Changes in physical activity and all-cause mortality among individuals with dementia: a cohort study using the National Health Insurance Service Database in Korea

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ABSTRACT

Objective To examine associations between the amount and changes in regular physical activity (PA) before and after diagnosis of dementia and all-cause mortality risk, and whether these associations differ by PA intensity (light, moderate or vigorous).

Methods This retrospective cohort study used data from the Korean National Health Insurance Service Database, including 60 252 individuals newly diagnosed with dementia between 2010 and 2016 who underwent health examinations both before and after diagnosis. PA was assessed using the International Physical Activity Questionnaire–Short Form. Multivariable Cox proportional hazards regression models were used to analyse the associations between PA (amount and changes) and all-cause mortality risk.

Results During a mean follow-up of 3.7 years, 16 431 (27.3%) deaths occurred. Higher PA levels after dementia diagnosis were associated with a dose-dependent decrease in mortality risk (p for trend <0.001). Maintaining regular PA, compared with remaining inactive, was associated with the lowest mortality risk (HR=0.71, 95% CI 0.65 to 0.79). Sustained engagement in PA of any intensity was associated with decreased mortality risk: light (HR=0.70, 95% CI 0.67 to 0.75), moderate (HR=0.74, 95% CI 0.64 to 0.86) and vigorous PA (HR=0.70, 95% CI 0.61 to 0.79). Initiating any PA intensity after dementia diagnosis was associated with at least 20% reduced mortality risk. These associations were consistent in Alzheimer's disease.

Conclusions Maintaining or initiating regular PA, regardless of intensity, after dementia diagnosis was associated with a reduced risk of all-cause mortality. Lifestyle modifications promoting PA might offer survival benefits for individuals with dementia.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Few studies have suggested that being physically active is associated with a decreased risk of mortality in individuals with dementia, but these studies are limited to measuring physical activity at a single time point. Whether changes in physical activity, including amount and intensity, before and after dementia diagnosis are associated with mortality risk has never been investigated.

WHAT THIS STUDY ADDS

⇒ In this nationwide population-based cohort study in Korea of 60 252 individuals with dementia, inverse linear dose–response associations were observed between the amount of physical activity after dementia diagnosis and all-cause mortality risk. Individuals who maintained or newly started regular physical activity before and after their dementia diagnosis had a decreased risk of mortality, which was also observed for any intensity of physical activity.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our study highlights the potential clinical value of encouraging people with dementia to maintain or start physical activity, regardless of its intensity, after their dementia diagnosis.

INTRODUCTION

Dementia is the most common neurodegenerative disease and affects nearly 50 million people worldwide, which is expected to increase to 130 million by 2050.[1 2] As of recent statistics, Alzheimer's disease (AD) is the seventh leading cause of death,[3] and mortality attributed to AD has substantially increased.[4] Patients with all subtypes of dementia experience significant reductions in life expectancy.[5] A population-based estimation of median survival time after diagnosis of dementia was 4.5 years.[6] As dementia cannot be reversed with any medications, a non-pharmacologic approach, such as lifestyle modification, is considered important to modify the progression of dementia.[7]

Exercise is associated with reduced risks of mortality and cardiovascular disease.[8 9] Among patients with dementia, physical activity (PA) has been known to potentially delay its onset and progression through modulation of the brain structure and function.[10] One multicentre observational study in Korea showed that performing PA more than 150 min per week was associated with a decreased risk of mortality in patients with AD.[11] Being active is associated with a mortality reduction of 36% among cognitively frail elderly in a population-based cohort study from Spain.[12]

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Furthermore, two prospective cohort studies showed that greater cardiorespiratory fitness, an objective measure of recent PA habits, was associated with a lower risk of dementia-related mortality,[13 14] emphasising the relevance of promoting physical fitness to mitigate mortality risk in individuals with dementia. However, prior studies have been limited to measuring PA at a single point in time in relation to mortality risk. The association between changes in PA before and after diagnosis of dementia and mortality risk remains unexplored while considering the amount and intensity of PA. Evidence from this approach would be valuable to inform exercise interventions for patients with dementia. Notwithstanding, it would be challenging to conduct a long-term randomised controlled study to assess the effects of PA on health outcomes in patients with dementia. This paucity of evidence prompted us to investigate the association between changes in the level of PA before and after the diagnosis of dementia and the risk of mortality using data from a nationally representative large-scale cohort of individuals with dementia in South Korea.

RESEARCH DESIGN AND METHODS

Data source

The National Health Insurance Service (NHIS) in Korea is a mandatory single-payer universal healthcare system that covers almost the entire Korean population. All insured Koreans at least 40 years old and their dependants can receive biennial health check-ups fully covered by the NHIS. Therefore, the NHIS obtains health information of the entire South Korean population on eligibility (age, sex, residential area and income level), health check-ups (health-related behaviours and anthropometric and laboratory measurements) and a claim database (medical utilisation, diagnosis based on the International Classification of Diseases, 10th revision (ICD-10), medication and procedures). The NHIS database is provided to researchers with appropriate research proposals.

