Moderate and vigorous leisure time physical activity in older adults and Alzheimer's disease-related mortality in the USA: a dose–response, population-based study

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Summary

Background Data for the dose–response associations of moderate physical activity (MPA) and vigorous physical activity (VPA) with Alzheimer's disease-related mortality are scarce. We aimed to examine the prospective associations of such activity with Alzheimer's disease-related mortality.

Methods In this dose–response, population-based study, we pooled data from 22 consecutive waves of the US National Health Interview Survey (from 1997 to 2018). Participants aged 68 years or older were included in the study if they had full data for physical or muscle-strengthening activity, chronic conditions, functional limitations, marital status, education level, alcohol consumption, smoking status, and BMI, and follow-up time after study entry. Participants were linked to the National Death Index until Dec 31, 2019. We defined Alzheimer's disease-related mortality as a leading cause by using the G-30 code of the International Statistical Classification of Diseases and Related Health Problems tenth revision. Information on MPA and VPA was self-reported, with participants asked to answer four questions on the frequency and duration of both types of physical activity. We calculated hazard ratios (HRs) and used restricted cubic splines models to assess dose–response associations, and we estimated the annual number of Alzheimer's disease-related deaths that could be prevented through physical activity using adjusted population attributable fractions.

Findings After excluding 21 377 participants, 91 298 adults were included in the analysis. The weighted mean participant age was 75·8 years (SE 0·0); 55 658 (56·7%) were female and 76 796 (87·6%) were White (weighted percentages). The median follow-up was 6·5 years (IQR 3·6–10·7), corresponding to 703 393 person-years. 2176 (2·4%) participants died due to Alzheimer's disease as the leading cause. For MPA, we did not find a significant dose–response association with Alzheimer's disease-related mortality, whereas for VPA, we observed a significant L-shaped association between 20 weekly min and 190 weekly min. For VPA, we identified a minimal amount (ie, 50% of the optimal amount) at 40 min/week (HR 0·91, 95% CI 0·84–0·95) and an optimal amount (ie, the nadir of the curve) at 140 min/week (0·79, 0·66–0·95) for reducing Alzheimer's disease-related mortality. For the USA, we estimated that 40 weekly min of VPA would prevent 12 238 deaths per year (95% CI 89–23 172) and 140 weekly min of VPA would prevent 37 710 deaths per year (311–63 567), compared with a scenario in which US adults did not do any VPA.

Interpretation These findings might inform future guidelines for preventing Alzheimer's disease-related mortality by emphasising the importance of VPA over MPA and providing specific VPA targets.

Funding None.

Lancet Healthy Longev 2023; 4: e703–10

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Introduction

Alzheimer's disease is one of the most common types of dementia. It is a chronic neurodegenerative disease characterised by cognitive and memory declines, personality and behaviour changes, executive dysfunctions, and usually involves mental health issues.[1] Alzheimer's disease might have its origins in early life owing to the complex interplay between genetic and environmental exposures.[2] Concerningly, the number of deaths attributed to Alzheimer's disease has substantially increased by more than 145% in the past two decades in the USA, becoming a leading underlying cause of mortality.[3] The number of people with Alzheimer's disease and other types of dementia in North America is expected to double by 2050.[4]

Several modifiable risk factors contribute to an increased risk of Alzheimer's disease, including smoking, overweight, or obesity.[5] However, sufficient amounts of physical activity have been associated with a decreased incidence of the disease.[6] Previous studies have reported an inverse association between increased amounts of light and moderate-to-vigorous intensity physical activity and a decreased incidence of disabling dementia in older adults (aged ≥50 years) from South Korea and Japan.[7,8] In the UK Biobank study, an L-shaped dose–response association has also been observed between objectively measured moderate-to-vigorous physical activity and incident dementia.[9] By contrast, findings from the Whitehall II cohort study suggest no association between total,

Research in context

Evidence before this study

The number of deaths attributed to Alzheimer's disease as the leading cause has increased substantially in the USA, with an increase of more than 145% in the past two decades, thus becoming one of the leading underlying causes of mortality in the country. Future projections show even more concerning figures for the next decades. Although some studies have examined the dose–response association of physical activity with the risk of developing Alzheimer's disease, we did not find studies investigating the dose–response association between intensity-specific, leisure-time, aerobic physical activity and the risk of Alzheimer's disease-related mortality, nor studies estimating the number of averted Alzheimer's disease-related deaths through a preventive factor such as physical activity. We searched PubMed for articles in English published between Jan 1, 2000, and Dec 31, 2022, relating to associations of physical activity with Alzheimer's disease-related mortality. Search terms were "Alzheimer disease", "Alzheimer's disease", "physical activity", and "physical exercise".

Added value of this study

To our knowledge, this study is the first to investigate the dose–response associations of leisure time moderate physical activity (MPA) and vigorous physical activity (VPA) with Alzheimer's disease-related mortality in the USA, and to examine the potential number of Alzheimer's disease-related deaths that could be averted with physical activity.

