studies have examined the potential dose-response relationship between late-life physical activity and dementia risk.[6–16] However, many studies did not collect detailed information on the duration, frequency, and intensity of physical activity for the calculation of amount (the product of duration, frequency, and intensity), instead measuring only the frequency or duration of physical activity.[6–12] In a few studies that did calculate the amount, the categorization of physical activity varied considerably and the results were inconsistent.[15,16] This makes it difficult to compare results across previous studies based on heterogeneous assessments and disparate categorizations of physical activity. Therefore, the exact shape of the dose-response curve for late-life physical activity and dementia is not yet understood.

Cohort Studies of Memory in an International Consortium (COSMIC) combines data from population-based longitudinal cohort studies to identify common risk and protective factors for dementia and cognitive decline.[17] This consortium provided us the opportunity to adopt a uniform approach to calculating and categorizing physical activity across multiple cohorts. To examine the dose-response association between late-life physical activity and the risk of incident dementia, we conducted a pooled analysis based on 10 cohorts from COSMIC.

2. METHODS

2.1. Study populations

We included 10 COSMIC member cohort studies (Figure 1): Sacramento Area Latino Study on Aging (SALSA),[18] Monongahela–Youghiogheny Healthy Aging Team (MYHAT),[19] and Einstein Aging Study (EAS)[20] in the USA; Bambuí Health and Aging Study (BHAS)[21] in Brazil; Ibadan Study of Aging (ISA)[22] in Nigeria; Hellenic Longitudinal Investigation of Aging and Diet (HELIAD)[23] in Greece; The Longitudinal Study on Neuroprotective Model for Healthy Longevity (LRGS TUA)[24] in Malaysia; Singapore Longitudinal Aging Study-2 (SLAS2)[25] in Singapore; Shanghai Aging Study (SAS)[26] in China; and Sydney Memory and Aging Study (MAS)[27] in Australia. Profiles of the 10 cohorts are shown in Table 1.

Cohorts were included if they (1) were willing to participate in the current study; (2) included adults aged ≥55 years recruited from the community; (3) evaluated cognitive function at baseline and at least one wave of follow-up (at least one-year interval); (4) measured physical activity at baseline through questionnaires; (5) collected data on risk factors or confounders related to dementia (age, sex, years of education, apolipoprotein E (APOE) genotype, body mass index (BMI), current smoking status, depression, history of hypertension, diabetes, and stroke) at baseline. Cohorts were excluded if they 1) did not inquire about information on the duration and type of physical activity in the questionnaires; 2) did not investigate physical activity during active recreation and sport, as well as for

transport. Initially, 13 cohorts met the inclusion criteria, but 2 were excluded due to a lack of data on the duration of physical activity, 1 was excluded due to a lack of complete information on physical activity during active recreation and sport, as well as for transport.

Participants were excluded from our analyses if they (1) had incomplete information on physical activity; (2) were not able to complete the cognitive function assessment or were diagnosed with dementia at baseline; (3) were lost to follow-up (Supplementary Table 1).

This study was approved by the University of New South Wales Human Research Ethics Committee (HC 12446 and HC 17292). All cohorts contributing data were approved by their respective institutional review boards, and all participants provided informed consent.

2.2. Measurement of the duration and amount of physical activity

In all the 10 cohort studies, physical activity data were obtained via self-reported questionnaires at baseline. This included physical activity during active recreation and sport, as well as for transport. The survey questionnaires inquired the duration and/or the frequency of various activities typically engaged in (Supplementary Table 2).

For each type of physical activity, we assigned an intensity unit (metabolic equivalent, MET) based on its rate of energy expenditure according to the compendium of physical activities (Supplementary Table 3).[28] One MET is defined as one kcal/kg/hour and is roughly equivalent to the energy cost of sitting quietly.[28] For example, walking was assigned a MET value of 3.0 and jogging was assigned a MET value of 6.0. The product of the duration (in hours) and intensity yields the amount of physical activity (in MET-hours). For the total duration of physical activity, we summed the hours per week across all activity types engaged in. For the total amount of physical activity, we summed the MET-hours per week across all activity types engaged in.[29,30]

2.3. Neuropsychological testing, functional ability, and dementia diagnosis

At baseline, most cohort studies administered a battery of neuropsychological tests for each participant (Supplementary Table 4). Activities of Daily Living and/or Instrumental Activities of Daily Living were used for evaluating the functional ability among the cohorts (Supplementary Table 4). Dementia was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, 4th version (DSM-IV) in SAS, SLAS2, HELIAD, EAS, and MAS.[20,23,25–27] MYHAT used the Clinical Dementia Rating (CDR) scale to diagnose dementia.[19] Dementia was based on a Mini-Mental State Examination (MMSE) score of 13 or lower in BHAS[21] and 14 or lower in LRGS TUA.[24] ISA applied the adapted Ten-Word Delay Recall Test (10-WDRT) and the Clinician Home-based Interview (CHIF) to assess cognitive function[31], and a psychiatrist reviewed all available information to determine the presence or absence of dementia.[22] The dementia diagnosis criteria of SALSA included clinically significant impairment in two or more separate cognitive domains that included a decline from premorbid function, and clinically significant impairment of independent functioning.[18]

2.4. Assessment of covariates at baseline

All 10 cohort studies collected data on demographic characteristics (age, sex, years of education), current smoking status, and medical history (self-reported history of hypertension, diabetes, and stroke) of participants at baseline. BMI was recorded by all except ISA, and APOE genotype was obtained by all except ISA and LRGS TUA. Depression was defined as a score ≥ 6 on the 15-item version of the Geriatric Depression Scale (GDS-15) by SLAS2, HELIAD, LRGS TUA, EAS, and MAS,[20,23–25,27] ≥ 16 on the Center for Epidemiologic Studies Depression Scale (CESD) by SAS and SALSA,[18,26] ≥ 5 on the modified CESD (mCESD) by MYHAT,[19] >4 on the 12-item General Health Questionnaire (GHQ-12) by BHAS,[21] and ≥ 10 on the 30-item version of the Geriatric Depression Scale (GDS-30) by ISA.[22]

2.5. Follow-up procedure

Cognitive function was evaluated and dementia was diagnosed at follow-up as per baseline. In SALSA, MYHAT, EAS, BHAS, LRGS TUA, and MAS, participants were followed every 12 to 24 months for a median of 3 to 11 years.[18–21,24,27] In ISA, SAS, HELIAD, and SLAS2, follow-up visits were conducted once after baseline. The median follow-up years ranged from 3 to 6 years.[22,23,25,26]