Study population

From the NHIS database, we initially included 66 234 individuals aged ≥40 years who had been newly diagnosed with dementia between 1 January 2010 and 31 December 2016 and who had undergone health check-ups provided by the NHIS within 2 years before and after the diagnosis of dementia. Dementia was defined as having received prescriptions for one or more anti-dementia medications (donepezil, rivastigmine, memantine or galantamine) on at least two occasions, identified under the following ICD-10 codes (F00, F01, F02, F03, G30 or G31 for all-cause dementia; F00 and/or G30 for AD; and F01 for vascular dementia (VaD)). The National Health Insurance reimbursement criteria in Korea requires documented cognitive impairment to claim expenses for anti-dementia medications, with a Mini-Mental State Examination score of ≤26 and either a Clinical Dementia Rating of ≥1 or a Global Deterioration Scale score of ≥3. Therefore, cases where anti-dementia medications were prescribed for other neurological conditions except dementia, were excluded from our study. We then excluded 3491 individuals with missing values and 2491 who died within 1 year after the diagnosis of dementia. Finally, data from 60 252 individuals were analysed.

Evaluation of physical activity

PA was self-reportedly measured during health check-ups using the International Physical Activity Questionnaire–Short Form (IPAQ–SF), developed by WHO and well-validated.[15 16] Participants were asked how many days per week they performed physical activities by intensity level. Vigorous PA was regarded as exercise such as running, aerobics, fast bicycling and climbing, for more than 20 min; moderate PA included fast walking, double tennis and bicycling at a regular pace, for more than 30 min; light PA included activities such as walking for commuting or leisure time and sweeping carpets for more than 30 min. With rating light, moderate and vigorous PA as 2.9, 4.0 and 7.0 metabolic equivalent of tasks (METs), respectively,[17] the total amount of PA (MET-min/week) was the sum of multiplying 2.9, 4.0 and 7.0 METs by the frequency of light, moderate and vigorous PA together with a minimum duration per week for each intensity level (30 min for light and moderate PA and 20 min for vigorous PA). We then divided the participants into four groups according to the total amount of PA (MET-min/week) after diagnosis of dementia (0, 1–499, 500–999 and ≥1000 MET-min/week); these cut-off points are based on the guidelines-recommended level (at least 150 min of moderate-intensity activity or 75 min of vigorous-intensity activity per week) as well as previous studies.[18 19]

Regular PA was defined as performing vigorous PA three or more times per week, with each session lasting at least 20 min or moderate PA five or more times per week, with each session lasting at least 30 min.[20 21] The individuals who did not engage in moderate or vigorous PA were considered as physically inactive. We categorised the study population into four groups according to the changes in regular PA within 2 years before and after the diagnosis of dementia: non-exercisers (no to no), quitters (yes to no), starters (no to yes) and maintainers (yes to yes). Similarly, individuals were categorised into four groups based on the changes in engagement in each intensity of PA. The mean (SD) duration between the two health check-ups for PA assessment was 2.01 (0.46) years, which consisted of 1.03 (0.53) years from the first health check-up to diagnosis of dementia and 0.98 (0.53) years from the diagnosis to the second health check-up.

All-cause mortality

The endpoint of this study was all-cause mortality up to 31 December 2019, confirmed through the linkage between the NHIS database and mortality data from the Korean National Statistical Office. The mean (SD) follow-up duration was 3.7 (1.9) years.

Measurement of covariates

Residential areas were categorised as urban or rural. With the NHIS premium as an income estimate, individuals in the lowest quartile or receiving medical aid were classified as low-income group. Smoking status was categorised as either ever-smokers or never-smokers. Individuals with an average alcohol intake of ≥1 g/day were considered alcohol drinkers. After fasting for at least 8 hours, a physical examination, including anthropometric and laboratory measurements, was performed by trained staffs. Body mass index was calculated as weight in kilograms divided by the square of the height in metres. Hypertension was defined as systolic/diastolic blood pressure ≥140/90 mm Hg or at least one prescription claim per year for an antihypertensive agent under ICD-10 codes (I10–I13, I15). Type 2 diabetes was defined as an ICD-10 code (E11–E14) diagnosis with at least a yearly claim for prescription of antidiabetic agents. Total cholesterol levels of ≥240 mg/dL or at least one prescription claim per year for lipid-lowering agents under ICD-10 codes (E78) indicated dyslipidaemia. Chronic kidney disease was defined as a glomerular filtration rate of <60 mL/min/1.73 m^2 as estimated by the

Modification of Diet in Renal Disease equation. The presence of disability was evaluated using the database from the National Disability Registry. The number (single, dual, triple or quadruple) of anti-dementia medications used was also assessed.

Statistical analysis

Demographic and clinical characteristics at the health check-up within 2 years after the diagnosis of dementia were presented as the mean±SD or number (percentage) according to the occurrence of death and compared using the analysis of variance for continuous variables and the X^2 test for categorical variables.

Cox proportional hazards regression models were applied to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between the amount of PA after dementia diagnosis (all-cause and subtypes such as AD and VaD) and risk of all-cause mortality, considering PA amount both as a continuous variable (per 100 MET-min/week) and as a categorical variable (0, 1–499, 500–999 and ≥1000 MET-min/week). In addition to an unadjusted model (model 1), we ascertained potential confounders a priori based on the literature review, including age, sex, residential area, income, smoking status, alcohol consumption, body mass index, hypertension, type 2 diabetes, dyslipidaemia and chronic kidney disease in model 2. Model 3 was further adjusted for disability and the number of anti-dementia medications used. A linear regression model was used to test for a linear trend in the dose–response association between the amount of PA after dementia diagnosis and all-cause mortality risk. To further examine this dose–response relationship, we conducted a cubic spline regression analysis, allowing for more flexible modelling beyond a simple linear trend, with the same multivariable adjustments as in model 3.

