Physical activity pre- and post-dementia: English Longitudinal Study of Ageing

Short title: Physical activity pre- and post-dementia (ELSA Cohort)

Mira Soni[1]; Martin Orrell[2]; Stephan Bandelow[1]; Andrew Steptoe[3]; Snorri Rafnsson[3]; Eleonora d'Orsi[4]; Andre Xavier[5]; & Eef Hogervorst[1*]

[1] School of Sport Exercise and Health Sciences, Loughborough University, UK (MS: m.soni@lboro.ac.uk; SB: s.bandelow@lboro.ac.uk; EH: e.hogervorst@lboro.ac.uk).

[2] Institute of Mental Health, University of Nottingham, UK (MO: m.orrell@ucl.ac.uk).

[3] Department of Epidemiology and Public Health, University College London, UK (AS: a.steptoe@ucl.ac.uk; SR: s.rafnsson@ucl.ac.uk).

[4] Department of Public Health, Federal University of Santa Catarina, Florianópolis, Brazil (ED: eleonora.dorsi@ufsc.br).

[5] Health Academic Unit, Universidade do Sul de Santa Catarina, Florianopolis, Florianópolis, Brazil (AX: andre.xavier@unisul.br).

Corresponding Author:

Eef Hogervorst

School of Sport Exercise and Health Sciences, National Centre for Sports and Exercise Medicine, Loughborough University, Loughborough, Leicestershire, LE11 3TU, UK

Email: E.Hogervorst@lboro.ac.uk

Telephone: +44(0)1509 223020

Fax: +44(0)1509 226301

ABSTRACT

Background: To inform public health interventions, further investigation is needed to identify: (1) frequency/intensity of everyday physical activity (PA) needed to reduce dementia risk; (2) whether post-diagnosis reduction in PA is associated with cognitive outcomes. **Methods:** Data from 11,391 men and women (aged ≥50) were obtained in the English Longitudinal Study of Ageing. Assessments were at baseline (2002-2003) and biannual follow-ups (2004-2013). **Results:** Older adults who carried out moderate to vigorous activity at least once per week had a 34%-50% lower risk for cognitive decline and dementia over an 8-10 year follow-up period. From pre- to post-diagnosis, those that decreased PA levels had a larger decrease in immediate recall score, compared to those that maintained or increased PA levels (adjusted for changes in physical function). **Conclusion:** These findings provide a guideline for everyday PA levels needed to reduce risk for dementia. Reduction in PA after diagnosis was also associated with accelerated cognitive decline.

KEYWORDS

Alzheimer's Disease, Other Dementias, Epidemiology (Dementia), Physical Activity, Cognitive Functioning

ABBREVIATIONS: Brain Derived Neurotrophic Factor (BDNF), Confidence Intervals (CI), Delta Change (∆), Epidemiological Studies Depression Scale (CES-D), English Longitudinal Study of Ageing (ELSA), European Prospective Investigation into Cancer (EPIC), Hazards Ratio (HR), Health Survey for England (HSE), Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), Metabolic Equivalent (MET), Mini-Mental State Examination (MMSE), Physical Activity (PA).

1. INTRODUCTION

Dementia is neurodegenerative condition characterised by progressive and marked decline in memory and other cognitions. Based on UK data in 2013, dementia prevalence was 1.3% in the total population and 7.1% in those over the age of 65 [1]. Without significant public health intervention, this was projected to increase by 40% over the next 12 years, due to population ageing. Comparatively, current worldwide prevalence is estimated at 5.2% in those above age 60 and expected to double within 20 years, making dementia one of the leading causes of disability and dependence globally [2]. Present global economic cost of dementia including medical care (20%), social care (40%) and unpaid care e.g. family/friends (40%) is estimated at US$818 billion [2]. Understanding modifiable lifestyle factors that could prevent or delay disease onset will therefore have implications for these economic costs and quality of life for those at risk for dementia.

Observational studies and randomized controlled trials provide evidence for the benefits of regular physical activity (PA) as a behavioral approach to reduce dementia risk [3–5]. PA refers to any bodily movement produced by the skeletal muscles that requires energy expenditure [6]. This can include everyday activities (e.g. walking, gardening, recreational sports) or targeted exercise training (e.g. gym workout). Several neurophysiological mechanisms may elucidate the benefits of physical activity on cognitive health. These include increased cerebral blood flow [7], reduced age-related loss of brain tissue [8] and increased levels of neurotrophins (particularly brain-derived neurotrophic factor; BDNF) associated with synaptic plasticity and neuronal survival [9]. PA has also been associated with reduced risk for age-related co-morbidities including

