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Physical activity and trajectories in cognitive function: English Longitudinal Study of Ageing

Physical activity and trajectories in cognitive function: English Longitudinal Study of Ageing

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What is already known

- The association between physical activity and trajectory in cognitive decline has not been examined.

What this study adds

- Over a ten year follow-up, physically inactive women experienced a greater decline in their memory and in executive function ability.

- In men the associations were weaker and less consistent.

Abstract

Background: There are limited data on physical activity in relation to trajectories in cognitive function. The aim was to examine the association of physical activity with trajectories in cognitive function, measured from repeated assessments over 10 years.

Methods: We conducted a ten year follow-up of 10,652 (aged 65 ± 10.1 years) men and women from the English Longitudinal Study of Ageing, a cohort of community dwelling older adults. Self-reported physical activity was assessed at baseline and neuropsychological tests of memory and executive function were administered at regular 2-year intervals. Data from six repeated measurements of memory over ten years and five repeated measurements of executive function over eight years were used.

Results: The multivariable models revealed relatively small baseline differences in cognitive function by physical activity status in both men and women. Over the ten year follow-up, physically inactive women experienced a greater decline in their memory (-0.20 recalled words, 95% CI, -0.29 to -0.11, per study wave) and in executive function ability (-0.33 named animals; -0.54 to -0.13, per study wave) in comparison with the vigorously active reference group. In men there were no differences in memory (-0.08 recalled words, 95% CI, -0.18 to 0.01, per study wave), but small differences in executive function (-0.23 named animals; -0.46 to -0.01, per study wave) between inactive and vigorously active.

Conclusion: Physical activity was associated with preservation of memory and executive function over ten years follow-up. The results were, however, more pronounced in women.

Key words: physical activity; ageing; cognition; memory; executive function

Introduction

Substantial research has focused on the role of physical activity in preserving cognitive function and preventing neurodegenerative diseases [1-4]. Evidence from experimental studies, however, have been inconsistent. Recent high profile trials, for example, have produced mixed findings [5-7] with some showing null effects and others demonstrating a favourable impact of physical activity. The relatively short duration of follow up in these studies has made it difficult to evaluate the true impact of physical activity on cognition. This is because cognitive decline is known to occur over a prolonged period, thus the benefits of a physically active lifestyle may accumulate over a number of years, which is challenging to test in an experimental setting. Observational studies with long term follow up are therefore a useful approach to overcome some of these issues by examination of trajectories over time.

Meta-analyses of cohort studies have demonstrated favourable associations between physical activity and cognitive outcomes at follow-up [2,3] although heterogeneity between studies was high. This heterogeneity is likely explained by variations in follow up period (effect sizes weakened with longer follow up), selection of covariates, sensitivity of physical activity measures, and specificity of cognitive assessments. Indeed, many studies used the Mini-Mental State examination that has received criticism for failure to detect mild forms of cognitive impairment [8].

To the best of our knowledge no studies have examined the association of physical activity with trajectories in cognitive function, measured from repeated assessments over time. Trajectories based on intra-individual data with multiple repeat observations can provide more robust evidence about the relationship between exposures and outcomes than studies based on only two measurement points, for example, allowing for an examination of rate in decline. The aim was to examine associations between physical activity and trajectories of memory and executive function using repeated neuropsychological tests over a 10-year follow up period.

Materials and Methods

Study sample and procedures

Participants were from the English Longitudinal Study of Ageing (ELSA), an ongoing panel study that contains a nationally representative sample of the English population living in households, previously described [9]. Interviews at baseline (2002-03) were carried out with 11,391 individuals (5,186 men and 6,205 women); the overall response rate was 70% at the household level and 67% at the individual level. After the baseline interview, follow-up interviews took place at regular 2-year intervals in 2004-05, 2006-07, 2008-09, 2010-11 and 2012-13. Our analytic sample comprised 10,652 individuals after the exclusion of participants with proxy or partial interviews (n=362); participants with self-reported Alzheimer's Disease or dementia of any kind (n=46) and those with missing values in any of the baseline variables used in the analysis (excluding BMI) (n=331). Participants gave full informed consent to participate in the study and ethical approval was obtained from the National Research Ethics Committee.