2.6. Statistical analysis

The mean and the standard deviation (SD) or median (IQR) and numbers with frequencies (%) were used to describe continuous and categorical variables, respectively. Follow-up time was the time from baseline to the assessment when dementia was diagnosed or to the final assessment in those not diagnosed with dementia. The incidence rate of dementia was calculated as the number of new-onset cases divided by the cumulative person-years of follow-up. Density plots were generated to show the distribution of the duration and amount of physical activity across cohorts and in the pooled population. Restricted cubic splines with four knots were fitted to determine the cut-off values of the duration and amount of physical activity (Figure 2B). For the duration of physical activity, we identified an inflection point of 6.0 hours/week. There was an initial steeper decline in the adjusted hazard ratio (HR) before 6.0 hours/week, followed by a gradual linear decline. Since the point of 6.0 hours/week split the population into about 60 percent and 40 percent, we created five levels of the duration of physical activity: level 1, 0.0 hours/week (N=2039, 17%); level 2, 0.1–3.0 hours/week (N=2654, 22%); level 3, 3.1–6.0 hours/week (N=2240, 19%); level 4, 6.1–11.0 hours/week (N=2633, 22%); and level 5, >11.0 hours/week (N=2422, 20%). Similarly, an inflection point of 18.0 MET-hours/week splitting the population into about 60 percent and 40 percent was identified. Five levels of amount were determined: level 1, 0.0 MET-hours/week (N=2039, 17%); level 2, 0.1–9.0 MET-hours/week (N=2315, 19%); level 3, 9.1–18.0 MET-hours/week (N=2072, 17%); level 4, 18.1–36.0 MET-hours/week (N=2839, 24%); and level 5, >36.0 MET-hours/week (N=2723, 23%). Multiple Cox regression models were used to estimate the HRs and 95% confidence intervals (CIs), with the lowest duration (0 hours/week) or amount (0 MET-hours/week) as the reference group. Model 1 adjusted for age, sex, years of education, and cohort. Model 2 further adjusted for BMI, APOE ε4, hypertension, diabetes, stroke, and depression. ISA and LRGS TUA did

not enter into model 2 because of missing information on BMI and APOE ε4. Proportional hazard assumptions were assessed with tests based on Schoenfeld residuals. Sensitivity analysis was conducted by excluding dementia cases identified within the first two years of follow-up. Statistical analyses were done using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). Statistical significance was set at $p<0.05$ (two-tailed).

3. RESULTS

During a median of 5-year follow-up, 11988 participants were successfully followed, 5607 participants were lost to follow-up. The comparison of the baseline characteristics between the two groups is shown in Supplementary Table 5. Participants who were lost to follow-up had less education and amount of physical activity, lower BMI, and a higher prevalence of stroke. No significant differences were observed for age, proportion of male participants, duration of physical activity, and prevalence of smoking, hypertension, diabetes, and depression.

Table 2 shows the baseline characteristics and the follow-up cognitive functioning of participants in each cohort and the pooled population (N=11988). Among the pooled population, participants spent a median of 4.3 hours (IQR: 1.3–9.5) per week doing physical activity, resulting in a median amount of 15.7 MET-hours/week (IQR: 4.5–33.5). Both duration and amount of physical activity varied among cohorts (Figure 2A). Participants from HELIAD were the least active, getting only one sixth as much time as that of their counterparts from SAS, SALSA, and SLAS2, who spent approximately one hour a day doing physical activity. During a median of 5-year follow-up, 800 cases of dementia were diagnosed. The incidence rate of dementia was 12.1 (95% CI: 11.3–13.0) per 1 000 person-years.

The forest plots in Figure 3 show dose-response relationships of both the duration and amount of physical activity with the risk of incident dementia. For the duration of physical activity, after adjusting for age, sex, years of education, and cohort (model 1), there was an initial large reduction in HR from 0.1 to 6.0 hours/week (HR 0.80, 95% CI 0.65–0.98 for 0.1–3.0 hours/week; HR 0.70, 95% CI 0.56–0.87 for 3.1–6.0 hours/week), followed by a gradual decline (HR 0.62, 95% CI 0.49–0.77 for 6.1–11.0 hours/week; HR 0.63, 95% CI 0.50–0.81 for >11.0 hours/week). In model 2 where APOE ε4, BMI, smoking, hypertension, diabetes, stroke, and depression were added, the risk of dementia decreased with duration of physical activity up to 3.1–6.0 hours/week (HR 0.88, 95% CI 0.67–1.15 for 0.1–3.0 hours/week; HR 0.68, 95% CI 0.52–0.89 for 3.1–6.0 hours/week), but plateaued with higher duration (HR 0.68, 95% CI 0.51–0.90 for 6.1–11.0 hours/week; HR 0.68, 95% CI 0.50–0.93 for >11.0 hours/week). For the amount of physical activity, after adjusting for age, sex, years of education, and cohort (model 1), there was a steady gradual decline in HR (HR 0.82, 95% CI 0.66–1.01 for 0.1–9.0 MET-hours/week; HR 0.70, 95% CI 0.56–0.87 for 9.1–18.0 MET-hours/week; HR 0.67, 95% CI 0.54–0.83 for 18.1–36.0 MET-hours/week; HR 0.58, 95% CI 0.46–0.74 for >36.0 MET-hours/week). In model 2 where APOE ε4, BMI, smoking, hypertension, diabetes, stroke, and depression were added, the risk of dementia decreased with amount of physical activity up to 9.1–18.0 MET-hours/week (HR 0.92, 95% CI 0.70–1.22 for 0.1–9.0 MET-hours/week; HR 0.70, 95% CI 0.53–0.93 for 9.1–18.0

MET-hours/week), then plateaued with higher amount (HR 0.70, 95% CI 0.53–0.92 for 18.1–36.0 MET-hours/week; HR 0.63, 95% CI 0.46–0.85 for >36.0 MET-hours/week).

These results were essentially unchanged in sensitivity analysis excluding individuals diagnosed with dementia within 2 years of baseline (Figure 4).

4. DISCUSSION

This cross-national analysis showed a dose-response relationship of late-life physical activity with the risk of incident dementia in 10 population-based cohorts, covering 8 countries from 5 continents. Dementia risk decreased with duration/amount of physical activity up to 3.1–6.0 hours/9.1–18.0 MET-hours per week, but plateaued with higher doses. Performing >3.0 hours or >9.0 MET-hours of physical activity per week was associated with a significantly lower risk of dementia, compared to no physical activity. Meanwhile, performing physical activity beyond 6.0 hours or 18.0 MET-hours may not provide additional protective effects, compared to performing physical activity 3.1–6.0 hours or 9.1–18.0 hours per week.

A major strength of this study is the cross-national data source from 10 population-based cohorts in 8 countries from 5 continents. All the cohorts collected detailed information on the duration and/or frequency of various physical activities via self-reported questionnaires. The combined data included both the most active and inactive older adults, making it possible to examine the dose-response curve in a full range of duration and amount of physical activity. We assigned each type of activity a specific MET value, and adopted a uniform approach to calculating and categorizing the duration and amount of physical activity across cohorts. The multiple population-based cohorts from diverse geographical, ethnic, genetic, and socioeconomic groups not only provide a sample size with suitable statistical power but also verify the general applicability of our findings.

Previous studies had not clarified the relationship between the dose of late-life physical activity and the risk of incident dementia. This could be partially attributed to the difficulty of obtaining consistent, detailed information about physical activity. The majority of previous studies measured only one or two components of late-life physical activity (BOX). Some measured only the frequency of physical activity[6–9] while others measured the weighted duration of physical activity.[10–12] Some studies assessed the combination of frequency and intensity of physical activity.[13,14] Several studies calculated the amount of physical activity, although the categorization varied and the results were inconsistent.[15,16] The heterogeneous and sometimes imprecise assessments and disparate categorizations of late-life physical activity in previous studies make it difficult to compare their results and draw a conclusion on the dose-response association for late-life physical activity and the risk of incident dementia.