cardiovascular disease, stroke, diabetes mellitus and depression, which are also risk factors for dementia [10]. However, limitations to interpret studies assessing the association between PA and dementia have been consistently noted. A number of studies do not adjust for relevant confounders of PA (e.g. alcohol consumption, smoking status, depression and cardiovascular factors [4,10–12], potentially exaggerating effect size and reducing reliability. Retrospective self-report measures often do not report details of frequency and intensity of PA, limiting their clinical applicability[4,11]. Studies offering a follow-up of at least 10 years are few, leading to issues with reverse causality, where undiagnosed symptoms of dementia may lead to less physical activity rather than the opposite [4]. Finally, the association between pre- to post-diagnosis changes in PA and cognition has not been previously investigated, but would be valuable to inform public health interventions.

The present study investigated the association between PA and dementia risk over a 10-year follow-up in the English Longitudinal Study of Ageing (ELSA).

2. METHOD

2.1. Participants

ELSA is an ongoing epidemiological study of men and women (≥50 years of age). The sample was drawn from those who participated in the Health Survey for England (HSE) between 1998-2000. The primary form data collection in ELSA is a computer assisted personal interview (CAPI) carried out at the persons home or residence. Details of data collection are described elsewhere [13]. The core ELSA cohort included 11,391

individuals (46% male, 54% female) who began at baseline (wave 1; 2002-2003) and had biannual follow up-interviews (waves 2-6; 2004-2013). Participants with dementia in wave 1 were excluded; therefore incident cases of dementia were recorded over waves 2-6. Participants were also excluded if they were diagnosed with Parkinson's disease or psychiatric ocnditions (e.g. hallucinations, schizophrenia, psychosis), which could significantly affect physical or cognitive function. The final sample included 11,289 participants. All participants gave informed consent before taking part and the London Multi-Centre Research Ethics Committee approved this study.

2.2. Physical Activity (PA) Definition

Self-reported PA data were collected using questionnaires administered at each wave. Respondents were given examples of PA at mild intensity (e.g. laundry, home repairs), moderate intensity (e.g. cleaning the car, walking at a moderate pace) and vigorous intensity (e.g. digging with a spade, cycling, aerobics). They were then asked to indicate their frequency of participation in mild, moderate and vigorous PA (hardly ever, one to three times per month, once per week or more than once per week). Items on the ELSA physical activity questionnaire were modified from the Whitehall II Health questionnaire [14]. The chosen examples of PA at different intensities were selected as they were most commonly reported in two UK-based population studies, carried out in a similar age group, namely the Ely Diabetes study and the UK sample from the European Prospective Investigation into Cancer (EPIC) cohort [15]. Different PA intensities were categorised based the activity's metabolic equivalent (MET) score [16]. MET scores between 2 to 3.5 corresponded to mild PA, scores 3.5 to 6 defined moderate PA and a score of greater than 6 was equivalent to vigorous PA.

Self-reported data were recorded at each wave (where available). For the purpose of this study we further categorized PA into four groups coded with numerical values: (1) PA less than once per week (<1x/wk); (2) mild PA once per week (1x/wk); (3) moderate or vigorous PA once per week (1x/wk); (4) moderate or vigorous PA twice per week or more (>1x/wk). For those without a dementia diagnosis, “average PA” was defined as the mean level of PA across waves 1-6. For those with incident dementia, average PA was defined as the mean level of PA using only the waves prior to diagnosis.

2.3. Dementia Assessment

Dementia was defined as a physician diagnosis of dementia or Alzheimer’s disease reported by the participant in the CAPI. If the individual was unable to take part in the CAPI for any reason, a family member or long-term carer was able to complete the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) [17]. The IQCODE consists of 26 questions, which ask the informant to rate how their friend or relative is in situations now compared to 10 years ago (e.g. “recognising faces of family and friends”, “remembering things that have happened recently”). Scores range on a 5-point scale from “1=much improved” to “5=much worse”. Scores for each question are summed and divided by 26 to give a final score between 1-5. Scores above 3.5 were a cut-off for identifying dementia cases. The IQCODE has been shown to be a valid predictor of dementia [18] performing as well as other commonly used screening methods (e.g. Mini-Mental State Examination (MMSE) [19]).