Physical activity assessment

Self-reported physical activity was measured using three questions on the frequency of participation in vigorous, moderate, and mild intensity physical activities (more than once per week, once per week, one to three times per month, hardly ever). Participants were shown examples of activities on a card to help them interpret the questions. Examples of mild activities included laundry and home repairs; moderate intensity activity included gardening, cleaning the car, walking at moderate pace, dancing, and floor or stretching exercises; vigorous intensity included running/jogging, swimming, cycling, aerobics/gym workout, tennis, and digging with a spade. Physical activity was further categorized into four groups, as previously described [10]: physically inactive (no activity on a weekly basis); only mild activity at least once a week; at least moderate but no vigorous activity at least once a week; any vigorous activity at least once a week.

Cognitive function

We measured two domains of cognitive function: memory and executive function. Memory was measured using a 10-word recall test that has earlier been used in the Health and Retirement Study [11,12]. Participants were presented with a list of 10 words that were read out to them and asked to recall as many words as they could both immediately and, with no prior notice, a few minutes later and after they had engaged in other cognitive tasks. A total of four 10-word lists were available and were randomly allocated by computer. The number of correctly recalled words was used as a measure of memory (range: 0 to 20 words). Executive function was measured using an animal naming test [11,12]. Participants were asked to name as many animals as they could in one minute. The observed range of this measure at baseline was from 0 to 50 named animals.

Repeated memory (word recall) measurements were used from the first six waves of ELSA (that is the baseline and the first five follow-up interviews) and repeated executive function measurements from the first five waves of ELSA (that is the baseline and the first four follow-up interviews). Because item non-response in memory and executive function scores could have biased our findings, we imputed missing values in any of the follow-up interviews for these two variables. Imputations were performed using chained equations in STATA 14. To avoid bias stemming from imputing missing values for those dead, we censored all imputed data at time of death. Analyses were based on 57199 observations of the summary recall score (of which 14855 were imputed) and 49289 observations of animal naming score (of which 11547 were imputed).

Covariates

Age, sex, marital status, and socioeconomic position (i.e. education, and household wealth) were measured. A binary variable (yes/no) was derived for each of the following self-reported doctor-diagnosed chronic diseases: hypertension, diabetes, heart disease, stroke, and chronic lung disease. Smoking (current, previous or non-smoker) and frequency of alcohol consumption (daily or almost daily, 1-2 times a week or monthly, never or almost never) were measured as behavioural covariates. Elevated depressive symptoms were defined as a score of ≥4 on the 8-item Centre of Epidemiological Studies Depression [CES-D] scale [13] were also measured. Nurses collected anthropometric data including weight and height during a health examination. Body weight was measured using electronic scales without shoes and in light clothing, and height was measured using a Stadiometer. Body mass index (BMI) was calculated using the standard formula [weight (kilograms)/height (meters) squared]. We categorized BMI into the following categories: <25, ≥25 to <30, ≥30. All covariates were measured at the ELSA baseline in 2002-03, except for BMI, which was measured in HSE 1998, 1999 and 2001. To avoid the unnecessary exclusion of 1089 participants with missing BMI values, we imputed missing BMI values.

Statistical analysis

We examined the distribution of all covariates by physical activity and tested the statistical significance of the observed differences using appropriate statistical tests (see Table 1). We then modelled the associations between physical activity at baseline and repeated measurements of memory and executive function using a mixed linear regression approach. Because the ELSA design was balanced with interviews taking place at 2-year intervals and memory and executive function were measured in a consecutive manner in the first six and five waves of the study, respectively, we derived a time variable that reflected the chronological order of the study waves, that is *t=1, 2, 3, 4, 5, (6)*, which we used in our models. We estimated random coefficient models, which were initially adjusted for age and time (Model 1), then for confounders such as chronic diseases and marital status (Model 2) and socioeconomic position (Model 3), and finally for behavioural and psychosocial covariates such as smoking, alcohol consumption, obesity and elevated depressive symptoms (Model 4). We estimated an additional model (Model 5), which was adjusted for all covariates included in Model 4 and in addition for the interaction term exposure*time. This model aimed to investigate whether physical inactivity was associated with an acceleration in cognitive decline over time. As our sample included both men and women aged 50 years and older, we tested whether the observed associations varied by sex or age using statistical interactions. Because we found significant statistical interactions by sex, but not age, we stratified all analyses by sex. For comparison reasons, in additional analyses (see eTables 1 and 2), we repeated our analyses using the observed data prior to imputing any missing value.