Regarding changes in regular PA engagement, Kaplan-Meier curves were plotted to illustrate survival probabilities across different categories of changes in regular PA engagement and were compared using the log-rank test. The same Cox proportional hazards regression models (models 1, 2 and 3 as described earlier) were applied to investigate the association between changes in regular PA (both overall and at each intensity level before and after dementia diagnosis) and mortality risk. Given that the definition of regular PA does not include light-intensity PA, we examined changes in light, moderate and vigorous PA intensities separately to assess their unique contributions to mortality risk in individuals with dementia, using consistent statistical models. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina, USA). The P values provided are two-sided, with the level of significance at 0.05.

Patient and public involvement statement

Patients or the public were not involved in the design or conduct or reporting or dissemination plans of our research.

Equity, diversity and inclusion statement

This study uses data from the National Health Insurance Database in South Korea, which includes only Korean participants, a limitation we acknowledge in the limitations section. The National Health Insurance Service covers almost the entire Korean population and we did not impose additional restrictions related to socioeconomic status or representation from marginalised groups during the study design or data analysis. The research team comprises clinical and academic researchers and statisticians from Korea and the United States, including both women and men (five women and four men).

Table 1 Baseline characteristics of the study population

Characteristics	Total	Mortality		P value
		No	Yes	
Number	60 252	43 821	16 431	
Age (years)	74.1±8.2	72.9±8.2	77.3±7.2	<0.001
Sex (men)	23 275 (38.6)	14 751 (33.7)	8524 (51.9)	<0.001
Residential area, urban	17 931 (29.8)	13 172 (30.1)	4759 (29.0)	0.009
Low income	11 876 (19.7)	8792 (20.1)	3084 (18.8)	<0.001
PA amount (MET-min/week)	414.4±570.6	446.2±584.6	330.0±522.1	<0.001
Ever-smoker	12 906 (21.4)	8590 (19.6)	4316 (26.3)	<0.001
Alcohol drinker	6485 (10.8)	4716 (10.8)	1769 (10.8)	0.998
Body mass index (kg/m^2)	23.4±3.4	23.7±3.3	22.4±3.4	<0.001
Systolic BP (mm Hg)	127.7±16.1	127.6±15.9	127.8±16.8	0.401
Diastolic BP (mm Hg)	76.5±10.2	76.5±10.1	76.5±10.6	0.823
Fasting glucose (mg/dL)	107.4±33.7	106.3±30.9	110.2±40.1	<0.001
Total cholesterol (mg/dL)	187.3±42.2	188.8±42.2	183.2±41.9	<0.001
eGFR (mL/min/1.73 m^2)	78.2±38.2	79.6±38.2	74.6±37.9	<0.001
Hypertension	41 440 (68.8)	29 762 (67.9)	11 678 (71.1)	<0.001
Type 2 diabetes	17 872 (29.7)	12 261 (28.0)	5611 (34.1)	<0.001
Dyslipidaemia	27 386 (45.5)	21 257 (48.5)	6129 (37.3)	<0.001
Chronic kidney disease	12 954 (21.5)	8442 (19.3)	4512 (27.5)	<0.001
Disability registration, yes	16 433 (27.3)	11 708 (26.7)	4725 (28.8)	<0.001
Type of dementia				<0.001
Alzheimer's disease	43 276 (71.8)	31 551 (72.0)	11 725 (71.4)	
Vascular dementia	7536 (12.5)	5641 (12.9)	1895 (11.5)	
Other dementia	9440 (15.7)	6629 (15.1)	2811 (17.1)	
Number of anti-dementia medications				<0.001
Single	52 400 (87.0)	38 519 (87.9)	13 881 (84.5)	
Dual	7196 (11.9)	4855 (11.1)	2341 (14.3)	
Triple	635 (1.1)	432 (1.0)	203 (1.2)	
Quadruple	21 (0.03)	15 (0.03)	6 (0.04)	
Type of anti-dementia medication				<0.001
Donepezil	52 065 (86.4)	38 141 (87.0)	13 924 (84.7)	
Rivastigmine	6210 (10.3)	4293 (9.8)	1917 (11.7)	
Memantine	5666 (9.4)	3747 (8.6)	1919 (11.7)	
Galantamine	4840 (8.0)	3404 (7.8)	1436 (8.7)	
Regular PA changes				<0.001
No to No	47 050 (78.1)	33 641 (76.8)	13 409 (81.6)	
Yes to No	6212 (10.3)	4590 (10.5)	1622 (9.9)	
No to Yes	4801 (8.0)	3834 (8.7)	967 (5.9)	
Yes to Yes	2189 (3.6)	1756 (4.0)	433 (2.6)	

Data are presented as mean±SD or number (percentage).
BP, blood pressure; eGFR, estimated glomerular filtration rate; MET-min/week, metabolic equivalent of task minutes per week; PA, physical activity.

RESULTS

Baseline characteristics

Table 1 shows the baseline characteristics of individuals with all-cause dementia (n=60 252) according to whether death occurred during the follow-up period. Men accounted for 38.6% (n=23 275); the mean (SD) age was 74.1 (8.2) years; 43 276 individuals (71.8%) had AD and 7536 (12.5%) had VaD. Among individuals with all-cause dementia, the proportion of non-exercisers, quitters, starters and maintainers in regular PA was 78.1% (n=47 050), 10.3% (n=6212), 8.0% (n=4801) and 3.6% (n=2189), respectively. There were significant differences