Overcoming the above-mentioned issues by adopting a uniform approach to calculating and categorizing physical activity across 10 cohorts, our study shows dose-response relationships of both the duration and amount of late-life physical activity with the risk of incident dementia. The recently published Lancet Commission 2020 and WHO guidelines for risk

reduction of cognitive decline and dementia suggest that older adults keep physically active but do not give specific recommendations on the duration or amount.[4,5] According to our results, the risk of dementia decreased with duration/amount of physical activity up to 3.1–6.0 hours/9.1–18.0 MET-hours per week, but plateaued with higher doses. As people age, their ability to undertake physical activity gradually declines due to an age-related reduction in the functional capacity of the cardiorespiratory and muscular systems. Moreover, the greater the dose of physical activity, the greater the risk of injury and harm. Therefore, when attempting to establish an optimal dose of physical activity for the older population, consideration should be given not only to the dose that induces the greatest cognitive benefit but also to the potential risks. Our findings suggest that older adults could do 3.1–6.0 hours or 9.1–18.0 MET-hours of physical activity per week, for dementia prevention. As an example, to meet the amount of 9.1–18.0 MET-hours, older adults could walk (MET=3) for 3.0–6.0 hours or carry out other physical activities in which they typically engaged for a specific length of time per week.

The Whitehall II cohort study showed no association between physical activity and risk of dementia over an average 28-year follow-up.[32] One potential explanation for the inconsistent findings might be that the Whitehall II cohort study measured midlife physical activity (aged 35–55 years). Our study measured late-life physical activity. Work-related physical activity was not investigated in both studies. However, when at midlife, work-related physical activity might constitute a considerable part of the total physical activity. In such a case, misclassification of physical activity level might happen, and this could have biased the findings toward a non-significant association in the Whitehall II cohort study. Younger people are usually more active and willing to participate in various activities. Thus, there may be no significant reduction in physical activity among young people. Besides, cognitive declines in late life may precede functional declines and reduce engagement in various physical activities. Additional investigations of mechanisms linking physical activity to cognitive ability might be useful to explain the difference. The effect of midlife and late-life physical activity on dementia might also be different.

Our findings are consistent with evidence supporting the benefits of regular physical activity in preventing cognitive impairment and dementia. Several pathways have been proposed to account for the neuroprotective and neuroplastic effects of physical activity in the brain, including elevated neurotrophin levels, improved vascularization, and mediation of inflammation.[33] In some animal studies using aerobic exercise as an intervention, increased expression of brain-derived neurotrophic factor (BDNF) and its receptor and mRNA was observed in the hippocampus.[34] Physical activity enhances hippocampal insulin-like growth factor (IGF) gene expression and increases serum levels of both IGF and vascular endothelial growth factor (VEGF), which have important roles in angiogenesis and neurogenesis.[35] Physical activity improves the overall immune condition of the brain by reducing brain inflammation in response to stroke or peripheral infection and reducing the load of amyloid beta in the brain.[36]

Our results should be interpreted with caution under the following limitations. First, we cannot make firm causal conclusions based on our observational study. Randomized trials (RCTs) with multiple arms provide the highest evidence to determine the optimal physical

activity dosage. In the absence of such RCTs, this cross-national analysis may provide important evidence to establish an informed physical activity recommendation. Second, the diagnostic criteria varied across the 10 cohorts. Compared to SAS, SLAS2, HELIAD, EAS, and MAS which used DSM-IV[20,23,25–27], dementia diagnosis might be less precise in BHAS[21], LRGS TUA[24], ISA[31], and MYHAT[19]. The diagnosis criteria of SALSA may be close to DSM-IV because it included clinically significant impairment of cognitive domains and independent functioning.[18] Thus, varying degrees of misclassification might happen in the 10 cohorts and bias the association. Third, there are four key domains of physical activity —i.e. for work, in the household, for transport, and during leisure time.[37] We were only able to include the latter two domains in our analyses because only these two domains were collected by all participating cohorts. Therefore, the duration and amount of physical activity might have been underestimated in our study. However, since the mean age of participants at baseline was greater than 65 years in all studies,work-related physical activity might have a limited contribution to total physical activity. Fourth, the number of activities available on the questionnaires differed across cohorts. Asking about more types of physical activity in cohorts such as BHAS and EAS is likely to have produced higher estimates of duration and amount than the actual level. Measurement error and misclassification of the duration and amount could bias the findings toward a less significant association. Fifth, self-reported physical activity measures used in our study are subject to recall bias and over-reporting, which may mask the genuine relationship between physical activity and dementia risk, and potentially explain the limited benefit of higher doses of physical activity. Pooled analysis focusing on studies with objective physical activity data, i.e. accelerometers or pedometers, could provide more solid evidence to explore the dose-response relationship between physical activity and incident dementia. Sixth, participants of the 10 cohorts were from different countries and regions with diverse ethnic, genetic, and socioeconomic backgrounds. Therefore, despite adjustment for important covariates in our analyses, the possibility of residual confounding from unmeasured variables cannot be completely discounted, such as race/ethnicity, diet, hearing loss, air pollution, etc. In addition, physically active people are usually younger than inactive people and have other healthy behaviors such as a lower rate of obesity, healthier diets, and less cigarette smoking and alcohol drinking. However, some of the participants may conceal intentionally their unhealthy lifestyles in the questionnaires which would affect considerably the adjustment for these confounding factors. Seventh, because of a lack of information, we were not able to adjust for physical function, which may be a potential confounder. Eighth, ISA and LRGS TUA did not enter into model 2 due to a lack of data on BMI and/or APOE ε4. Therefore, model 2 was limited to smaller sample size. However, we have rerun model 2 (all 10 cohorts were included) without adjusting for BMI and APOE ε4 and the results remain similar to those of the original model 2 (Supplementary Figure 1). Ninth, 5607 (31.9%) participants were lost to follow-up. They had less education and amount of physical activity, lower BMI, and a higher prevalence of stroke, compared to those who were successfully followed. Since less education and amount of physical activity, lower BMI, and stroke are all potential risk factors of dementia, participants who were lost to follow-up might have had a higher incidence of dementia than those who were successfully followed. Our estimated association between physical activity and the risk of dementia may have been underestimated. Tenth, a previous study of a female population showed that physical activities are independently

associated with reduced risk of dementia and dementia subtypes.[38] In our study, 42.1% of the participants were male. Males performed a significantly higher level of physical activity than females (median MET-hours/week 21.0 vs. 12.0, respectively). It is reasonable to speculate that the optimal dosage between males and females might be different. Although males performed a significantly higher level of physical activity than females, males usually have more unhealthy behaviors, such as alcohol drinking and smoking. Thus, the relationship between physical activity and dementia risk among males is susceptible to these confounding factors. However, we did not conduct a subgroup analysis for gender because the aim of the current analysis was to examine the dose-response association between late-life physical activity and the risk of incident dementia. Future studies with larger sample sizes sufficient for subgroup analyses may explore any gender difference. Last, the median follow-up period of 5.0 years in the current study was not long enough to avoid reverse causality. Dementia is an evolving disease that may start decades before any clinical symptom manifests. There is a possibility that individuals in the preclinical phase of dementia might reduce their engagement in physical activity. Though the sensitivity analysis was conducted by excluding participants who were diagnosed with dementia in the first 2 years of follow-up, and the magnitude of the protective association was not significantly attenuated, it still could not entirely rule out the role of reverse causation.