Implications of all the available evidence

Our findings indicate that a minimal and an optimal amount of VPA might reduce the number of annual Alzheimer's disease-related deaths in the USA. Benefits might start with 20 weekly min of VPA. Our study also emphasises the importance of VPA over MPA when recommending physical activity to reduce the risk of Alzheimer's disease-related mortality and provides specific VPA targets that might be useful for clinical and public health advice.

recommended (moderate-to-vigorous physical activity of at least 2·5 h/week), mild, and moderate-to-vigorous physical activity with dementia.[10] These findings are particularly relevant because of the growing interest in non-pharmacological treatments for Alzheimer's disease to complement standardised pharmacological treatments.[11] Estimates indicate that around 40% of all dementia cases might be prevented or delayed by targeting modifiable risk factors, including physical inactivity.[12] Despite being relevant, the shape of the dose–response association between physical activity and Alzheimer's disease-related mortality is currently unknown. Understanding the shape of this relationship is crucial to identifying the minimal and optimal amounts of physical activity that might efficiently reduce the risk of Alzheimer's disease-related mortality. Moreover, information on the number of Alzheimer's disease-related deaths that could potentially be prevented through physical activity is also lacking.

We aimed to investigate the dose–response associations between leisure time moderate physical activity (MPA) and vigorous physical activity (VPA) and Alzheimer's disease-related mortality in a representative sample of US adults. We also sought to estimate the annual number of Alzheimer's disease-related deaths in the USA that could potentially be averted with minimal and optimal amounts of MPA and VPA.

Methods

Study design and participants

This dose–response, population-based study used de-identified data from 22 consecutive waves of the US National Health Interview Survey (NHIS) between 1997 and 2018. The NHIS is an annual, nationally representative survey of the non-institutionalised population in the USA, done by the Centers for Disease Control and Prevention's National Center for Health Statistics. More detailed information on the NHIS is available elsewhere.[13] The NHIS was approved by the National Center for Health Statistics Ethics Review Board, and written informed consent was obtained from all participants. For this study, we followed the STROBE reporting guidelines.

Participants were eligible if they were aged 68 years or older—the age at which Alzheimer's disease begins to represent a substantial burden of mortality in the NHIS population according to an optimal cutoff point obtained through the Liu procedure.[14] We excluded individuals with missing data for physical or muscle-strengthening activity, and individuals with missing data for other covariates, including chronic conditions, functional limitations, marital status, education level, alcohol consumption, smoking status, and BMI. Participants without follow-up time after study entry were also excluded.

Alzheimer's disease-related mortality

Participants were linked to the National Death Index records until Dec 31, 2019. Mortality related to Alzheimer's disease was defined on the basis of the International Statistical Classification of Diseases and Related Health Problems tenth revision (ICD-10). To ascertain the vital status of the participants, we did a probabilistic record matching method with the National Death Index records.[15] The accuracy of information of the National Death Index records has been previously validated.[16] Further information on the linkage of NHIS data with National Death Index records is publicly available elsewhere.[15] We identified specific Alzheimer's

disease-related mortality (as a leading cause only) using the G-30 code of the ICD-10.[17]

Moderate and vigorous leisure time physical activity

Information on leisure time physical activity was self-reported by participants, by answering a set of questions used in previous research:[18] (1) "How often do you do light or moderate leisure-time physical activities for at least 10 minutes that cause only light sweating or a slight to moderate increase in breathing or heart rate?" ("for at least 20 minutes" for participants of the 1997 NHIS), to assess frequency of light-intensity physical activity or MPA; (2) "About how long do you do these light or moderate leisure-time physical activities each time?", to assess the duration of MPA; (3) "How often do you do vigorous leisure-time physical activities for at least 10 minutes that cause heavy sweating or large increases in breathing or heart rate?" ("for at least 20 minutes" for participants of the 1997 NHIS), to assess the frequency of VPA; and (4) "About how long do you do these vigorous leisure-time physical activities each time?", to assess the duration of VPA. We calculated the total weekly duration of MPA and VPA in minutes by multiplying frequency and duration.

Statistical analysis

We adjusted our models according to a priori defined directed acyclic graph (appendix p 2) for age; sex; race; marital status; educational attainment; smoking status; alcohol consumption; prevalent major cardiometabolic conditions (ie, diabetes, hypertension, coronary heart disease, angina pectoris, heart attack, stroke, cancer, emphysema, or asthma); BMI; functional limitation, defined as having any degree of difficulty while doing a specific physical task (ie, walking a quarter of a mile, walking up ten steps, standing for 2 h, sitting for 2 h, carrying a 10 pound [4·5 kg] object, overhead arm reach, stooping, bending, kneeling, pushing a large object, or grasping an object), or engaging in social activities and recreation (ie, relaxing, going shopping, attending club meetings, visiting friends, sewing, reading, visiting a doctor's office, or going to parties) without the assistance of another person or using special equipment; survey year, defined as the year when the survey was done; and weekly strength training, defined as the number of strength training sessions per week. Additionally, we adjusted our models for either MPA or VPA—that is, we used VPA as covariate when MPA was the exposure and vice versa.