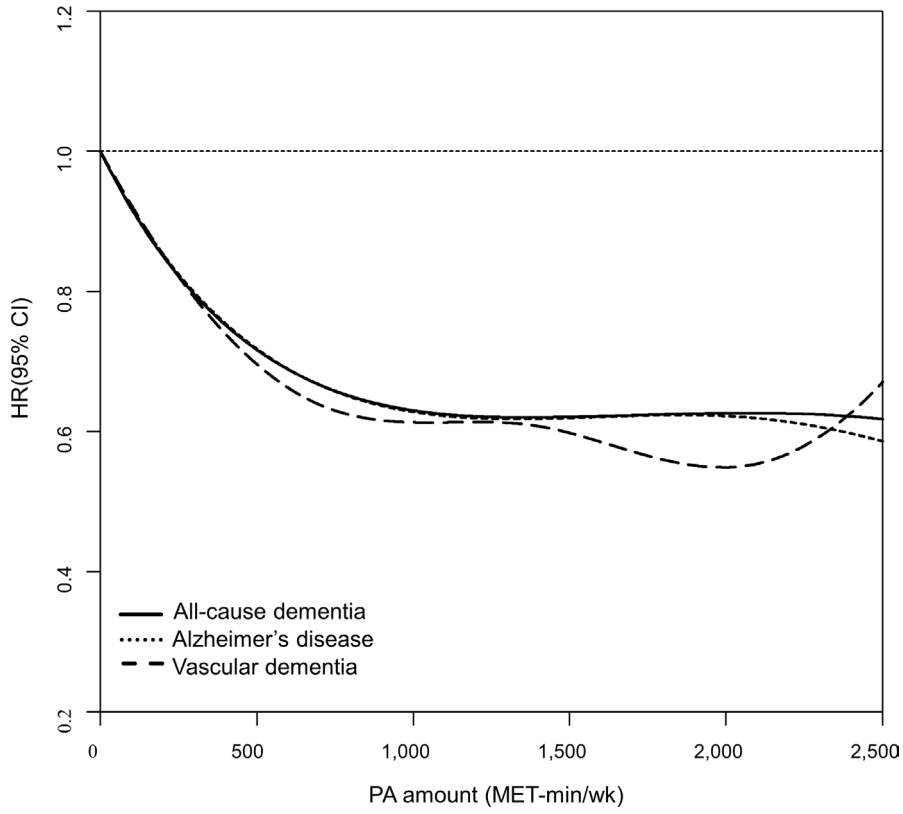

Figure 1 Cubic spline curves for the associations between the amount of PA after diagnosis of dementia and the risk of mortality among individuals with all-cause dementia, Alzheimer's disease and vascular dementia. HRs were adjusted for age, sex, residential area, income, smoking status, alcohol consumption, body mass index, hypertension, type 2 diabetes, dyslipidaemia, chronic kidney disease, disability and the number of anti-dementia medications used. MET-min/week, metabolic equivalent of task minutes per week; PA, physical activity.

in the presence of disability and the number and type of anti-dementia medications between individuals who did and did not die (p<0.001). The proportions of ever-smokers and comorbidities such as hypertension, type 2 diabetes and chronic kidney disease were higher among deceased individuals with dementia (p<0.001).

Association between the amount of physical activity after the diagnosis of dementia and all-cause mortality

Among a total of 60 252 individuals with dementia, there were 16 431 (27.3%) deaths during 3.7 years of mean follow-up. The cubic spline curves shown in figure 1 shows the reverse dose–response associations between the amount of PA after the diagnosis of dementia and the risk of mortality across all subtypes of dementia. Kaplan–Meier curves in figure 2 show that survival probabilities increased in individuals who maintained regular PA before and after their dementia diagnosis (log-rank p<0.001). We observed a gradually reduced risk of mortality among individuals with all-cause dementia as the amount of PA after the diagnosis of dementia increased from 1 to 499 MET-min/week (HR=0.82, 95% CI 0.79 to 0.85) to ≥1000 MET-min/week (HR=0.66, 95% CI 0.62 to 0.70), compared with those who did not exercise at all (p for trend <0.001), after adjusting for potential confounding factors

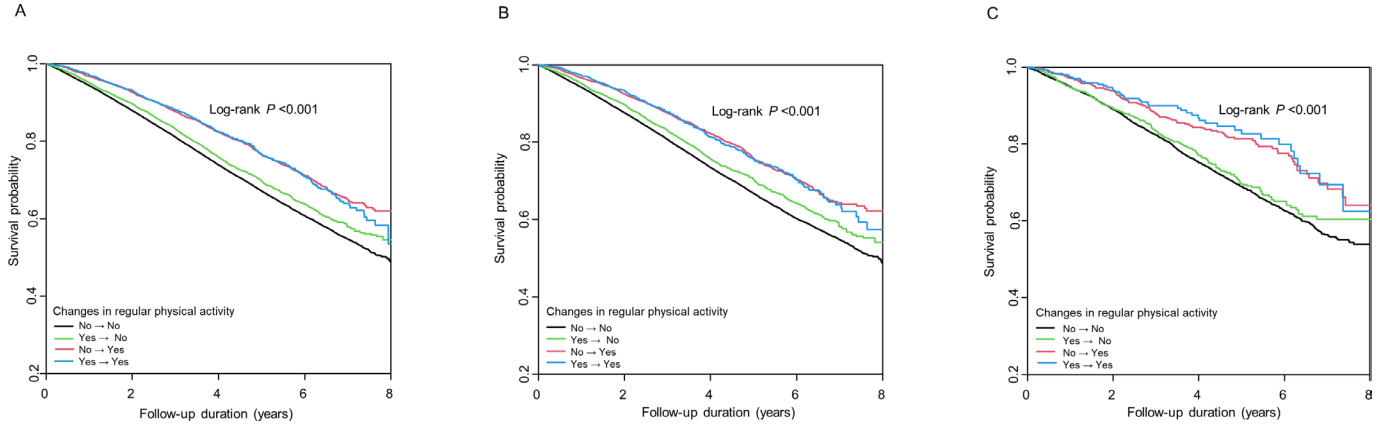

Figure 2 Kaplan-Meier estimates for the survival probabilities according to changes in regular physical activity engagement before and after the diagnosis of (A) all-cause dementia, (B) Alzheimer's disease and (C) vascular dementia (all log-rank p<0.001).