5. CONCLUSION

This cross-national analysis showed a dose-response relationship of late-life physical activity with the risk of incident dementia in 10 population-based cohorts. Dementia risk decreased with duration/amount of physical activity up to 3.1–6.0 hours/9.1–18.0 MET-hours per week, but plateaued for higher doses. Our results suggest that performing 3.1–6.0 hours of physical activity and expending 9.1–18.0/MET-hours of energy per week may reduce dementia risk, while performing physical activity more than 6.0 hours or 18.0 MET-hours per week may not provide additional protective benefits among older adults. Further cross-national studies with uniform protocols, larger sample sizes, longer follow-up periods, objective physical activity data, as well as multi-armed RCTs, are encouraged to attribute the causation between physical activity and dementia and examine the dose-response effect.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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COSMIC management: The head of COSMIC is Perminder S. Sachdev, and the Study Co-Ordinator is Darren M. Lipnicki. The Research Scientific Committee leads the scientific agenda of COSMIC and provides ongoing support and governance; it is comprised of member study leaders (in alphabetical order): Kaarin Anstey, Carol Brayne, Henry Brodaty, Liang-Kung Chen, Erico Costa, Michael Crowe, Oscar Del Brutto, Ding Ding, Jacqueline Dominguez, Mary Ganguli, Antonio Guaita, Maëlenn Guerchet, Oye Gureje, Jacobijn Gussekloo, Mary Haan, Hugh Hendrie, Ann Hever, Ki-Woong Kim, Seb Koehler, Murali Krishna, Linda Lam, Bagher Larijani, Richard Lipton, Juan Llibre-Rodriguez, Antonio Lobo, Richard Mayeux, Kenichi Meguro, Vincent Mubangizi, Toshiharu Ninimiya, Stella-Maria Paddick, Maria Skaalum Petersen, Ng Tze Pin, Steffi Riedel-Heller, Karen Ritchie, Kenneth Rockwood, Nikolaos Scarmeas, Marcia Scazufca, Suzana Shahar, Xiao Shifu, Kumagai Shuzo, Ingmar Skoog, Yuda Turana.

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DECLARATION OF INTERESTS

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of Australia. He is a member of the Advisory Committee in Biogen Australia. He has held a leadership in the Society Executive Committee of the International Society of Vascular Behavioural and Cognitive Disorders and the Executive Committee of the International Neuropsychiatric Association. WW, ZX, JL, TFH, EJ, KD, MFLC, SLB, ECC, XG, QG, AO, TB, SS, NFMR, and CAAhave declared no conflict of interest.

AVAILABILITY OF DATA AND MATERIAL

Requests for access to anonymized study data for legitimate academic purposes should be directed to the corresponding author. Approval by COSMIC Research Scientific Committee and the principal investigator of each cohort in the study will be required before data can be shared.

REFERENCES

1. https://www.who.int/news-room/fact-sheets/detail/dementia. Accessed June 6th, 2021.
2. https://www.alzint.org/about/dementia-facts-figures. Accessed July 6th, 2021.
3. WHO. WHO guidelines on physical activity and sedentary behaviour. Geneva: World Health Organization, 2020.
4. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet. 2020;396(10248):413–446. [PubMed: 32738937]
5. WHO. Risk reduction of cognitive decline and dementia: WHO guidelines. Geneva: World Health Organization, 2019.
6. Boongird P, Chamnan P, Laptikultham S, et al. Dose-response relationship between physical exercise and risk of physician-diagnosed dementia in 206 073 Thai community-dwelling men and women: HCUR study. Eur J Neurol. 2020;27(10):1879–1886. [PubMed: 32441421]
7. Wang HX, Karp A, Winblad B, Fratiglioni L. Late-life engagement in social and leisure activities is associated with a decreased risk of dementia: a longitudinal study from the Kungsholmen project. Am J Epidemiol. 2002;155(12):1081–1087. [PubMed: 12048221]
8. Neergaard JS, Dragsbæk K, Hansen HB, Henriksen K, Christiansen C, Karsdal MA. Late-Life Risk Factors for All-Cause Dementia and Differential Dementia Diagnoses in Women. Medicine. 2016;95(11):e3112. [PubMed: 26986157]
9. Liu Y, Mitsuhashi T, Yamakawa M, et al. Physical activity and incident dementia in older Japanese adults: The Okayama study. Int J Geriatr Psych. 2019;34(10):1429–1437.
10. 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). J Int Neuropsych Soc. 2015;21(10):861–867.
11. Tan ZS, Spartano NL, Beiser AS, et al. Physical Activity, Brain Volume, and Dementia Risk: The Framingham Study. The journals of gerontology. Series A, Biological sciences and medical sciences. 2017;72(6):789–795. [PubMed: 27422439]
12. Taaffe DR, Irie F, Masaki KH, 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):529–535. [PubMed: 18511759]
13. Feter N, Mielke GI, Leite JS, Brown WJ, Coombes JS, Rombaldi AJ. Physical activity in later life and risk of dementia: Findings from a population-based cohort study. Exp Gerontol. 2021;143:111145. [PubMed: 33189834]
14. Laurin D, Verreault R, Lindsay J, MacPherson K, Rockwood K. Physical activity and risk of cognitive impairment and dementia in elderly persons. Arch Neurol. 2001;58(3):498–504. [PubMed: 11255456]
15. Ogino E, Manly JJ, Schupf N, Mayeux R, Gu Y. Current and past leisure time physical activity in relation to risk of Alzheimer's disease in older adults. Alzheimers Dement. 2019;15(12):1603–1611. [PubMed: 31587996]