We used restricted cubic splines to assess the dose–response associations of MPA and VPA (modelled as continuous exposures) with Alzheimer's disease-related mortality, allowing for potential non-linearity. Observations greater than 95% of the distribution were trimmed, and prespecified knots were placed at the 25th, 50th, and 75th percentiles of the exposure distribution. Non-linearity was assessed with a Wald test evaluating the null hypothesis that the coefficient of the second spline was equal to zero. We assumed linearity for values above the 95th percentile. Time-on-study in quarter-years was used as the time scale, and participants were censored at the date of death when they died due to causes other than Alzheimer's disease as the leading cause. The end of follow-up was registered when a participant died due to Alzheimer's disease as the leading cause (ie, the event of interest) or at the end of the follow-up period (Dec 31, 2019). All the main analyses, including descriptive statistics, accounted for weights, primary sampling units, and strata from the complex multistage sampling design of the NHIS to obtain hazard ratios (HRs) and adjusted population attributable fractions with their corresponding 95% CIs. An adjusted Wald test found no evidence of an age, sex, or race interaction with either MPA or VPA; thus, the results are presented for all participants (ie, age, sex, and race combined).

After obtaining the restricted cubic splines, we used the punaf postestimation command in Stata[19] to calculate the population attributable fractions. This procedure estimated the adjusted proportion of preventable deaths attributable to two hypothetical scenarios by estimating the log of the mean rate ratio in Alzheimer's disease-related deaths. Exposure (ie, physical activity) was set to specific values, whereas the rest of the covariates in the model remained standardised. We compared a scenario in which the sample population did not engage in any weekly physical activity with a counterfactual scenario in which the whole study population engaged in either a minimal or an optimal amount of physical activity according to the spline models. We estimated the minimal amount (ie, the exposure value at which the risk reduction was 50% of the observed maximum significant risk reduction) and the optimal amount (ie, the exposure value at which the maximum significant risk reduction was observed). We then multiplied the proportion of preventable deaths obtained from each comparison of hypothetical scenarios by the number of Alzheimer's disease-related deaths in the USA in 2019 (121 499),[3] which estimated the final annual number of Alzheimer's disease-related deaths. Additionally, we estimated adjusted differences of survival years between participants with 0 min of VPA, and participants with minimal and optimal amounts of VPA by using a Poisson regression, which predicted life expectancy for each category and calculated the differences among groups in years. We used a two-tailed test with a significance level of 0·05 to identify statistical significance.

We did sensitivity analyses to ensure the robustness of our findings. First, to mitigate the potential for reverse causation bias, we excluded the first 2 years of observation time from our analysis.[7] Second, to minimise the possibility of residual confounding bias, we did additional analyses that included adjustments for other potential confounders not accounted for in our main analyses

See Online for appendix

because of a high number of missing data: sleep time and employment status. Third, we also repeated the analyses on the dose–response associations by imputing missing values. We did multiple imputation of missing values through a chained equation comprising all the covariates and the outcome. No auxiliary variables were used, and five datasets were imputed. We assumed data to be missing at random.

We did additional survival analyses accounting for competing risks (ie, deaths due to unintentional injuries) using a fully adjusted and weighted Fine and Gray model, which provided subhazard ratios. We also examined the distribution of Alzheimer's disease-related deaths over time and by age using bar plots. We did all statistical analysis using Stata, version 16.1. Additional technical notes on some of the analyses used are given in the appendix (p 15).

Role of the funding source

There was no funding source for this study.

Results

From an eligible sample of 112 675 participants aged 68 years or older, we excluded individuals with missing data for physical activity (n=10 577), muscle-strengthening activity (n=440), chronic conditions (n=1392), functional limitations (n=267), marital status (n=153), education level (n=765), alcohol consumption