Table 2 HRs (95% CIs) of all-cause mortality according to the amount of physical activity after diagnosis of dementia

PA amount (MET-min/week)	Dementia (n)	Mortality (n)	Person-years	Mortality rate*	HR (95% CI) Model 1†	Model 2‡	Model 3§
All-cause dementia							
0	24 997	8232	90 243	91.2	1 (reference)	1 (reference)	1 (reference)
1–499	15 547	3941	58 163	67.8	0.74 (0.71 to 0.77)	0.81 (0.78 to 0.85)	0.82 (0.79 to 0.85)
500–999	12 609	2820	47 728	59.1	0.65 (0.62 to 0.67)	0.70 (0.67 to 0.73)	0.71 (0.68 to 0.74)
≥1000	7099	1438	27 559	52.2	0.57 (0.54 to 0.60)	0.65 (0.62 to 0.69)	0.66 (0.62 to 0.70)
P for trend					<0.001	<0.001	<0.001
Continuous							
Per 100 MET-min/week of PA					0.97 (0.96 to 0.97)	0.97 (0.97 to 0.98)	0.97 (0.97 to 0.98)
P value					<0.001	<0.001	<0.001
Alzheimer's disease							
0	17 995	5855	63 860	91.7	1 (reference)	1 (reference)	1 (reference)
1–499	11 304	2841	41 639	68.2	0.74 (0.71 to 0.78)	0.81 (0.78 to 0.85)	0.82 (0.79 to 0.86)
500–999	9092	2045	33 813	60.5	0.66 (0.63 to 0.69)	0.71 (0.67 to 0.74)	0.71 (0.68 to 0.75)
≥1000	4885	984	18 744	52.5	0.57 (0.53 to 0.61)	0.64 (0.60 to 0.69)	0.65 (0.61 to 0.70)
P for trend					<0.001	<0.001	<0.001
Continuous							
Per 100 MET-min/week of PA					0.96 (0.96 to 0.97)	0.97 (0.97 to 0.98)	0.97 (0.97 to 0.98)
P value					<0.001	<0.001	<0.001
Vascular dementia							
0	3179	1015	11 596	87.5	1 (reference)	1 (reference)	1 (reference)
1–499	1827	432	6778	63.7	0.73 (0.65 to 0.82)	0.81 (0.73 to 0.91)	0.82 (0.73 to 0.91)
500–999	1552	284	6005	47.3	0.54 (0.47 to 0.61)	0.60 (0.53 to 0.69)	0.61 (0.53 to 0.69)
≥1000	978	164	3736	43.9	0.50 (0.42 to 0.59)	0.64 (0.54 to 0.76)	0.65 (0.55 to 0.77)
P for trend					<0.001	<0.001	<0.001
Continuous							
Per 100 MET-min/week of PA					0.95 (0.95 to 0.96)	0.97 (0.96 to 0.98)	0.97 (0.96 to 0.98)
P value					<0.001	<0.001	<0.001

HRs (95% CIs) were calculated using multivariable Cox proportional hazards regression analysis.
*Mortality rate per 1000 person-years.
†Model 1 was unadjusted.
‡Model 2 was adjusted for age, sex, residential area, income, smoking status, alcohol consumption, body mass index, hypertension, type 2 diabetes, dyslipidaemia and chronic kidney disease.
§Model 3 was adjusted for age, sex, residential area, income, smoking status, alcohol consumption, body mass index, hypertension, type 2 diabetes, dyslipidaemia, chronic kidney disease, disability and number of anti-dementia medications used.
CI, confidence interval; HR, hazard ratio; MET-min/week, metabolic equivalent of task minutes per week; PA, physical activity.

(model 3) (table 2). Similar trends were observed in individuals with AD (HR=0.65, 95% CI 0.61 to 0.70 in the group with ≥1000 MET-min/week, p for trend<0.001) and in those with VaD (HR=0.65, 95% CI 0.55 to 0.77 in the group with ≥1000 MET-min/week, p for trend<0.001). When treating PA as a continuous variable, we observed a significant 3% reduction in mortality risk for every 100 MET-min/week increase in PA after dementia diagnosis, consistent across all-cause dementia and its subgroups (table 2).

Association between changes in regular physical activity before and after the diagnosis of dementia and all-cause mortality

In table 3, individuals with all-cause dementia who remained physically active both before and after dementia diagnosis had the lowest mortality risk after adjusting for confounders, compared with those who have never engaged in regular PA (model 3, HR=0.71, 95% CI 0.65 to 0.79). Similar associations were observed in those with AD who maintained regular PA (HR=0.71, 95% CI 0.63 to 0.79) and in those with VaD (HR=0.64, 95% CI 0.47 to 0.86). Individuals who started to engage in regular PA after the diagnosis of dementia also had a lower risk of mortality (HR=0.77, 95% CI 0.72 to 0.82 for all-cause dementia, HR=0.76, 95% CI 0.71 to 0.83 for AD and HR=0.81, 95% CI 0.66 to 0.98 for VaD). Individuals who stopped regular PA after the diagnosis of all-cause dementia and AD showed a slight reduction in the risk of mortality (HR=0.91, 95% CI 0.86 to 0.95 for all-cause dementia and HR=0.87, 95% CI 0.82 to 0.93 for AD).