16. Podewils LJ. Physical Activity, APOE Genotype, and Dementia Risk: Findings from the Cardiovascular Health Cognition Study. Am J Epidemiol. 2005;161(7):639–651. [PubMed: 15781953]
17. Sachdev PS, Lipnicki DM, Kochan NA, et al. COSMIC (Cohort Studies of Memory in an International Consortium): an international consortium to identify risk and protective factors and biomarkers of cognitive ageing and dementia in diverse ethnic and sociocultural groups. Bmc Neurol. 2013;13(1):165. [PubMed: 24195705]
18. Haan MN, Mungas DM, Gonzalez HM, Ortiz TA, Acharya A, Jagust WJ. Prevalence of Dementia in Older Latinos: The Influence of Type 2 Diabetes Mellitus, Stroke and Genetic Factors. J Am Geriatr Soc. 2003;51(2):169–177. [PubMed: 12558712]
19. Ganguli M, Snitz B, Bilt JV, Chang CH. How much do depressive symptoms affect cognition at the population level? The Monongahela-Youghiogheny Healthy Aging Team (MYHAT) study. Int J Geriatr Psych. 2009;24(11):1277–1284.
20. Katz MJ, Lipton RB, Hall CB, et al. Age-specific and sex-specific prevalence and incidence of mild cognitive impairment, dementia, and Alzheimer dementia in blacks and whites: a report from the Einstein Aging Study. Alzheimer Dis Assoc Disord. 2012;26(4):335–343. [PubMed: 22156756]
21. Lima-Costa MF, Firmo JO, Uchoa E. Cohort Profile: The Bambui (Brazil) Cohort Study of Ageing. Int J Epidemiol. 2011;40(4):862–867. [PubMed: 20805109]
22. Gureje O, Ogunniyi A, Kola L, Abiona T. Incidence of and Risk Factors for Dementia in the Ibadan Study of Aging. J Am Geriatr Soc. 2011;59(5):869–874. [PubMed: 21568957]
23. Dardiotis E, Kosmidis MH, Yannakoulia M, Hadjigeorgiou GM, Scarmeas N. The Hellenic Longitudinal Investigation of Aging and Diet (HELIAD): Rationale, Study Design, and Cohort Description. Neuroepidemiology. 2014;43(1):9–14. [PubMed: 24993387]
24. Shahar S, Omar A, Vanoh D, et al. Approaches in methodology for population-based longitudinal study on neuroprotective model for healthy longevity (TUA) among Malaysian Older Adults. Aging Clin Exp Res. 2016;28(6):1089–1104. [PubMed: 26670602]
25. Feng L, Chong MS, Lim WS, et al. Metabolic Syndrome and Amnestic Mild Cognitive Impairment: Singapore Longitudinal Ageing Study-2 Findings. J Alzheimer's Dis. 2013;34(3):649–657. [PubMed: 23246920]
26. Ding D, Zhao Q, Guo Q, et al. The Shanghai Aging Study: Study Design, Baseline Characteristics, and Prevalence of Dementia. Neuroepidemiology. 2014;43(2):114–122. [PubMed: 25376362]
27. Sachdev PS, Brodaty H, Reppermund S, et al. The Sydney Memory and Ageing Study (MAS): methodology and baseline medical and neuropsychiatric characteristics of an elderly epidemiological non-demented cohort of Australians aged 70–90 years. Int Psychogeriatr. 2010;22(8):1248–1264. [PubMed: 20637138]
28. Ainsworth BE, Haskell WL, Herrmann SD, et al. 2011 Compendium of Physical Activities: a second update of codes and MET values. Med Sci Sports Exerc. 2011;43(8):1575–1581. [PubMed: 21681120]
29. Shih I, Paul K, Haan M, Yu Y, Ritz B. Physical activity modifies the influence of apolipoprotein E ε4 allele and type 2 diabetes on dementia and cognitive impairment among older Mexican Americans. Alzheimers Dement. 2018;14(1):1–9. [PubMed: 28692819]
30. Scarmeas N, Luchsinger JA, Schupf N, et al. Physical activity, diet, and risk of Alzheimer disease. JAMA. 2009;302(6):627–637. [PubMed: 19671904]
31. Hendrie HC, Lane KA, Ogunniyi A, et al. The development of a semi-structured home interview (CHIF) to directly assess function in cognitively impaired elderly people in two cultures. Int Psychogeriatr. 2006;18(4):653–666. [PubMed: 16640794]
32. Sabia S, Dugravot A, Dartigues JF, 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. Kirk-Sanchez N, McGough E. Physical exercise and cognitive performance in the elderly: current perspectives. Clin Interv Aging. 2013;9:51–62. [PubMed: 24379659]
34. de Sousa Fernandes MS, Ordônio TF, Santos GCJ, et al. Effects of Physical Exercise on Neuroplasticity and Brain Function: A Systematic Review in Human and Animal Studies. Neural Plast. 2020;2020:1–21.

35. van Praag H. Exercise and the brain: something to chew on. Trends Neurosci. 2009;32(5):283–290. [PubMed: 19349082]

36. Cotman CW, Berchtold NC, Christie L. Exercise builds brain health: key roles of growth factor cascades and inflammation. Trends Neurosci. 2007;30(9):464–472. [PubMed: 17765329]

37. Guthold R, Stevens GA, Riley LM, Bull FC. Worldwide trends in insufficient physical activity from 2001 to 2016: a pooled analysis of 358 population-based surveys with 1.9 million participants. Lancet Global Health.

38. Najar J, Östling S, Gudmundsson P, et al. Cognitive and physical activity and dementia: A 44-year longitudinal population study of women. Neurology. 2019;92:e1322–30. [PubMed: 30787164]

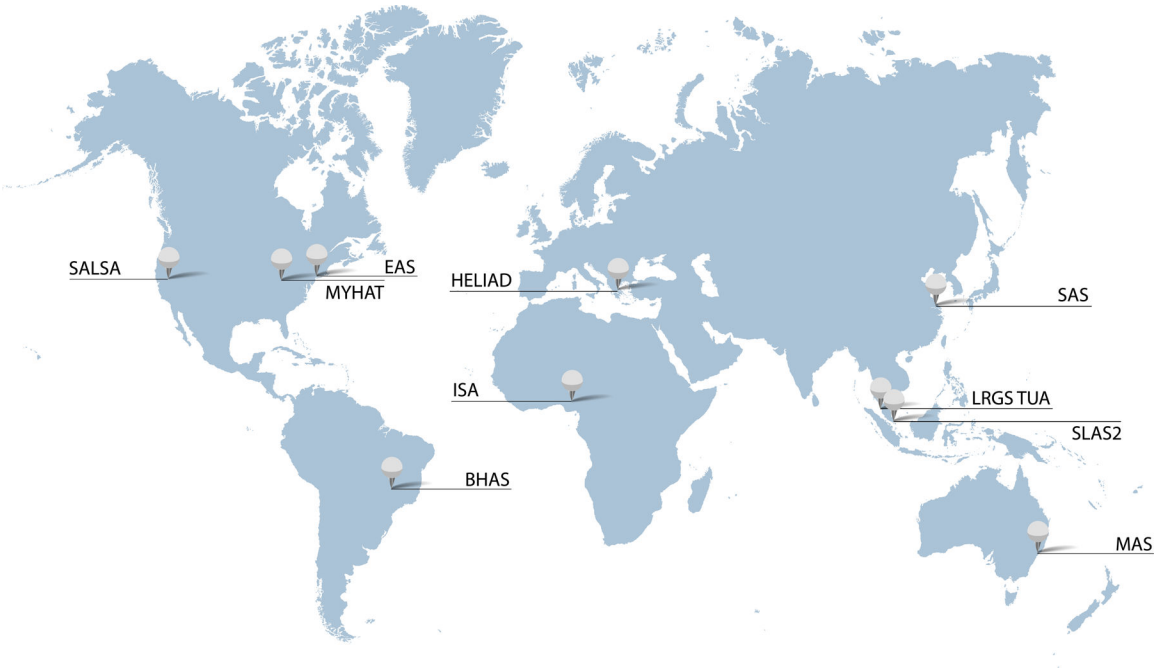

Figure 1. Location of each cohort.

SALSA=Sacramento Area Latino Study on Aging, USA. MYHAT=Monongahela–Youghiogheny Healthy Aging Team, USA. EAS=Einstein Aging Study, USA. BHAS=Bambuí Health and Aging Study, Brazil. ISA=Ibadan Study of Aging, Nigeria. HELIAD=Hellenic Longitudinal Investigation of Aging and Diet, Greece. LRGS TUA=The Longitudinal Study on Neuroprotective Model for Healthy Longevity, Malaysia. SLAS2=Singapore Longitudinal Aging Study-2, Singapore. SAS=Shanghai Aging Study, China. MAS=Sydney Memory and Aging Study, Australia.