2.4 Covariates

Several baseline factors were accounted for as possible covariates that could affect cognition, physical activity or health status [10,20]. Demographic factors included age (years) and gender (male/female). Socioeconomic variables were derived for education (degree level/below degree/no qualification) and wealth (3rd quintile or less [least wealthy]//4th quintile or above [most wealthy]). Wealth was calculated as net of debt and included the value of housing (excluding mortgage), financial assets (e.g. savings, business assets) and physical wealth (e.g. artwork, jewelry). Presences of several self-reported doctor diagnosed cardiovascular disease factors were accounted for, including high blood pressure, diabetes, stroke and heart attack (binary yes/no). In sensitivity analysis, binary variables for presence of *any* self-reported doctor-diagnosed heart condition (including the latter cardiovascular factors plus any other reported) or chronic disease (lung disease, asthma, osteoporosis, cancer, neurological or psychiatric problems) were included. Depressive symptoms were assessed using an eight-tem Epidemiological Studies Depression Scale (CES-D) validated for use in older adults [21]. Here, a CES-D score of 4 or higher identified elevated symptoms of major depression. Other health related covariates included smoking status (non-smoker/previous smoker/current smoker) and frequency of alcohol consumption (more than once daily/ daily/ one to two times per week/ less than once per week). Validated neuropsychological measures of cognition [20] included immediate recall (of 10 words in a list) and verbal fluency (naming category items in 1 minute i.e. animals). Finally, physical function was measured using gait speed, defined as the time in seconds taken to walk a course of 2.44 meters (averaged across 2 trials).

2.5. Statistical Analysis

Descriptive analyses were performed on data stratified by incidence of dementia. Chi-squared statistics were computed to assess baseline group differences for categorical data and independent samples *t*-statistics were used for continuous data.

The association between PA and dementia risk was estimated using Cox proportional hazards regression, calculating multivariate-adjusted hazards ratios (HR's) with 95% confidence intervals (CI's). The timescale variable was the number of completed assessment waves and the censor variable was whether a dementia diagnosis was reported (yes/no). Separate models were used to predict dementia risk from (i) baseline PA and (ii) average PA levels across the follow-up period. Covariates were adjusted in a step-wise approach. In the first step, models contained variables for age, gender, education, wealth, baseline cognitive function and physical function. The second step adjusted for additional variables including alcohol consumption, smoking status, depression, mood problems, cardiovascular factors and chronic disease. In sensitivity analysis exclusion criteria were manipulated to assess the possibility of reverse causality. Here, participants were excluded if they had a dementia diagnosis in waves 1-2 (i.e. up to two years since baseline). This examined robustness of findings and reduced the likelihood that undiagnosed prodromal symptoms of dementia contributed to decreased PA, rather than the opposite. Imputation methods were not performed on missing data.

Subgroup analysis was carried out in those with dementia, who carried out an average of moderate/vigorous at least once per week before diagnosis. Multivariate regression

was used to investigate whether reduction in PA after diagnosis were associated with cognitive outcomes (immediate recall and verbal fluency). Here, delta change (Δ) scores were calculated as post-diagnosis minus pre-diagnosis score. Age, gender, education, and changes in physical function (pre- to post-diagnosis) were also controlled for.

In sensitivity analysis exclusion criteria were manipulated to assess the possibility of reverse causality. In the first analysis, participants were excluded if they had a dementia diagnosis in waves 1-2 (i.e. up to 2 years since baseline). This examined robustness of findings and reduced the likelihood that undiagnosed prodromal symptoms of dementia contributed to decreased PA, rather than the opposite. In the second analysis, participants were excluded if they had any type of chronic disease at baseline that could affect PA levels.

In all analyses, two-sided p values are reported and values ≤0.05 were considered statistically significant. Analyses were performed using IBM SPSS Statistics (Version 22).

3. RESULTS

Of the core-interviewed participants (N=11,391), 2,576 participants died and 3,156 were lost over the follow-up period (e.g. moved out of UK, became institutionalised and were unproductive, were unable/unwilling to continue with study) (see *Figure 1*).

Compared to those who left the study, participants with data available in final wave (N=5659) tended to be younger, female, more physically active, wealthier, have a higher

educational level and score higher on measures of cognitive and physical function at baseline. They also consumed more alcohol, but were less likely to smoke or have reported a psychiatric condition, cardiovascular condition or chronic disease at baseline.

3.1. Baseline PA and incident dementia

For the included sample (N=11,289), the cohort was divided into those that received a dementia diagnosis (across waves 2-6) versus those that did not. Approximately 3.5% of the sample received a dementia diagnosis. Baseline characteristics for the sample are outlined in *Table 1*.

In cox proportional hazards regression (see *Table 2*), PA levels were independently associated with dementia incidence in a dose-dependant manner. In the fully adjusted model, mild PA 1x/wk (multivariate adjusted HR=0.69, 95%CI=0.50–0.95, p=0.02), moderate/vigorous PA 1x/wk (multivariate adjusted HR=0.66, 95%CI=0.46–0.94, p=0.02) and moderate/vigorous PA >1x/wk (multivariate adjusted HR=0.50, 95%CI=0.37–0.67, p<0.001) lowered the HR for dementia, compared to those that reported doing PA<1x/wk.