	Total (n=91 298)	Moderate physical activity				Vigorous physical activity			
		No activity (n=49 524 [52·7%])	Tertile 1 (10 min to ≤100 min; n=14 228 [15·9%])	Tertile 2 (>100 min to ≤210 min; n=15 172 [17·1%])	Tertile 3 (>210 min; n=12 374 [14·3%])	No activity (n=74 375 [80·0%])	Tertile 1 (10 min to ≤105 min; n=5726 [6·7%])	Tertile 2 (>105 min to ≤210 min; n=5636 [6·7%])	Tertile 3 (>210 min; n=5561 [6·7%])
Age, years	75·8 (0·0)	76·5 (0·0)	75·2 (0·1)	75·3 (0·1)	74·6 (0·1)	76·2 (0·0)	74·2 (0·1)	74·1 (0·1)	73·6 (0·1)
Sex									
Male	35 640 (43·3%)	17 914 (40·0%)	5411 (42·5%)	6198 (45·3%)	6117 (54·1%)	27 042 (40·3%)	2672 (50·9%)	2703 (52·9%)	3223 (61·9%)
Female	55 658 (56·7%)	31 610 (60·0%)	8817 (57·5%)	8974 (54·7%)	6257 (45·9%)	47 333 (59·7%)	3054 (49·1%)	2933 (47·1%)	2338 (38·1%)
Race									
White	76 796 (87·6%)	40 580 (86·1%)	12 039 (87·9%)	13 246 (89·8%)	10 931 (90·6%)	62 072 (87·1%)	4916 (88·6%)	4942 (90·0%)	4866 (90·3%)
Black	10 482 (8·3%)	6935 (10·2%)	1577 (8·1%)	1152 (5·5%)	818 (4·9%)	9040 (8·8%)	584 (7·9%)	438 (5·7%)	420 (5·4%)
Other	4020 (4·1%)	2009 (3·7%)	612 (4·0%)	774 (4·7%)	625 (4·5%)	3263 (4·1%)	226 (3·5%)	256 (4·3%)	275 (4·3%)
Education									
Lower than high school degree	24 278 (23·7%)	16 738 (30·1%)	2812 (17·4%)	2681 (15·4%)	2047 (15·0%)	21 925 (26·6%)	930 (14·7%)	701 (10·8%)	722 (11·1%)
High school degree	9729 (10·0%)	5732 (10·9%)	1350 (8·9%)	1511 (9·3%)	1136 (8·4%)	8417 (10·7%)	468 (7·5%)	446 (7·0%)	398 (6·7%)
Higher than high school degree	57 291 (66·3%)	27 054 (58·4%)	10 066 (73·7%)	10 980 (75·3%)	9191 (76·6%)	44 033 (62·7%)	4328 (77·8%)	4489 (82·2%)	4441 (82·2%)
Marital status									
Married or living with a partner	38 059 (56·5%)	18 723 (52·0%)	6181 (58·7%)	6863 (60·7%)	6292 (65·4%)	29 095 (53·7%)	2891 (65·1%)	2953 (67·5%)	3120 (70·4%)
Widowed, divorced, or separated	48 734 (39·9%)	28 299 (44·2%)	7379 (37·9%)	7552 (35·8%)	5504 (31·3%)	41 531 (42·6%)	2571 (31·5%)	2421 (29·3%)	2211 (26·9%)
Never married	4505 (3·6%)	2502 (3·8%)	668 (3·4%)	757 (3·5%)	578 (3·3%)	3749 (3·8%)	264 (3·5%)	262 (3·3%)	230 (2·7%)
Alcohol consumption									
Never drinker	40 583 (47·1%)	17 833 (38·3%)	7280 (53·6%)	8185 (56·2%)	7285 (61·3%)	30 208 (42·9%)	3375 (61·1%)	3536 (65·2%)	3464 (64·9%)
Former drinker	22 924 (24·7%)	13 338 (27·0%)	3490 (23·8%)	3403 (21·9%)	2693 (20·7%)	19 583 (26·1%)	1201 (20·4%)	1057 (17·8%)	1083 (18·5%)
Current drinker	27 791 (28·3%)	18 353 (34·8%)	3458 (22·6%)	3584 (22·0%)	2396 (18·0%)	24 584 (31·0%)	1150 (18·5%)	1043 (17·0%)	1014 (16·6%)
Smoking									
Never smoker	48 487 (51·8%)	26 812 (52·6%)	7538 (52·0%)	8069 (52·0%)	6068 (48·0%)	40 095 (52·4%)	2848 (49·1%)	2816 (49·7%)	2728 (48·6%)
Former smoker	35 051 (40·3%)	17 675 (37·7%)	5698 (41·5%)	6202 (42·5%)	5476 (45·7%)	27 535 (38·9%)	2494 (44·7%)	2512 (45·5%)	2510 (46·4%)
Current smoker	7760 (8·0%)	5037 (9·7%)	992 (6·5%)	901 (5·5%)	830 (6·3%)	6745 (8·6%)	384 (6·2%)	308 (4·8%)	323 (5·0%)
Chronic condition, n	1·8 (0·0)	1·8 (0·0)	1·7 (0·0)	1·7 (0·0)	1·6 (0·0)	1·8 (0·0)	1·6 (0·0)	1·5 (0·0)	1·4 (0·0)
BMI, kg/m²	26·9 (0·0)	27·1 (0·3)	27·0 (0·1)	26·5 (0·0)	26·1 (0·0)	26·9 (0·0)	26·9 (0·1)	26·3 (0·1)	26·3 (0·1)
Functional limitation									
No	31 853 (35·7%)	14 386 (29·5%)	4883 (35·4%)	6476 (43·1%)	6108 (50·0%)	22 987 (31·3%)	2560 (45·8%)	2987 (54·2%)	3319 (59·4%)
Yes	59 445 (63·1%)	35 138 (70·5%)	9345 (64·7%)	8696 (56·9%)	6266 (50·0%)	51 388 (68·7%)	3166 (54·2%)	2649 (45·8%)	2242 (40·6%)

(Table continues on next page)

(n=860), smoking status (n=118), and BMI (n=2417). We also excluded 4388 participants without follow-up time after study entry. The final study cohort included 91 298 adults with a weighted mean age of 75·8 years (SE 0·0), of whom 55 658 (56·7%) were female, 35 640 (43·3%) were male, 76 796 (87·6%) were White, 10 482 (8·3%) were Black, and 4020 (4·1%) were of another race (weighted percentages; table). The median follow-up was 6·5 years (IQR 3·6–10·7), corresponding to 703 393 person-years. Of 91 298 participants, 2176 (2·4%) died due to Alzheimer's disease and 38 232 (41·9%) died due to other causes.