Results

The sample consisted of 10,652 participants (45.6% men). Regular vigorous activity was reported in 30.5 % and 24.8% of men and women, respectively. The physically active tended to be younger, married, more highly educated, wealthier, less likely to smoke, more likely to consume alcohol on a daily basis and demonstrated a lower prevalence of disease including obesity and depressive symptoms (Tables 1 and 2).

The multivariable models revealed relatively small baseline differences in memory by physical activity status in both men and women, which in the case of women became significantly greater over time (see eFigure 1). At the end of the 10-year follow-up women who were physically inactive at baseline were able to recall approximately 1.4 fewer words compared with their baseline score, while their difference with women who reported engaging in vigorous physical activity (reference category) grew from -0.28 recalled words at baseline to -1.5 recalled words. Women who engaged in mild-intensity physical activity at baseline experienced a similar acceleration in the decline of their memory ability to that of the physically inactive women, while those who engaged in moderate-intensity physical activity experienced a much smaller decline in their memory in comparison with the vigorously active reference group (Table 3). Memory decline followed a different pattern in men. All men experienced a slight decline in their memory ability over the 10-year follow-up but differences between the reference category and physically inactive men were not significant. In women only the lack of vigorous intensity physical activity also appeared to be associated with the executive function over the eight year follow-up (eFigure 2; Table 4).

The analyses of the observed data (prior to imputation) produced results that were comparable to those of the main analyses (see eTables 1 and 2).

Discussion

The aim was to examine the association of physical activity with trajectories in cognitive function, measured from repeated assessments over time in a large population sample of older adults. Our analyses were based on intra-individual data with six repeated measurements of memory over ten years and five repeated observation of executive function over eight years allowing for an examination of rate of cognitive decline. The results showed a graded association between physical activity and cognitive decline in women, with the smallest decline in those reporting vigorous activity for both memory and executive function. Thus our data suggest physical activity behaviour is a key modifiable risk factor for cognitive function particularly in women.

In a recent meta-analysis of physical activity and cognitive decline the pooled effect estimates were similar between men and women [3]. However, our results are consistent with some studies [14,15] that have found associations only in women. These results could possibly reflect differences in physical activity reporting bias between men and women. Alternatively they may reflect real sex differences possibly driven by interactions between physical activity and hormone metabolism in women [16]. The link between physical activity and cognitive function is biologically plausible as various mechanisms have been highlighted, including maintenance of cerebrovascular integrity [17], reduction in cardiovascular risk factors [18], and neurotrophic effects [19].

In particular, cardiovascular risk factors are likely to act as an important mechanism in explaining the link between physical activity and cognitive decline [18, 20]. In the present study hypertension and diabetes were dose-dependently associated with physical activity in an inverse fashion (ie, lowest prevalence of hypertension and diabetes in the vigorously active). We also recently demonstrated a link between diabetes and cognition in this cohort [21]. When we adjusted for hypertension and diabetes (Table 3; model 2) there were noticeable changes in the coefficients, further supporting the notion that these risk factors may partly explain the link between physical activity and cognitive decline.