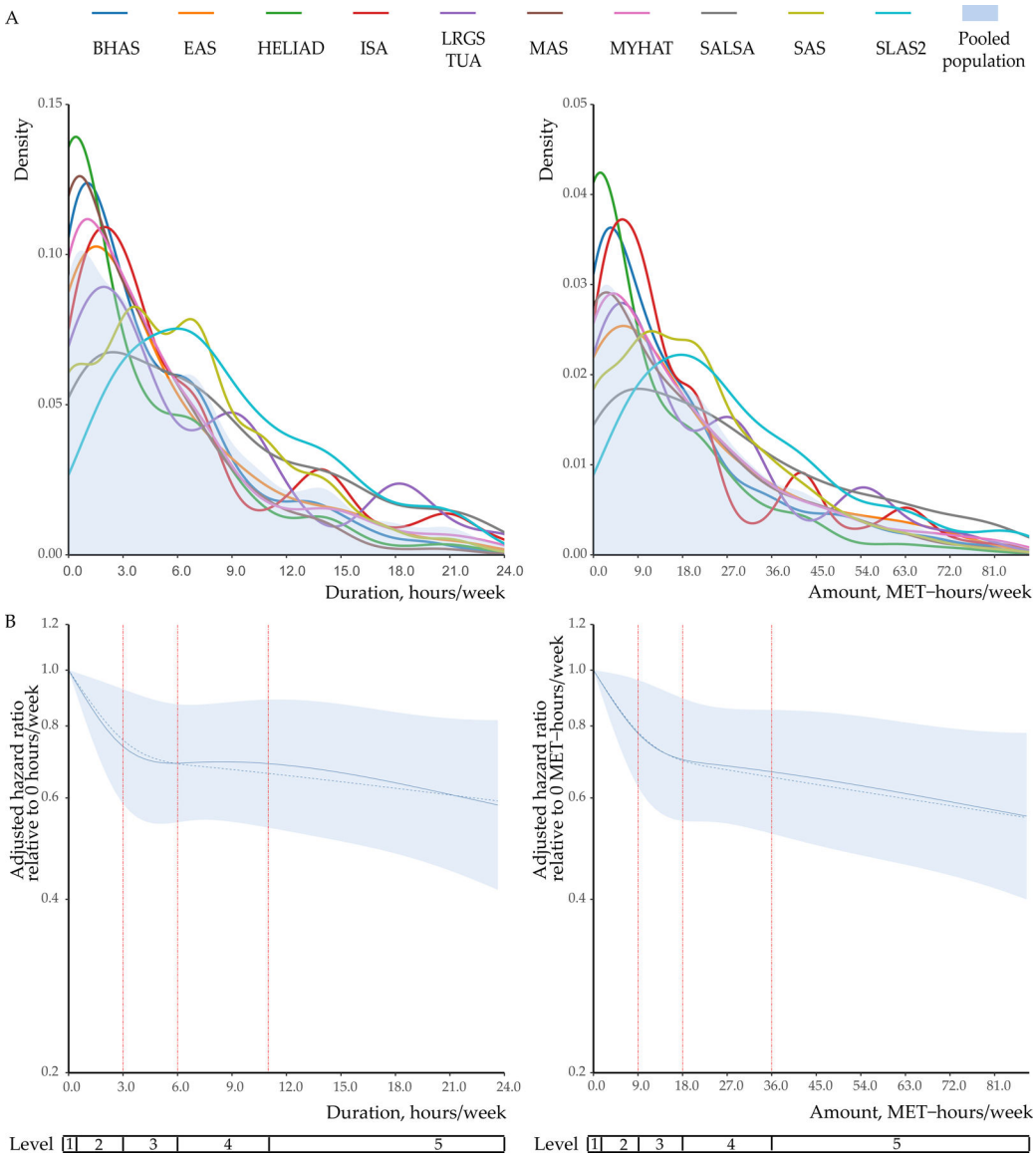

Figure 2. Categorization of physical activity based on restricted cubic splines.

(A) Density plot of the frequency distribution of the duration and amount of physical activity. (B) Adjusted hazard ratios of dementia relative to 0 hours/week (or 0 METhours/week) of physical activity. The dotted line represented hazard ratios adjusting for age, sex, years of education, and cohorts (model 1). The solid line and the ribbon represented hazard ratios and 95% confidence intervals further adjusting for APOE ε4, BMI, smoking, hypertension, diabetes, stroke, and depression (model 2). ISA and LRGS TUA were not entered into model 2 because of missing information on confounders.

Model 1	N	Dementia case	HR (95% CI)
Duration (hours/week)			
0.0	2039	207	1
0.1-3.0	2654	197	0.80 (0.65-0.98)
3.1-6.0	2240	156	0.70 (0.56-0.87)
6.1-11.0	2633	130	0.62 (0.49-0.77)
>11.0	2422	110	0.63 (0.50-0.81)
Amount (MET-hours/week)			
0.0	2039	207	1
0.1-9.0	2315	178	0.82 (0.66-1.01)
9.1-18.0	2072	143	0.70 (0.56-0.87)
18.1-36.0	2839	155	0.67 (0.54-0.83)
>36.0	2723	117	0.58 (0.46-0.74)
Model 2			
Duration (hours/week)			
0.0	1764	187	1
0.1-3.0	1958	125	0.88 (0.67-1.15)
3.1-6.0	1858	118	0.68 (0.52-0.89)
6.1-11.0	2236	110	0.68 (0.51-0.90)
>11.0	1834	80	0.68 (0.50-0.93)
Amount (MET-hours/week)			
0.0	1764	187	1
0.1-9.0	1622	106	0.92 (0.70-1.22)
9.1-18.0	1719	108	0.70 (0.53-0.93)
18.1-36.0	2379	129	0.70 (0.53-0.92)
>36.0	2166	90	0.63 (0.46-0.85)

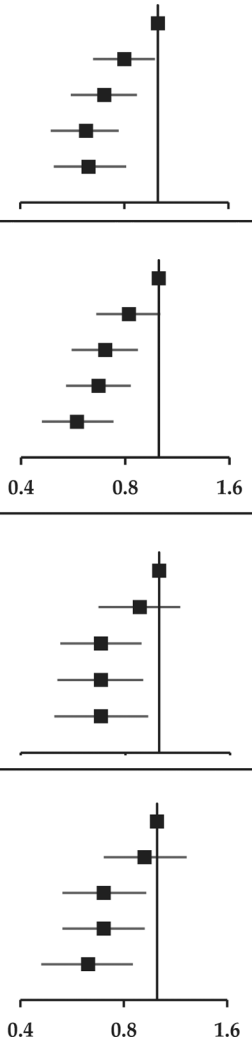

Figure 3. Dose-response relationship of the duration and amount of physical activity with incident dementia.

Model 1 adjusted for age, sex, years of education, and cohort. Model 2 further adjusted for APOE ε4, BMI, smoking, hypertension, diabetes, stroke, and depression. ISA and LRGS TUA were not entered into model 2 because of missing information on confounders. HR=hazard ration. CI=confidence interval.