Overall, 49 524 (52·7%) participants did not report any weekly minutes of MPA, whereas 74 375 (80·0%) did not report any weekly minutes of VPA. Participants with higher amounts of MPA or VPA were more likely to be White, male, and younger, were more likely to have higher education levels, lower functional limitations, and lower BMI, and were more likely to engage in strength training (table).

The dose–response analyses showed a nearly inverse, but non-significant, linear trend for the association between MPA and Alzheimer's disease-related mortality (figure 1A). By contrast, a significant L-shaped association was observed for VPA and Alzheimer's disease-related mortality between 20 weekly min and 190 weekly min (figure 1B). The nadir of the curve, representing the highest risk reduction for Alzheimer's disease-related death (ie, the optimal amount), was found at 140 weekly min of VPA (HR 0·79, 95% CI 0·66–0·95) compared

	Total (n=91 298)	Moderate physical activity				Vigorous physical activity			
		No activity (n=49 524 [52·7%])	Tertile 1 (10 min to ≤100 min; n=14 228 [15·9%])	Tertile 2 (>100 min to ≤210 min; n=15 172 [17·1%])	Tertile 3 (>210 min; n=12 374 [14·3%])	No activity (n=74 375 [80·0%])	Tertile 1 (10 min to ≤105 min; n=5726 [6·7%])	Tertile 2 (>105 min to ≤210 min; n=5636 [6·7%])	Tertile 3 (>210 min; n=5561 [6·7%])
(Continued from previous page)									
Survey year									
1997	4705 (3·9%)	3019 (4·6%)	446 (2·4%)	693 (3·4%)	547 (3·6%)	4119 (4·3%)	166 (2·2%)	214 (2·9%)	206 (2·9%)
1998	4100 (3·9%)	2519 (4·4%)	534 (3·2%)	584 (3·3%)	463 (3·2%)	3540 (4·1%)	196 (3·0%)	181 (2·8%)	183 (2·9%)
1999	3938 (4·0%)	2371 (4·4%)	476 (3·1%)	620 (3·7%)	471 (3·5%)	3394 (4·2%)	202 (3·3%)	183 (3·1%)	159 (2·7%)
2000	3925 (3·8%)	2324 (4·1%)	510 (3·2%)	607 (3·6%)	484 (3·6%)	3338 (4·0%)	200 (3·1%)	199 (3·2%)	188 (3·1%)
2001	3820 (3·7%)	2272 (4·1%)	524 (3·4%)	567 (3·3%)	457 (3·4%)	3200 (3·9%)	211 (3·4%)	228 (3·5%)	181 (2·9%)
2002	3567 (3·7%)	2106 (4·0%)	516 (3·5%)	537 (3·3%)	408 (3·4%)	3011 (3·9%)	207 (3·6%)	182 (3·0%)	167 (3·1%)
2003	3471 (3·8%)	1929 (3·9%)	497 (3·5%)	588 (3·8%)	457 (3·8%)	2906 (3·9%)	187 (3·4%)	205 (3·5%)	173 (3·3%)
2004	3717 (3·9%)	2125 (4·1%)	522 (3·4%)	605 (3·8%)	465 (3·7%)	3166 (4·1%)	191 (3·4%)	195 (3·4%)	165 (3·0%)
2005	3640 (3·8%)	2147 (4·2%)	492 (3·5%)	549 (3·5%)	452 (3·5%)	3090 (4·0%)	198 (3·2%)	175 (3·1%)	177 (3·2%)
2006	2912 (4·1%)	1726 (4·4%)	399 (3·6%)	450 (3·9%)	337 (3·8%)	2485 (4·3%)	152 (3·3%)	146 (3·6%)	129 (2·9%)
2007	2838 (4·1%)	1699 (4·6%)	367 (3·3%)	417 (3·7%)	355 (3·5%)	2429 (4·3%)	139 (3·1%)	127 (2·9%)	143 (3·5%)
2008	2783 (4·3%)	1557 (4·4%)	415 (4·0%)	436 (4·2%)	375 (4·2%)	2317 (4·4%)	151 (4·0%)	158 (4·2%)	157 (3·9%)
2009	3563 (4·5%)	1893 (4·4%)	624 (5·5%)	574 (4·3%)	472 (4·3%)	2932 (4·6%)	233 (4·8%)	210 (4·4%)	188 (4·1%)
2010	3580 (4·6%)	2040 (4·9%)	584 (4·8%)	575 (4·7%)	381 (3·7%)	2937 (4·7%)	233 (5·0%)	231 (5·0%)	179 (3·9%)
2011	4561 (4·8%)	2445 (4·9%)	736 (4·9%)	754 (4·8%)	626 (5·0%)	3723 (4·8%)	254 (4·2%)	256 (4·5%)	328 (5·8%)
2012	4722 (4·9%)	2404 (4·5%)	844 (5·5%)	803 (5·1%)	721 (5·5%)	3777 (4·7%)	318 (5·4%)	337 (6·2%)	340 (5·5%)
2013	4977 (5·2%)	2504 (4·8%)	864 (5·6%)	869 (5·5%)	740 (5·7%)	3909 (5·1%)	341 (5·2%)	369 (5·6%)	358 (5·7%)
2014	5529 (5·3%)	2709 (4·8%)	967 (5·8%)	999 (5·9%)	854 (5·9%)	4368 (5·1%)	388 (5·8%)	392 (6·1%)	381 (6·1%)
2015	5498 (5·6%)	2803 (5·2%)	910 (6·1%)	965 (5·8%)	820 (6·0%)	4260 (5·2%)	386 (6·2%)	417 (7·3%)	435 (7·4%)
2016	5792 (5·8%)	2654 (5·0%)	1100 (6·9%)	1104 (6·3%)	934 (6·5%)	4344 (5·3%)	506 (7·7%)	459 (6·9%)	483 (7·8%)
2017	4804 (6·0%)	2134 (5·1%)	954 (7·3%)	936 (6·8%)	780 (7·1%)	3630 (5·6%)	416 (8·1%)	353 (6·8%)	405 (7·7%)
2018	4806 (6·2%)	2144 (5·2%)	947 (7·6%)	940 (7·3%)	775 (7·2%)	3500 (5·7%)	451 (8·6%)	419 (8·1%)	436 (8·8%)
Vigorous physical activity, min/week	51·3 (1·0)	26·0 (0·9)	46·3 (2·0)	67·9 (1·6)	130·3 (4·4)	..	..	..	..
Moderate physical activity, min/week	117·4 (1·5)	..	..	..	..	92·1 (1·4)	163·7 (5·8)	200·3 (5·8)	291·6 (7·5)
Strength training, sessions per week	0·7 (0·0)	0·3 (0·0)	0·8 (0·0)	1·2 (0·0)	1·5 (0·0)	0·5 (0·0)	1·3 (0·0)	1·7 (0·0)	2·1 (0·1)