3.2. Average PA levels (across follow-up) and incident dementia

Average PA levels before diagnosis in those with incident dementia (2.63 ± 0.05; i.e. mild PA 1x/wk) were lower than the average PA levels of those with no diagnosis (3.17 ± 0.01; i.e. moderate/vigorous PA 1x/wk) (p<0.001). Trajectory of PA levels across all waves (stratified by diagnosis) is illustrated in *supplementary Figure 1*. In cox

proportional hazards analyses, higher average PA levels across the follow-up period lowered the HR for dementia (full multivariate adjusted HR=0.79, 95%CI=0.69–0.91, p=0.001) (see *Table 3*).

3.3. Subgroup analysis

In those with dementia, mean PA levels, immediate recall score and verbal fluency score dropped from pre- to post-diagnosis (p≤0.01) (see *supplementary Table 1*). This was the case even though physical function appeared to increase (i.e. quicker walking speed). Those who were active before diagnosis (i.e. averaged ≥ moderate/vigorous PA 1x/wk) but reduced their PA levels after diagnosis (N=282), had a larger drop in immediate recall score from pre- to post-diagnosis (*ß*=0.41, p<0.001), in comparison to those who maintained or increased their PA levels (see *Table 4* and *Figure 2*). The decrease in PA was proportionate to decrease in cognitive score. This association was independent of changes in physical function, age, gender and education. Although not statistically significant, there was a similar trend between PA and verbal fluency.

3.4. Sensitivity analysis

Excluding anyone with a dementia diagnosis at waves 1-2 reduced the possibility of reverse causality. After exclusion, there were 271 remaining dementia cases (total sample N=8,564), which decreased the power to detect significant effects. In basic and fully adjusted models, lower levels of PA independently increased the HR for dementia. However, the effect of moderate/vigorous PA became marginally significant (multivariate adjusted HR=0.69, 95%CI=0.46–1.04, p=0.07). In the fully adjusted model, mild PA

1x/wk (multivariate adjusted HR=0.66, 95%CI=0.45–0.96, p=0.03) and moderate/vigorous PA>1x/wk (multivariate adjusted HR=0.51, 95%CI=0.35–0.72, p<0.001) lowered the HR for dementia, compared to those that reported doing PA<1x/wk. Higher average PA levels (across the follow-up) also reduced dementia risk (full multivariate adjusted HR=0.80, 95%CI=0.68–0.94, p=0.01). Therefore, dementia incidence up to two years after baseline assessment did not significantly affect the association between PA and dementia risk.

4. DISCUSSION

Using prospective longitudinal data from the ELSA cohort, the present study examined the association between self-reported PA and dementia over a 10-year follow-up period. In the present study, PA was associated with a lowered the risk for dementia in a dose-dependent manner. Here, moderate/vigorous PA>1x/wk appeared to be the most risk reducing, followed by moderate/vigorous PA 1x/wk and then mild PA 1x/wk. These findings were replicated in models adjusted for lifestyle and clinical covariates. Results also remained consistent in sensitivity analysis that reduced the possibility of reverse causality, although the effect of moderate/vigorous PA 1x/wk became marginally significant, possibly due to the lower sample size and reduced power to detect effects. The present results support previous analysis within this cohort, which found that higher levels of PA predicted healthy ageing, including survival from major chronic disease, depressive symptoms, physical or cognitive impairment [20]. This study also validates a number of longitudinal studies, which have found an association between higher levels of PA and reduced risk for dementia and cognitive dysfunction [4].

A novel finding was observed in those who were active before dementia diagnosis (i.e. carried out ≥ moderate/vigorous activity 1x/wk), but reduced their PA levels after diagnosis. In this subgroup, those who reduced PA levels after diagnosis had a larger drop in immediate recall score (pre- to post-diagnosis), compared to those who maintained or increased their PA levels. Furthermore, those with larger decreases in PA after diagnosis had a correspondingly larger decrease in recall score. This did not appear to be explained by changes in physical function. It is possible that reduction in PA levels after dementia diagnosis is due to loss of confidence or anxiety associated with cognitive symptoms of dementia (i.e. confusion, memory loss, disorientation). On the other hand, it could also be caused by the stigma of having dementia or perceived dependency on carers for day-to-day activities [22]. Further research with a larger sample size is needed to investigate the reasons why those who were active before diagnosis may become less active after diagnosis, as this will provide insight into public health intervention adherence. Even still, these results suggest that maintenance of PA after dementia diagnosis may be beneficial for memory.