Model 1	N	Dementia cases	HR (95% CI)
Duration (hours/week)			
0.0	1999	167	1
0.1-3.0	2615	158	0.75 (0.60-0.95)
3.1-6.0	2225	141	0.76 (0.60-0.95)
6.1-11.0	2615	112	0.66 (0.51-0.84)
>11.0	2408	96	0.67 (0.51-0.88)
Amount (MET-hours/week)			
0.0	1999	167	1
0.1-9.0	2280	143	0.77 (0.61-0.98)
9.1-18.0	2056	127	0.74 (0.58-0.94)
18.1-36.0	2816	132	0.71 (0.56-0.90)
>36.0	2711	105	0.63 (0.48-0.81)
Model 2			
Duration (hours/week)			
0.0	1729	152	1
0.1-3.0	1930	97	0.81 (0.60-1.09)
3.1-6.0	1847	107	0.74 (0.55-0.99)
6.1-11.0	2223	97	0.73 (0.53-0.98)
>11.0	1824	70	0.70 (0.50-0.99)
Amount (MET-hours/week)			
0.0	1729	152	1
0.1-9.0	1598	82	0.85 (0.62-1.16)
9.1-18.0	1707	96	0.75 (0.55-1.01)
18.1-36.0	2363	113	0.73 (0.55-0.98)
>36.0	2156	80	0.66 (0.48-0.92)

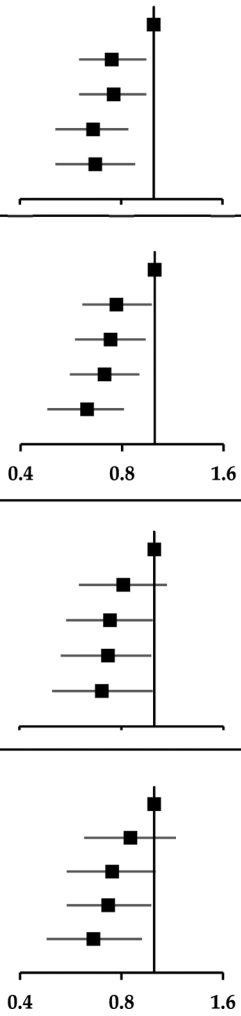

Figure 4. Dose-response relationship of the duration and amount of physical activity with incident dementia in the sensitivity analysis.

Dementia cases identified less than 2 years from baseline interview were excluded. Model 1 adjusted for age, sex, years of education, and cohort. Model 2 further adjusted for APOE ε4, BMI, smoking, hypertension, diabetes, stroke, and depression. ISA and LRGS TUA were not entered into model 2 because of missing information on confounders. HR=hazard ration. CI=confidence interval.

Table 1:

Profile of the cohort studies

	Sacramento Area Latino Study on Aging	Monongahela–Youghiogheny Healthy Aging Team	Einstein Aging Study	Bambuí Health and Aging Study	Ibadan Study of Aging	Hellenic Longitudinal Investigation of Aging and Diet	The Longitudinal Study on Neuroprotective Model for Healthy Longevity	Singapore Longitudinal Aging Study-2	Shanghai Aging Study	Sydney Memory and Aging Study
Abbreviation	SALSA	MYHAT	EAS	BHAS	ISA	HELIAD	LRGS TUA	SLAS2	SAS	MAS
Location	Sacramento, USA	Pittsburgh, USA	New York, USA	Bambuí, Brazil	Eight states, Nigeria	Larissa and Marousi, Greece	Four states, Malaysia	Singapore, Singapore	Shanghai, China	Sydney, Australia
Starting year	1998	2006	2012	1997	2003	2011	2012	2009	2009	2005
Age range	60+	65+	70+	60+	65+	65+	60+	55+	60+	70–90
Sample size	1415	1649	368	1407	1243	1007	1095	1327	1658	819
Dementia diagnosis criteria	Clinically significant impairment in two or more separate cognitive domains that included a decline from premorbid function and clinically significant impairment of independent functioning	Clinical Dementia Rating scale	DSM-IV	MMSE≤13	Ten-Word Delay Recall Test; Clinician Home-based Interview	DSM-IV	MMSE≤14	DSM-IV	DSM-IV	DSM-IV

MMSE=Mini-Mental State Examination; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition).

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Table 2:

Baseline characteristics and follow-up cognitive functioning of participants in the cohort studies

	Sacramento Area Latino Study on Aging	Monongahela–Youghiogheny Healthy Aging Team	Einstein Aging Study	Bambuí Health and Aging Study	Ibadan Study of Aging	Hellenic Longitudinal Investigation of Aging and Diet	The Longitudinal Study on Neuroprotective Model for Healthy Longevity	Singapore Longitudinal Aging Study-2	Shanghai Aging Study	Sydney Memory and Aging Study	Total
Sample size, n	1415	1649	368	1407	1243	1007	1095	1327	1658	819	11988
Baseline											
Age, years, mean±sd	70.1±6.6	77.4±7.4	79.7±5.9	68.7±6.9	74.1±8.3	72.6±5.4	69.7±5.6	65.7±6.9	71.5±7.4	78.5±4.7	72.1±7.9
Male, n (%)	591 (41.8)	624 (37.8)	129 (35.1)	543 (38.6)	604 (48.6)	405 (40.2)	550 (50.2)	470 (35.4)	758 (45.7)	374 (45.7)	5048 (42.1)
Education, years, mean±sd	7.6±5.4	12.9±2.4	14.8±3.3	2.8±3.0	3.5±4.6	7.8±4.7	5.4±3.9	6.5±4.3	11.9±4.0	11.7±3.5	8.1±5.5
APOE ε4+, n (%)	197 (14.5)	319 (20.9)	39 (21.9)	317 (25.1)	NA	124 (17.4)	NA	215 (17.9)	260 (16.8)	188 (23.2)	1659 (19.3)
Duration of physical activity, hours/week, median (IQR)	7.0 (3.0–15.0)	3.5 (1.0–7.3)	3.5 (0.8–7.1)	3.3 (0.8–6.7)	4.1 (1.8–12.5)	1.0 (0.0–7.0)	4.5 (1.8–9.8)	7.9 (4.5–14.0)	6.5 (3.5–10.0)	2.5 (0.0–6.0)	4.3 (1.3–9.5)
Amount of physical activity, MET-hours/ week, median (IQR)	28.0 (9.0–60.0)	13.0 (2.9–30.1)	13.0 (2.7–30.1)	9.9 (2.5–23.7)	14.0 (5.3–42.0)	4.5 (0.0–21.0)	15.0 (5.3–31.5)	25.5 (14.0–44.0)	20.5 (10.5–31.5)	11.0 (0.0–25.6)	15.7 (4.5–33.5)
Body Mass Index, mean±sd	29.9±5.6	28.2±5.6	28.7±5.1	25.2±4.9	NA	29.1±4.4	25.3±4.5	24.0±4.0	24.6±3.5	27.2±4.4	26.7±5.2
Current smoking, n (%)	152 (10.7)	106 (6.4)	9 (2.5)	249 (17.7)	504 (43.3) *	106 (10.7)	187 (17.1)	111 (8.4)	169 (10.2)	26 (6.0)	1619 (14.1)
Hypertension, n (%)	628 (44.8)	1069 (64.9)	243 (66.0)	830 (62.0)	121 (9.8)	645 (65.0)	547 (50.0)	560 (42.2)	894 (53.9)	491 (60.2)	6028 (50.8)
Diabetes, n (%)	438 (31.0)	355 (21.5)	72 (19.6)	197 (14.8)	26 (2.1)	167 (16.8)	282 (25.8)	174 (13.1)	220 (13.3)	95 (11.7)	2026 (17.1)
Stroke, n (%)	114 (8.1)	70 (4.3)	13 (3.6)	46 (3.4)	9 (0.7)	73 (7.3)	14 (1.3)	39 (2.9)	215 (13.0)	31 (3.8)	624 (5.3)
Depression, n (%)	345 (24.4)	82 (5.0)	23 (6.3)	515 (37.0)	364 (29.8)	133 (13.2)	124 (11.3)	13 (1.0)	244 (14.7)	49 (6.0)	1892 (15.9)
MMSE, mean±sd	87.1±9.8 †	27.1±2.3	26.8±1.3 ‡	25.0±3.8	NA	NA	24.3±3.6	28.5±1.9	28.2±2.1	28.1±1.5	NA