Association between the intensity of physical activity before and after diagnosis of dementia and all-cause mortality

Table 4 shows the mortality risk according to the engagement in each intensity of PA before and after the diagnosis of dementia. Individuals with all-cause dementia who maintained each intensity of PA showed the lowest risk of mortality, regardless of PA intensities (light PA, HR=0.70, 95% CI 0.67 to 0.75; moderate PA, HR=0.74, 95% CI 0.64 to 0.86; vigorous PA, HR=0.70, 95% CI 0.61 to 0.79). Similarly, a persistent engagement in light, moderate and vigorous PA among individuals with AD was associated with 31% (HR=0.69, 95% CI 0.64 to 0.74), 29% (HR=0.71, 95% CI 0.60 to 0.85) and 30% (HR=0.70, 95% CI 0.61 to 0.82) reduced mortality risk, respectively. Both PA starters and quitters with all-cause dementia and AD had a lower mortality risk than those who never engaged in any intensity of PA. Among individuals with VaD, sustained engagement in either light or vigorous PA was associated with decreased mortality risks (light PA, HR=0.70, 95% CI 0.59 to 0.83; vigorous PA, HR=0.48, 95% CI 0.30 to 0.75).

Table 3 HRs (95% CIs) of all-cause mortality according to the changes in regular physical activity before and after the diagnosis of dementia

Regular PA change	Dementia (n)	Mortality (n)	Person-years	Mortality rate*	HR (95% CI) Model 1†	Model 2‡	Model 3§
All-cause dementia							
No to No	47 050	13 409	173 171	77.4	1 (reference)	1 (reference)	1 (reference)
Yes to No	6212	1622	23 364	69.4	0.89 (0.85 to 0.94)	0.90 (0.85 to 0.95)	0.91 (0.86 to 0.95)
No to Yes	4801	967	18 753	51.6	0.66 (0.62 to 0.70)	0.76 (0.71 to 0.82)	0.77 (0.72 to 0.82)
Yes to Yes	2189	433	8404	51.5	0.66 (0.60 to 0.73)	0.71 (0.64 to 0.78)	0.71 (0.65 to 0.79)
Alzheimer's disease							
No to No	34 083	9635	123 300	78.1	1 (reference)	1 (reference)	1 (reference)
Yes to No	4368	1121	16 271	68.9	0.88 (0.83 to 0.93)	0.86 (0.81 to 0.92)	0.87 (0.82 to 0.93)
No to Yes	3313	668	12 767	52.3	0.66 (0.61 to 0.72)	0.76 (0.70 to 0.82)	0.76 (0.71 to 0.83)
Yes to Yes	1512	301	5717	52.7	0.67 (0.60 to 0.75)	0.69 (0.62 to 0.78)	0.71 (0.63 to 0.79)
Vascular dementia							
No to No	5734	1529	21 288	71.8	1 (reference)	1 (reference)	1 (reference)
Yes to No	866	213	3226	66.0	0.92 (0.80 to 1.06)	0.95 (0.82 to 1.10)	0.96 (0.83 to 1.11)
No to Yes	640	109	2479	44.0	0.61 (0.50 to 0.74)	0.80 (0.66 to 0.98)	0.81 (0.66 to 0.98)
Yes to Yes	296	44	1123	39.2	0.54 (0.40 to 0.74)	0.63 (0.47 to 0.85)	0.64 (0.47 to 0.86)

HRs (95% CIs) were calculated using multivariable Cox proportional hazards regression analysis.
Regular PA engagement was defined as performing vigorous PA for ≥3 times per week or moderate PA for ≥5 times per week.
*Mortality rate per 1,000 person-years.
†Model 1 was unadjusted.
‡Model 2 was adjusted for age, sex, residential area, income, smoking status, alcohol consumption, body mass index, hypertension, type 2 diabetes, dyslipidaemia and chronic kidney disease.
§Model 3 was adjusted for age, sex, residential area, income, smoking status, alcohol consumption, body mass index, hypertension, type 2 diabetes, dyslipidaemia, chronic kidney disease, disability and number of anti-dementia medications used.
CI, confidence interval; HR, hazard ratio; PA, physical activity.

DISCUSSION

Using a nationwide cohort data of 60 252 individuals with dementia, the present study found a dose–response association between an increased amount of PA and the decreased risk of all-cause mortality. Sustained engagement in regular PA before and after the diagnosis of dementia was associated with the greatest reduction in mortality risk for individuals with all dementia subtypes. In particular, a mortality risk was reduced by 36% among those with VaD who maintained regular PA compared with those who had never engaged in regular PA. Engagement in regular PA after dementia diagnosis was associated with reduced mortality risk by 24% among those with AD; however, discontinuing regular PA was associated with a slight mortality reduction. A reduced mortality risk was similarly observed when individuals maintained or started any intensity of PA before and after the diagnosis of dementia, whether light, moderate or vigorous.

Building on the established protective effect of PA against all-cause mortality,[8 9] our study suggests that even at low levels, PA might significantly diminish mortality risk in individuals with dementia. Current WHO guideline for older adults recommends at least 150 to 300 min of moderate-intensity PA or 75 to 150 min of vigorous PA or an equivalent combination.[20] Evidence indicates that fewer than one-third of older adults engage in the recommended level of PA,[22] and people with dementia are more likely to fail to meet the adequate level of PA than their cognitively healthy counterparts.[23] Forty-two percent of our study participants were sedentary and only 11.8% reached the recommended level of PA of more than 1000 MET-min/week. As with the recent PA guidelines suggesting that engagement in some PA is better than none at all and sedentary behaviour should be limited,[20] our results suggest even a small amount of PA could be beneficial in decreasing the risk of mortality in patients with dementia.