There is heterogeneity within the existing epidemiological evidence base, and various weaknesses in the area have been highlighted. Reverse causation is a concern and studies with longer follow up periods have often demonstrated weaker effect sizes. Studies have used a variety of cognitive assessments, some with limited specificity. Indeed, many studies used the Mini-Mental State examination that has received criticism for failure to detect mild forms of cognitive impairment [8]. Our study contains one of the longest follow up periods to date and we have used widely validated neuropsychological tests. We chose to model scores on executive function and memory separately as each measure may have different sensitivity to change [22], so by combining them, one would loose the ability to examine the role of covariates and the change in each outcome. Furthermore, episodic memory and executive function measure different cognitive abilities and in doing so may contribute to different aspects of disease etiology [23]. It is also plausible that physical activty could influence these different cognitive abilities in diverse ways. We cannot discount the possibility of reverse causation [24] although we removed participants with known dementia at baseline in order to address this issue. The self-reported nature of our physical activity measure is a limitation, particularly in the context of cognition as recall bias may be greater in the cognitively impaired. However, this potential misclassification would have biased our results to the null.

In conclusion, physical activity was associated with preservation of memory and executive function over ten years follow-up in women. With treatments for dementia and cognitive impairment elusive, prevention via modifiable risk factors such as physical activity may have great potential.

Author contribution

PD had full access to the data, and takes responsibility for the integrity and accuracy of the results. MH drafted the paper and designed the study. PD and GM contributed to the concept and design of the study and critical revision of the manuscript. All authors agree to be included, have seen and approved mention of their names in the article, and endorse the data and conclusions.

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Table 1. The baseline characteristics of men aged ≥50 years by physical activity					
	Vigorous-intensity physical activity at least once a week	**Moderate-intensity physical activity at least once a week**	**Mild-intensity physical activity at least once a week**	**Physically inactive**	***P value*[a]**
N	1480	2355	506	517	
Mean age (SD)	62.1 (8.7)	64.7 (9.5)	67.6 (10.7)	69.1 (11.0)	<0.001
Marital status (%)					<0.001
Married	1190 (80.4)	1797 (76.3)	310 (61.3)	362 (70.0)	
Other	290 (19.6)	558 (23.7)	196 (38.7)	155 (30.0)	
Education (%)					<0.001
A-level or higher	660 (44.6)	866 (36.8)	100 (19.8)	85 (16.4)	
Secondary or equivalent	405 (27.4)	696 (29.5)	130 (25.7)	142 (27.5)	
No qualifications	415 (28.0)	793 (33.7)	276 (54.5)	290 (56.1)	
Total net household wealth (%)					<0.001
Wealthiest tertile (>£203,500)	661 (44.7)	881 (37.4)	88 (17.4)	107 (20.7)	
Intermediate tertile (>£78,144 & ≤£203,500)	533 (36.0)	808 (34.3)	150 (29.6)	124 (24.0)	
Poorest tertile (≤£78,144)	286 (19.3)	666 (28.3)	268 (53.0)	286 (55.3)	
Elevated depressive symptoms					<0.001
No	1386 (93.8)	2103 (89.3)	390 (77.1)	375 (72.5)	
Yes	94 (6.2)	252 (10.7)	116 (22.9)	142 (27.5)	
Smoking (%)					<0.001
Current smoker	202 (13.6)	419 (17.8)	120 (23.7)	116 (22.4)	
Former smoker	815 (55.1)	1330 (56.5)	298 (58.9)	302 (58.4)	
Never smoker	463 (31.3)	606 (25.7)	88 (17.4)	99 (19.2)	
Body mass index[b] (%)					<0.001
<25kg/m^2	371 (25.0)	522 (22.2)	95 (18.8)	102 (19.7)	
25 to <30 kg/m^2	756 (51.1)	1115 (47.3)	219 (43.3)	190 (36.8)	
≥ 30 kg/m2	232 (15.7)	509 (21.6)	127 (25.1)	123 (23.8)	
Missing	121 (18.2)	209 (8.9)	65 (12.8)	102 (19.7)	
Alcohol consumption (%)					<0.001
Daily or almost daily	601 (40.6)	851 (36.1)	142 (28.1)	142 (27.5)	
1-2 times a week or monthly	671 (45.3)	1038 (44.1)	219 (43.3)	193 (37.3)	