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	Sacramento Area Latino Study on Aging	Monongahela–Youghiogheny Healthy Aging Team	Einstein Aging Study	Bambuí Health and Aging Study	Ibadan Study of Aging	Hellenic Longitudinal Investigation of Aging and Diet	The Longitudinal Study on Neuroprotective Model for Healthy Longevity	Singapore Longitudinal Aging Study-2	Shanghai Aging Study	Sydney Memory and Aging Study	Total
Follow-up											
Median follow-up, years, median (IQR)	7.4 (3.9–8.1)	6.2 (3.0–10.7)	2.8 (1.8–3.7)	11.0 (5.0–15.0)	6.0 (5.0–6.0)	3.0 (2.5–3.3)	3.5 (1.3–3.9)	4.1 (2.9–5.5)	5.3 (4.7–5.7)	5.8 (5.8–5.9)	5.0 (3.3–6.4)
MMSE, mean±sd	78.9±20.7[†]	25.7±4.0	26.5±1.7[‡]	23.0±5.5	NA	NA	24.3±4.6	28.1±2.4	26.7±4.1	27.4±3.0	NA
Incident dementia, n (%)	82 (5.8)	124 (7.5)	13 (3.5)	69 (4.9)	136 (10.9)	56 (5.6)	44 (4.0)	10 (0.8)	167 (10.1)	99 (12.1)	800 (6.7)
Dementia incidence, 1000 person-years (95% CI)	9.4 (7.3–11.4)	11.7 (9.6–13.7)	13.7 (6.2–21.1)	5.0 (3.8–6.2)	20.1 (16.7–23.5)	18.7 (13.8–23.6)	13.5 (9.5–17.4)	1.7 (0.7–2.8)	19.4 (16.5–22.3)	23.0 (18.4–27.5)	12.1 (11.3–13.0)

APOE=apolipoprotein E. MET=metabolic equivalent. sd=standard deviation. IQR=interquartile range. MMSE=Mini-Mental State Examination. NA=Not applicable. CI= confidence interval.

[*]Smoking history.

[†]Modified Mini-Mental State Examination.

[‡]Mini-Mental State Examination score was derived from an alogorithm that translates the Blessed Information and Memory Concentration Test into the Mini-Mental State Examination.

Box.

Previous studies on the dose-response association between late-life physical activity and dementia risk.

Reference	Country	No. of participants	Age at baseline, mean±sd	Follow-up years	Incident dementia,	Exposure	HR (95% CI)	P for trend
Boongird P, et al.[6]	Thailand	206073	62.5±10.0	6	480 (0.2%)	Frequency of physical activity	No physical activity: 1 1–2 days/week: 0.864 (0.661–1.129) 3–5 days/week: 0.629 (0.504–0.785) >5 days/week: 0.413 (0.257–0.663)	NI
Wang HX, et al.[7]	Sweden	776	81.1±4.9	6	124 (15.9%)	Frequency of physical activity	No physical activity: 1[†] less than daily: 0.97 (0.42–2.22) daily: 0.41 (0.13–1.31)	NI
Neergaard JS, et al.[8]	Netherland	5512	70.1±6.4	11.9	592 (10.7%)	Frequency of physical activity	no physical activity: 1 1 time/ week: 0.77 (0.61–0.96) 2 times/week: 0.80 (0.61–1.04) ≥3 times/week: 0.79 (0.64–0.97)	NI
Liu Y, et al.[9]	Japan	51477	71.3±7.5	7	13816 (26.8%)	Frequency of physical activity	≤1 time/week:1 ≥2 times/week but not every day: 0.79 (0.75-0.84) every day: 0.94 (0.89-0.98)	NI
Llamas-Velasco S, et al.[10]	Spain	3100	72.8 ± 6.1	3	134 (4.3%)	Duration of physical activity. Number of hours was weighted. Weighting facotrs were: 1.0 for sedentary, 1.2 for slight, 1.4 for moderate, and 1.8 for heavy activity.	≤15.6 hours: 1 15.6<hours≤17.6 hours: 0.53 (0.34–0.82) 17.6<hours≤19.4 hours: 0.45 (0.27–0.76) >19.4 hours: 0.29 (0.16–0.52)	NS
Tan ZS, et al.[11]	USA	3174	70±7	7.5	236 (7.4%)	Duration of physical activity. Number of hours was weighted. Weighting facotrs were: 1.0 for basal, 1.1 for sedentary, 1.5 for slight, 2.4 for moderate, and 5.0 for heavy activity.	1st quintile: 1 2nd quintile: 0.44 (0.27–0.73) 3rd quintile: 0.80 (0.52–1.22) 4th quintile: 0.63 (0.40–1.00) 5th quintile: 0.95 (0.63–1.41)	NI
Taaffe DR, et al.[12]	Hawaii	2263	71–93 (range)	6.1	173 (7.6%)	Duration of physical activity. Number of hours was weighted. Weighting facotrs were: 1.0 for basal, 1.1 for sedentary, 1.5 for slight, 2.4	≤28.7 hours:1 28.8–32.4 hours: 0.57 (0.32–0.99) ≥ 32.5 hours: 0.50 (0.28–0.89)	NI

Reference	Country	No. of participants	Age at baseline, mean±sd	Follow -up years	Incident dementia,	Exposure	HR (95% CI)	P for trend
						for moderate, and 5.0 for heavy activity.		
Feter N, et al.[13]	England	9275	63.8±10.8	15	631 (6.8%)	A composite score was genarated by summing answers to the frequency question and the intensity question.	Inactive: 1 Low: 0.40 (0.32–0.49) Moderate/ high: 0.22 (0.17–0.30)	NI
Laurin D, et al.[14]	Canada	4615	≥65 (range)	5	80 (1.7%) *	A composite score was genarated by summing answers to the frequency question and the intensity question.	No physical activity: 1.0 Low: 0.67 (0.39–1.14) Moderate: 0.67 (0.46–0.98) High: 0.50 (0.28–0.90)	0.02
Ogino E, et al.[15]	USA	1345	75.1±6.30	4.1	106 (7.9%) *	Amount of physical activity (unit: MET-minute/2 weeks)	0 MET-minutes/2 weeks:1.00 0<MET-minutes/2 weeks<1260: 0.71 (0.44–1.15) ≥1260 MET-minutes/2 weeks: 0.42 (0.21–0.86)	0.014
Podewils LJ, et al.[16]	USA	3375	74.8±4.9	5.4	480 (14.2%)	Amount of physical activity (unit: kcal/week)	<248 kcal/week: 1 † 248–742 kcal/week: 1.22 (0.93–1.60) 743–1,657 kcal/week: 0.94 (0.69–1.28) >1,657 kcal/week: 0.85 (0.61–1.19)	0.11

sd=standard deviation. HR=hazard ration. CI=confidence interval. NI=no information. NS=not significant.

*: incident Alzheimer's disease

†: relative risk