Data are n (weighted %) or weighted mean (SE), unless otherwise stated. Moderate and vigorous physical activity have different data distributions; thus, the cutoff points for tertiles slightly differ. Percentages might not add up to 100% due to rounding.

Table: **Baseline characteristics**

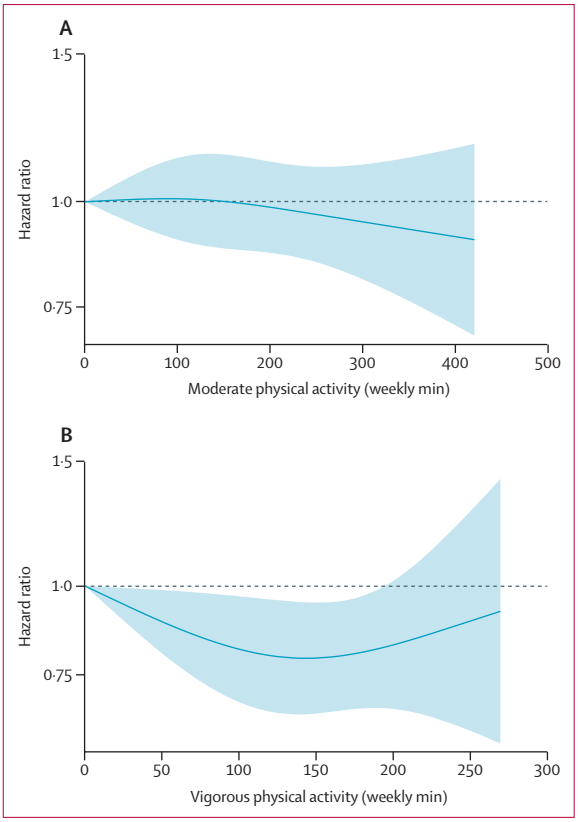

Figure 1: **Dose–response association of physical activity with mortality due to Alzheimer's disease**

(A) Moderate physical activity. (B) Vigorous physical activity. Shaded areas show 95% CIs. Hazard ratios were adjusted for age, sex, race, marital status, educational attainment, smoking status, alcohol consumption, chronic condition, BMI, functional limitation, survey year, and strength training. Models were also mutually adjusted for either vigorous or moderate physical activity. Models accounted for the National Health Survey Interview complex design and weights.