Never or almost never	208 (14.1)	466 (19.8)	145 (28.6)	182 (35.2)	
Heart disease (%)					<0.001
No	1395 (94.3)	2153 (91.4)	433 (85.6)	424 (82.0)	
Yes	85 (5.7)	202 (8.6)	73 (14.3)	93 (18.0)	
Stroke (%)					<0.001
No	1437 (97.5)	2252 (96.2)	465 (92.3)	450 (88.6)	
Yes	37 (2.5)	90 (3.8)	39 (7.7)	59 (11.4)	
Hypertension (%)					<0.001
No	1028 (69.5)	1483 (63.0)	273 (54.0)	285 (55.1)	
Yes	452 (30.5)	872 (37.0)	233 (46.0)	232 (44.9)	
Diabetes (%)					<0.001
No	1401 (94.7)	2125 (90.2)	449 (88.7)	443 (85.7)	
Yes	79 (5.3)	230 (9.8)	57 (11.3)	74 (14.3)	
Chronic Lung Disease (%)					<0.001
No	1433 (96.8)	2213 (94.0)	450 (88.9)	423 (81.8)	
Yes	47 (3.2)	142 (6.0)	56 (11.1)	94 (18.2)	

[a] P values were calculated using chi-square, Kruskal-Wallis and analysis of variance tests for categorical ordinal and continuous covariates respectively

[b] The missing category was not used in the calculation of the P value

Table 2. The baseline characteristics of women aged ≥50 years by physical activity

	Vigorous-intensity physical activity at least once a week	Moderate-intensity physical activity at least once a week	Mild-intensity physical activity at least once a week	Physically inactive	*P value*[a]
N	1435	2723	1068	568	
Mean age (SD)	61.4 (8.3)	64.6 (9.7)	68.6 (11.0)	72.5 (11.4)	<0.001
Marital status (%)					<0.001
Married	942 (65.6)	1677 (61.6)	577 (54.0)	221 (38.9)	
Other	493 (34.4)	1046 (38.4)	491 (46.0)	347 (61.1)	
Education (%)					<0.001
A-level or higher	482 (33.6)	589 (21.6)	145 (13.6)	70 (12.3)	
Secondary or equivalent	519 (36.2)	900 (33.1)	241 (22.6)	105 (18.5)	
No qualifications	434 (30.2)	1234 (45.3)	682 (63.8)	393 (69.2)	
Total net household wealth (%)					<0.001
Wealthiest tertile (>£203,500)	657 (45.8)	889 (32.6)	202 (18.9)	89 (15.7)	
Intermediate tertile (>£78,144 & ≤£203,500)	498 (34.7)	955 (35.1)	346 (32.4)	145 (25.5)	
Poorest tertile (≤£78,144)	280 (19.5)	879 (32.3)	520 (48.7)	334 (58.8)	
Elevated depressive symptoms					<0.001
No	1280 (89.2)	2274 (83.5)	769 (72.0)	344 (60.6)	
Yes	155 (10.8)	449 (16.5)	299 (28.0)	224 (39.4)	
Smoking (%)					<0.001
Current smoker	189 (13.2)	531 (19.5)	234 (21.9)	104 (18.3)	
Former smoker	570 (39.7)	1016 (37.3)	408 (38.2)	231 (40.7)	
Never smoker	676 (47.1)	1176 (43.2)	426 (39.9)	233 (41.0)	
Body mass index[b] **(%)**					<0.001
<25kg/m^2	523 (36.5)	851 (31.2)	256 (24.0)	117 (20.6)	
25 to <30 kg/m^2	510 (35.5)	996 (36.6)	357 (33.4)	150 (26.4)	
≥ 30 kg/m2	294 (20.5)	670 (24.6)	325 (30.4)	153 (26.9)	
Missing	108 (7.5)	206 (7.6)	130 (12.2)	148 (26.1)	
Alcohol consumption (%)					<0.001
Daily or almost daily	406 (28.3)	598 (22.0)	158 (14.8)	90 (15.9)	
1-2 times a week or monthly	637 (44.4)	1101 (40.4)	347 (32.5)	140 (24.6)	