Our findings suggest the necessity for engaging in regular PA after the diagnosis of dementia. Compared with those who had never engaged in regular PA, individuals who maintained recommended PA levels before and after diagnosis of dementia had the lowest mortality risk. Prior studies have shown that regular exercise is associated with improved cognitive decline in patients with dementia compared with sedentary controls.[24–27] While a randomised controlled trial reported that an aerobic and strengthening exercise programme for patients with dementia improved physical fitness, but not cognitive function,[28] another study highlighted that being physically active preserved the quality of life in people with dementia.[29] Evidence is inconsistent on whether regular PA could improve several domains, such as cognition, physical function or quality of life, in people with dementia; however, our results demonstrated that encouraging individuals with dementia to partake in regular PA would help to reduce their mortality risk.

Based on our findings, it is noteworthy that the effect of sustained engagement in light PA on the decreased mortality risk might be comparable to that of maintaining moderate or vigorous PA. Prior research proved that light PA is as beneficial in reducing mortality as moderate and vigorous PA.[30 31] Considering light PA and individualisation of PA prescription for patients with dementia could be crucial, especially for patients who are less likely to engage in moderate and vigorous PA owing to various barriers.[32 33]

The post-diagnosis PA level in individuals with dementia measured in our study might represent the PA level during various stage of dementia, considering dementia has a long preclinical period with insidious onset. Abundant experimental studies have shown that PA potentially modifies the pathogenesis of AD by reducing extracellular β-amyloid disposition and τ hyperphosphorylation.[34 35] Exercise has been shown to improve

Table 4 HRs (95% CIs) of all-cause mortality according to the physical activity changes at each intensity before and after diagnosis of dementia

PA change	Dementia (n)	Mortality (n)	Person-years	Mortality rate*	HR (95% CI) Model 1†	Model 2‡	Model 3§
All-cause dementia							
Light PA							
No to No	33 778	9951	124 461	80.0	1 (reference)	1 (reference)	1 (reference)
Yes to No	10 456	2934	38 515	76.2	0.95 (0.92 to 1.00)	0.92 (0.89 to 0.96)	0.93 (0.89 to 0.97)
No to Yes	9580	2183	36 742	59.4	0.74 (0.71 to 0.78)	0.78 (0.75 to 0.82)	0.79 (0.75 to 0.83)
Yes to Yes	6438	1363	23 975	56.9	0.71 (0.67 to 0.76)	0.69 (0.66 to 0.74)	0.70 (0.67 to 0.75)
Moderate PA							
No to No	52 563	14 605	194 224	75.2	1 (reference)	1 (reference)	1 (reference)
Yes to No	3707	984	13 869	71.0	0.94 (0.88 to 1.01)	0.90 (0.85 to 0.97)	0.91 (0.86 to 0.98)
No to Yes	3128	655	12 281	53.3	0.70 (0.65 to 0.76)	0.78 (0.72 to 0.84)	0.78 (0.72 to 0.84)
Yes to Yes	854	187	3318	56.4	0.75 (0.65 to 0.86)	0.73 (0.63 to 0.85)	0.74 (0.64 to 0.86)
Vigorous PA							
No to No	50 142	14 191	184 981	76.7	1 (reference)	1 (reference)	1 (reference)
Yes to No	4938	1242	18 638	66.6	0.87 (0.82 to 0.92)	0.89 (0.84 to 0.94)	0.89 (0.84 to 0.95)
No to Yes	3798	743	14 772	50.3	0.65 (0.61 to 0.70)	0.76 (0.70 to 0.82)	0.76 (0.71 to 0.82)
Yes to Yes	1374	255	5302	48.1	0.62 (0.55 to 0.71)	0.69 (0.61 to 0.78)	0.70 (0.61 to 0.79)
Alzheimer's disease							
Light PA							
No to No	24 372	7117	88 271	80.6	1 (reference)	1 (reference)	1 (reference)
Yes to No	7521	2098	27 185	77.2	0.96 (0.91 to 1.01)	0.92 (0.88 to 0.97)	0.93 (0.88 to 0.97)
No to Yes	6681	1526	25 344	60.2	0.74 (0.70 to 0.79)	0.78 (0.74 to 0.82)	0.78 (0.74 to 0.83)
Yes to Yes	4702	984	17 256	57.0	0.71 (0.66 to 0.76)	0.68 (0.63 to 0.73)	0.69 (0.64 to 0.74)
Moderate PA							
No to No	37 887	10 473	137 624	76.1	1 (reference)	1 (reference)	1 (reference)
Yes to No	2654	681	9847	69.2	0.91 (0.84 to 0.98)	0.86 (0.80 to 0.93)	0.88 (0.81 to 0.95)
No to Yes	2124	440	8215	53.6	0.70 (0.64 to 0.77)	0.75 (0.68 to 0.83)	0.76 (0.69 to 0.83)
Yes to Yes	611	131	2370	55.3	0.72 (0.61 to 0.86)	0.70 (0.59 to 0.83)	0.71 (0.60 to 0.85)
Vigorous PA							
No to No	36 282	10 177	131 556	77.4	1 (reference)	1 (reference)	1 (reference)
Yes to No	3435	858	12 880	66.6	0.86 (0.80 to 0.92)	0.86 (0.80 to 0.92)	0.87 (0.81 to 0.93)
No to Yes	2603	508	9992	50.8	0.65 (0.60 to 0.71)	0.75 (0.69 to 0.82)	0.76 (0.69 to 0.83)
Yes to Yes	956	182	3629	50.2	0.65 (0.56 to 0.75)	0.69 (0.60 to 0.80)	0.70 (0.61 to 0.82)
Vascular dementia							
Light PA							
No to No	4180	1175	15 538	75.6	1 (reference)	1 (reference)	1 (reference)
Yes to No	1295	337	4813	70.0	0.93 (0.82 to 1.05)	0.90 (0.80 to 1.02)	0.90 (0.80 to 1.02)
No to Yes	1300	243	4962	49.0	0.65 (0.56 to 0.74)	0.73 (0.63 to 0.83)	0.73 (0.64 to 0.84)
Yes to Yes	761	140	2802	50.0	0.67 (0.56 to 0.79)	0.69 (0.58 to 0.83)	0.70 (0.59 to 0.83)
Moderate PA							
No to No	6469	1669	24 057	69.4	1 (reference)	1 (reference)	1 (reference)
Yes to No	526	135	1964	68.8	0.99 (0.83 to 1.18)	0.93 (0.78 to 1.10)	0.93 (0.78 to 1.11)
No to Yes	440	70	1721	40.7	0.58 (0.46 to 0.74)	0.76 (0.60 to 0.96)	0.76 (0.60 to 0.97)
Yes to Yes	101	21	374	56.1	0.81 (0.53 to 1.25)	0.85 (0.55 to 1.31)	0.84 (0.55 to 1.30)
Vigorous PA							
No to No	6158	1624	22 934	70.8	1 (reference)	1 (reference)	1 (reference)
Yes to No	698	161	2577	62.5	0.88 (0.75 to 1.04)	0.95 (0.80 to 1.11)	0.95 (0.81 to 1.12)
No to Yes	507	91	1939	46.9	0.66 (0.54 to 0.82)	0.84 (0.68 to 1.04)	0.85 (0.69 to 1.05)
Yes to Yes	173	19	667	28.5	0.40 (0.26 to 0.63)	0.47 (0.30 to 0.74)	0.48 (0.30 to 0.75)