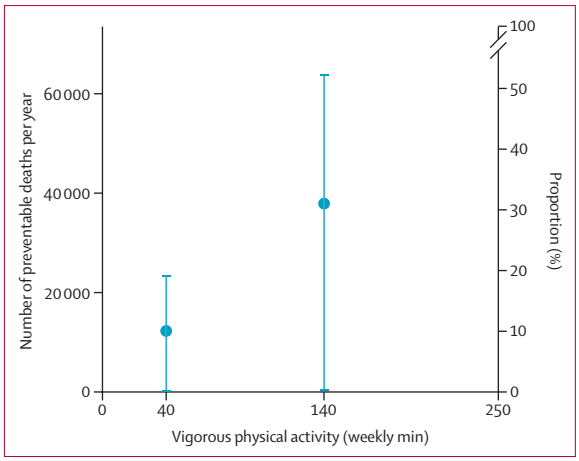

Figure 2: **Number of preventable Alzheimer's disease-related deaths and equivalent proportion of total deaths with minimal and optimal amounts of vigorous physical activity**

Error bars show 95% CIs. Counterfactual scenario using a study population with 0 min of vigorous physical activity as reference. The model used restricted cubic splines adjusted for age, sex, race, marital status, educational attainment, smoking status, alcohol consumption, chronic condition, BMI, functional limitation, survey year, moderate physical activity, and strength training. The model accounted for the National Health Survey Interview complex design and weights. Total preventable deaths and percentages were derived from adjusted population attributable fractions (95% CIs) of previously estimated hazard ratios (95% CIs), considering a total of 121 499 deaths due to Alzheimer's disease in the USA in 2019.

with the reference of 0 weekly min of VPA. The lower and upper thresholds for significant risk reductions were observed at 20 weekly min (0·95, 0·91–0·99) and at 190 weekly min of VPA (0·82, 0·67–0·99), respectively, compared with the reference of 0 weekly min of VPA. The minimal amount of VPA (ie, that leading to a risk reduction of 50% from the optimal amount) was identified at 40 weekly min (0·91, 0·84–0·95).

The minimal amount of 40 weekly min of VPA was associated with a 10·1% (95% CI 0·1–19·0) reduction in annual deaths related to Alzheimer's disease in the USA (12 238 deaths, 95% CI 89–23 172) compared with a hypothetical scenario in which the entire US adult population did not do any weekly minutes of VPA (figure 2). Engaging in the optimal amount of 140 weekly min of VPA was associated with a 31·0% (95% CI 0·3–52·3) reduction in annual deaths related to Alzheimer's disease in the USA, which corresponds to 37 710 fewer deaths per year (95% CI 311–63 567). Additional analyses showed that, compared with the survival expectancy of participants not doing any VPA, the minimal and optimal amounts of VPA increased survival expectancy by 1·6 years (95% CI 0·7–3·4) and 2·3 years (1·3–4·1), respectively, (appendix p 13).

The exclusion of the first 2 years of follow-up yielded similar estimates to those of the main dose–response analyses for both MPA and VPA (appendix pp 3, 5). The addition of sleep time and employment status as confounders resulted in an inverse L-shaped association for MPA (although not significant; appendix p 4), and in higher risk reductions of Alzheimer's disease-related mortality for the minimal and optimal amount of VPA (appendix p 6). Similar dose–response associations to those of the main dose–response analyses for both MPA and VPA were also observed when imputing missing values (appendix pp 7–8).

Additional survival analyses accounting for competing risks showed an inverse L-shaped association (although not significant) for the dose–response between MPA and Alzheimer's disease-related mortality, and a significant L-shaped association between VPA and Alzheimer's disease-related mortality (appendix pp 9–10). We identified an optimal dose for reducing incidence of Alzheimer's disease-related mortality at 140 weekly min of VPA (subhazard ratio 0·80, 95% CI 0·66–0·97) and a minimal dose at 50 weekly min (0·90, 0·80–1·00; appendix p 10). A minimal number of Alzheimer's disease-related deaths was always present during the whole follow-up period as well as for all ages of the study population (appendix pp 11–12). The exclusion of the first 2 years of follow-up did not substantially vary the number

of annual prevented deaths due to Alzheimer's disease compared with the main analysis (appendix p 14).

Discussion

To our knowledge, this study is the first to examine the dose–response associations of leisure time MPA and VPA with Alzheimer's disease-related mortality. The study also provides new estimates of the potential number of Alzheimer's disease-related deaths that could be averted through physical activity in the USA. Our results show that 20–190 weekly min of VPA are associated with a reduced risk of Alzheimer's disease-related mortality. We found a minimal dose of 40 weekly min of VPA and an optimal dose of 140 weekly min of VPA for reducing the risk of Alzheimer's disease-related mortality, potentially preventing 10% and 31% of annual Alzheimer's disease-related deaths in the USA, respectively. These findings have practical implications because a feasible goal of 10 min of VPA for 4 days per week or any other combination that adds up to 40 weekly min of VPA could reduce the risk of Alzheimer's disease-related mortality; additionally, lower but still significant risk reductions might be possible by doing 20 weekly min of VPA solely.