Never or almost never	392 (27.3)	1024 (37.6)	563 (52.7)	338 (59.5)	
Heart disease (%)					<0.001
No	1409 (98.2)	2653 (97.4)	984 (92.1)	504 (88.7)	
Yes	26 (1.8)	70 (2.6)	84 (7.9)	64 (11.3)	
Stroke (%)					<0.001
No	1421 (99.0)	2652 (97.4)	1012 (94.8)	494 (87.0)	
Yes	14 (1.0)	71 (2.6)	56 (5.2)	74 (13.0)	
Hypertension (%)					<0.001
No	1008 (70.2)	1675 (61.5)	565 (52.9)	282 (49.7)	
Yes	427 (29.8)	1048 (38.5)	503 (47.1)	286 (50.3)	
Diabetes (%)					<0.001
No	1391 (96.9)	2601 (95.5)	947 (88.7)	499 (88.8)	
Yes	44 (3.1)	122 (4.5)	121 (11.3)	69 (12.2)	
Chronic Lung Disease (%)					<0.001
No	1385 (96.5)	2571 (94.4)	965 (90.4)	511 (90.0)	
Yes	50 (3.5)	152 (5.6)	103 (9.6)	57 (10.0)	

[a] P values were calculated using chi-square, Kruskal-Wallis and analysis of variance tests for categorical ordinal and continuous covariates respectively

[b] The missing category was not used in the calculation of the P value

Table 3. The longitudinal association between physical activity and word recall summary score (memory) over 10 years in 10652 participants aged ≥50 years

	Vigorous-intensity physical activity at least once a week	**Moderate-intensity physical activity at least once a week**	**Mild -intensity physical activity at least once a week**	**Physically inactive**
		Men		
Slope (rate of decline)[a]				
Model 1[b]	1.00 (reference)	-0.17 (-0.34 to 0.002)	-1.20 (-1.47 to -0.94)	-1.35 (-1.62 to -1.08)
Model 2[c]	1.00 (reference)	-0.11 (-0.28 to 0.06)	-1.03 (-1.30 to -0.76)	-1.17 (-1.45 to -0.89)
Model 3[d]	1.00 (reference)	0.004 (-0.15 to 0.16)	-0.49 (-0.75 to -0.23)	-0.61 (-0.88 to -0.35)
Model 4[e]	1.00 (reference)	0.04 (-0.12 to 0.20)	-0.39 (-0.64 to -0.13)	-0.46 (-0.73 to -0.20)
Model 5[f]	1.00 (reference)	0.19 (-0.02 to 0.40)	-0.07 (-0.40 to 0.270)	-0.24 (-0.58 to 0.11)
Slope acceleration (exposure*time interaction)[a]				
Model 5[f]	1.00 (reference)	-0.05 (-0.10 to 0.001)	-0.12 (-0.20 to -0.03)	-0.08 (-0.18 to 0.01)
		Women		
Slope (rate of decline)[a]				
Model 1[b]	1.00 (reference)	-0.39 (-0.55 to -0.22)	-1.35 (-1.56 to -1.13)	-1.81 (-2.08 to -1.53)
Model 2[c]	1.00 (reference)	-0.38 (-0.54 to -0.21)	-1.29 (-1.51 to -1.07)	-1.70 (-1.98 to -1.43)
Model 3[d]	1.00 (reference)	-0.06 (-0.22 to 0.10)	-0.65 (-0.87 to -0.44)	-1.03 (-1.10 to -0.76)
Model 4[e]	1.00 (reference)	-0.007 (-0.17 to 0.15)	-0.52 (-0.73 to -0.30)	-0.83 (-1.10 to -0.56)
Model 5[f]	1.00 (reference)	0.28 (0.07 to 0.48)	-0.06 (-0.33 to 0.21)	-0.28 (-0.63 to 0.07)
Slope acceleration (exposure*time interaction)[a]				
Model 5[f]	1.00 (reference)	-0.10 (-0.15 to -0.05)	-0.16 (-0.23 to -0.10)	-0.20 (-0.29 to -0.11)