HRs (95% CIs) were calculated using multivariable Cox proportional hazards regression analysis.
Light PA engagement was defined as performing ≥30 min of light-intensity PA for ≥5 times/week; Moderate PA as performing ≥30 min of moderate-intensity PA for ≥5 times/week; vigorous PA as performing ≥20 min of vigorous-intensity PA for ≥3 times/week.
*Mortality rate per 1000 person-years.
†Model 1 was unadjusted.
‡Model 2 was adjusted for age, sex, residential area, income, smoking status, alcohol consumption, body mass index, hypertension, type 2 diabetes, dyslipidaemia and chronic kidney disease.
§Model 3 was adjusted for age, sex, residential area, income, smoking status, alcohol consumption, body mass index, hypertension, type 2 diabetes, dyslipidaemia, chronic kidney disease, disability and number of anti-dementia medications used.
CI, confidence interval; HR, hazard ratio; PA, physical activity.

mitochondrial function and reduce apoptotic signalling and neuronal death.[36] Our results highlight the beneficial impact of continuous regular PA during the course of the disease.

Clinical implications

Our study has important public health implications, highlighting the significance of continuous engagement in regular PA both before and after the diagnosis of dementia among individuals with all dementia subtypes. Light PA might be as beneficial as moderate to vigorous PA for reduction of mortality risk. Reducing sedentary behaviour and promoting engaging in PA of any intensity could be recommended for patients with dementia.

Limitations

First, the retrospective cohort design could not rule out the possibility of reverse causality, even though there was a 1-year lag period. Individuals with less severe dementia and fewer functional limitations might be more likely to remain physically active. Second, using administrative data for detecting dementia might be different from the actual diagnosis of dementia. However, strict criteria, such as the National Health Insurance Reimbursement mandating documented evidence of cognitive impairment for filing claims for anti-dementia medication prescription, might mitigate this issue. Third, there was a lack of data on the type of PA—for example, resistance or muscle-strengthening exercise. Also, the IPAQ–SF questionnaire requires a specific minimum duration for each intensity of PA (eg, at least 30 min for light and moderate PA and 20 min for vigorous PA). This might not accurately capture shorter bouts of PA that can still contribute to overall PA levels, potentially leading to underestimation or misclassification of PA. However, the use of established minimum durations aligns with widely accepted PA guidelines,[20 21] ensuring comparability with other studies using the IPAQ–SF. Fourth, using self-reported data on PA and other lifestyle habits among individuals with dementia could introduce recall bias, with varying degrees depending on the nature and severity of cognitive impairment among individuals. However, given that the study included individuals with newly diagnosed dementia and the actual interval between the two check-ups was 2 years and that most participants were taking only one anti-dementia medication as observed from the baseline characteristics, the disease progression and severity were probably mild in most cases. Additionally, the NHIS health check-up questionnaires can be completed with assistance from caregivers, which can help to mitigate potential recall bias in individuals with cognitive impairment. Finally, the ethnic homogeneity of Asians in our data could limit the generalisability of our results.

CONCLUSIONS

This study demonstrated an association between changes in PA, encompassing both amount and intensity, before and after a dementia diagnosis and the risk of all-cause mortality in the Asian population across dementia subtypes using a large-scale nationwide database. Considering lifestyle factors, health examination data and severity of dementia, our results emphasise the maintenance and initiation of PA after dementia diagnosis, regardless of intensity, to reduce mortality risk. Future studies are warranted to elucidate the causal association between PA and mortality risk in individuals with dementia.

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