To date, research on overall physical activity and risk of Alzheimer's disease has often focused on older adults, and findings have shown inverse associations between the two.[20,21] Our results partly support the findings from a previous study done in a Norwegian cohort of older adults (aged 65–80 years), which reported inverse, significant associations between light (ie, not causing perspiration or panting) and hard (ie, causing perspiration or panting) leisure time physical activity and mortality related to all-cause dementia. Hard physical activity for less than 3 h/week was associated with higher risk reductions than inactivity, light physical activity, and hard physical activity for more than 3 h/week.[22] Compared with our study, in which we did not find a significant association between MPA and Alzheimer's disease-related mortality, different population characteristics, outcome measures (ie, pooled dementia diseases), and exposure assessments might explain the results observed for light physical activity in the Norwegian cohort. For example, the Norwegian study used a threshold of 3 weekly h of physical activity (ie, inactive, active for <3 h, and active for ≥3 h) to categorise the two types of physical activity, which might have reflected a more beneficial effect of physical activity, particularly light physical activity, on the outcome, when compared with an inactive category (0 min).[22]

For VPA, the results of our study suggest the existence of a maximal threshold after which no significant associations with Alzheimer's disease-related mortality were observed, which is consistent with the findings from a review observing that physical exercise might not be beneficial to the same extent for the cognitive functioning of all individuals diagnosed with Alzheimer's disease, particularly if the disease is accompanied by any cardiovascular risk factor.[23] Our study also featured an L-shaped dose–response association between VPA and Alzheimer's disease-related mortality, which is similar to the shape of the dose–response associations observed in a prospective analysis examining the association between steps and incident dementia,[24] as well as those reported in a previous meta-analysis examining associations between accelerometer-derived physical activity and all-cause mortality.[25] The study done in the UK on adults aged 40–79 years,[24] which measured the number and cadence of steps with accelerometery, found increased risk reductions of dementia in adults with a peak 30-min cadence of 112 steps per min, underscoring the importance of the intensity of physical activity in reducing incident fatal and non-fatal all-cause dementia.

With regard to the minimal dose of VPA associated with a lower risk of Alzheimer's disease-related mortality, the estimate we observed in our study (ie, 40 min/week) is substantially lower than the currently recommended duration of VPA reported in public health guidelines (ie, 75 min/week).[26] Considering that only around 80% of the participants in our study did not do any amount of VPA, there is a substantial margin for improvement in effectively conveying the message regarding public health recommendations. Overall, these findings suggest the existence of specific minimal and optimal amounts of physical activity to exhibit beneficial effects on the incidence of disease and mortality outcomes.

Additionally, given the nature of the exposure measurement, we could not capture data on less than 10 min of VPA bouts, but the potential benefits of incorporating a lower amount of physical activity at higher intensity into everyday life have been previously observed.[27] For older adults or individuals with functional-limiting diseases, this approach might be more suitable than long periods of lighter physical activity to provide crucial health benefits.

This study is the first study to investigate the associations between MPA and VPA and Alzheimer's disease-related mortality using a large representative sample of US adults from the NHIS. However, several limitations should be considered, including potential recall and misclassification biases due to self-reported data, the possibility of residual reverse causation despite the sensitivity analyses, and the potential for residual confounding. Additionally, respondents who were health conscious might have been more prone to participate in the NHIS, which might have led to selection bias, thus attenuating the observed association of VPA with Alzheimer's disease-related mortality; the estimation of preventable deaths relied on the latest official figures, which might be underestimated;[28] because participants with missing data were excluded, the amounts of MPA and VPA reported in this study might have been lower than the current self-reported amounts of MPA and VPA in the US population,[29] which might affect straightforward generalisations of the findings of the present study; and

the late incorporation of Alzheimer's disease diagnosis questions might have introduced some reversal causation, although the exclusion of participants unable to do physical activity at baseline and the analysis in which the first 2 years of follow-up were removed reduce this possibility. Finally, the right part of the dose–response curves in this study was affected by the sparsity of data and events, which might have contributed to the wide confidence intervals of our estimates in this part of the curves.

Contributors

RL-B and BdPC conceptualised and designed the study, had access to the raw data, did the data analysis, and wrote the first draft of the manuscript. RL-B collected the data. All authors interpreted the data, and accessed and verified the underlying data reported in the manuscript. All authors contributed to the critical review of the manuscript. All authors have seen and approved the final version of the manuscript. RL-B had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

The data used in this study are publicly available in the Survey Data and Documentation section at https://www.cdc.gov/nchs/nhis/index.htm.

Acknowledgments

RL-B is supported by NextGenerationEU. ES is funded by an Australian National Health and Medical Research Council investigator grant (APP 1194510). BdPC is supported by the Government of Andalusia, Research Talent Recruitment Programme (EMERGIA 2020/00158).

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