[a] The estimates are β regression coefficient (95% confidence intervals)
[b] Model 1 is adjusted for time and age
[c] Model 2 is adjusted for time, age, marital status and self-reported chronic conditions i.e. heart disease, stroke, hypertension, diabetes and chronic lung disease
[d] Model 3 is adjusted for time, age, marital status, self-reported chronic conditions i.e. heart disease, stroke, hypertension, diabetes and chronic lung disease, education and total net household wealth
[e] Model 4 is adjusted for time, age, marital status, self-reported chronic conditions i.e. heart disease, stroke, hypertension, diabetes and chronic lung disease, education, total net household wealth, smoking, alcohol consumption, body mass index, and elevated depressive symptoms
[f] Model 5 is adjusted for all covariates that Model 4 plus adjustment for the exposure*time interaction term

Table 4. The longitudinal association between physical activity and and animal naming score (executive function) over 8 years in 10590 participants aged ≥50 years

	Vigorous-intensity physical activity at least once a week	Moderate-intensity physical activity at least once a week	Mild -intensity physical activity at least once a week	Physically inactive
		Men		
Slope (rate of decline)[a]				
Model 1[b]	1.00 (reference)	-0.27 (-0.61 to 0.07)	-2.01 (-2.54 to -1.47)	-2.68 (-3.23 to -2.13)
Model 2[c]	1.00 (reference)	-0.22 (-0.55 to 0.12)	-1.77 (-2.31 to -1.22)	-2.48 (-3.04 to -1.92)
Model 3[d]	1.00 (reference)	-0.02 (-0.35 to 0.30)	-0.91 (-1.44 to -0.37)	-1.58 (-2.13 to -1.03)
Model 4[e]	1.00 (reference)	0.04 (-0.28 to 0.37)	-0.72 (-1.25 to -0.18)	-1.31 (-1.86 to -0.76)
Model 5[f]	1.00 (reference)	0.43 (0.01 to 0.84)	0.14 (-0.55 to 0.82)	-0.76 (-1.46 to -0.07)
Slope acceleration (exposure*time interaction)[a]				
Model 5[f]	1.00 (reference)	-0.16 (-0.27 to -0.04)	-0.36 (-0.56 to -0.17)	-0.23 (-0.46 to -0.01)
		Women		
Slope (rate of decline)[a]				
Model 1[b]	1.00 (reference)	-1.01 (-1.32 to -0.69)	-2.50 (-2.91 to -2.08)	-3.39 (-3.92 to -2.86)
Model 2[c]	1.00 (reference)	-0.97 (-1.29 to -0.65)	-2.38 (-2.79 to -1.96)	-3.17 (-3.72 to -2.63)
Model 3[d]	1.00 (reference)	-0.40 (-0.70 to -0.09)	-1.28 (-1.68 to -0.87)	-2.03 (-2.55 to -1.50)
Model 4[e]	1.00 (reference)	-0.33 (-0.63 to -0.03)	-1.11 (-1.52 to -0.70)	-1.77 (-2.31 to -1.24)
Model 5[f]	1.00 (reference)	0.21 (-0.18 to 0.60)	-0.31 (-0.82 to 0.21)	-0.98 (-1.63 to -0.33)
Slope acceleration (exposure*time interaction)[a]				
Model 5[f]	1.00 (reference)	-0.22 (-0.32 to -0.11)	-0.33 (-0.48 to -0.18)	-0.33 (-0.54 to -0.13)

[a] The estimates are β regression coefficient (95% confidence intervals)
[b] Model 1 is adjusted for time and age
[c] Model 2 is adjusted for time, age, marital status and self-reported chronic conditions i.e. heart disease, stroke, hypertension, diabetes and chronic lung disease
[d] Model 3 is adjusted for time, age, marital status, self-reported chronic conditions i.e. heart disease, stroke, hypertension, diabetes and chronic lung disease, education and total net household wealth
[e] Model 4 is adjusted for time, age, marital status, self-reported chronic conditions i.e. heart disease, stroke, hypertension, diabetes and chronic lung disease, education, total net household wealth, smoking, alcohol consumption, body mass index, and elevated depressive symptoms
[f] Model 5 is adjusted for all covariates that Model 4 plus adjustment for the exposure*time interaction term