Neuroimaging studies and randomised controlled trials provide biological plausibility for the neuroprotective effects of regular PA. Regular PA is associated with increased hippocampal, prefrontal cortex and basal ganglia brain volumes, increased white matter integrity, as well as increased brain function and connectivity between frontal and hippocampal brain regions [23]. Additionally, both animal and human studies suggest that exercise induced increases in BDNF may promote neurite outgrowth even in older adults [24,25]. It is theorised that these neuroprotective factors may all contribute to an individuals cognitive reserve; meaning that regular PA may increase a persons ability to recruit compensatory cognitive processing in order to reduce the effects of brain

pathology [26]. Indeed, mechanisms contributing to neurodegeneration in dementia include synaptic loss, neuronal death, inflammation and accumulation of toxic β-amyloid plaques and intracellular neurofibrillary tangles. Regular PA has been shown to alleviate or delay pathogenesis of dementia [27].

Limitations of the present study are acknowledged. Firstly, self-reported measures of PA have been criticised, as adults may not adequately recall PA, particularly low-intensity activities [28]. Therefore, despite our large effect sizes we may have underestimated the strength of the effects of PA in this study due to regression dilution bias [4]. Secondly, within the present sample, 3.5% of participants were classified as having dementia. Given the average age of our sample at baseline (62 ± 0.1), dementia incidence is slightly lower than reported national prevalence rates [1]. There is evidence that approximately half of the cases of dementia in the UK remain undiagnosed [1] meaning that physician diagnosis may underestimate dementia prevalence rates in our sample. Physician diagnosis of dementia reported in the CAPI was not formally validated and so results must be interpreted with this consideration in mind. Moreover, those with dementia or experiencing symptoms of dementia may have chosen not to participate in this study or may have been excluded in the baseline wave leading to further attrition bias, which may have led to an underestimation of effect size.

Finally, in the present study, only complete cases were included in regression analyses. Imputation methods were not used and missing data (due to death or loss to follow-up) may have impacted the study findings. Those with available data throughout the study follow-up period (waves 1 to 6) were more likely to be younger, female, more physically active, wealthier, have a higher educational level and score higher on measures of

cognitive and physical function at baseline; they also consumed more alcohol, but were less likely to smoke or have reported a psychiatric condition, cardiovascular condition or chronic disease at baseline. Therefore results of this study must be interpreted in the context of this missing data. For instance, participants that had the lowest cognitive or physical ability may have been less likely to be represented in the final sample. Nevertheless, in clinical practice, PA lifestyle interventions would be designed to target populations prior to disease onset or cases were disease activity is in its earliest stages and disease progression is limited. Therefore, although the final sample may be biased towards a healthier population, these participants would also be those who would be most likely to carry out and benefit from a PA intervention designed to maintain cognitive health in older age.

This study also has a number of important strengths, including the ability to utilise longitudinal data from a large cohort. Sensitivity analysis in a recent meta-analysis [4], found that only 7 of 26 reviewed cohort studies had a follow-up period of greater than ten years and the majority of these investigated risk for cognitive decline rather than dementia. Furthermore, studies tended to look at the relationship between baseline PA and incident dementia (many years later) without consideration of intermediary time-points. The present data is rare in that repeated measures of PA were taken at a number of regular intervals across the follow-up period and in synchrony with recorded dementia diagnosis. Furthermore, a definition of PA was used that outlined both intensity and frequency of activity, and this is relevant for increasing the clinical applicability of these findings. To inform intervention guidelines, the present study found that average PA levels in those without cognitive impairment or dementia remained above moderate

to vigorous PA 1x/wk. Moderate PA includes any type of activity with a MET score of 3.5-6 and vigorous PA includes activity with a MET score above 6.

Overall, maintaining higher levels of PA in older age was associated with decreased risk for dementia. For those who were active before diagnosis, reducing PA levels after diagnosis may be detrimental for dementia prognosis, however further research is needed to investigate this possibility.

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6. REFERENCES

1. Prince M, Knapp M, Guerchet M, McCrone P, Prina M, Comas-Herrera A, et al.: Dementia UK: Update (Second Edition). London, 2014.
2. Prince M, Wimo A, Guerchet M, Ali G-C, Wu Y-T, Prina M: The global impact of dementia: an analysis of prevalence, incidence, cost and trends. London, 2015.
3. Clifford A, Bandelow S, Hogervorst E: The effects of physical exercise on cognitive function in the elderly. Handbook of Cognitive Aging: Causes Processes and Mechanisms. New York, Nova Sciences, 2010.
4. Blondell SJ, Hammersley-Mather R, Veerman J: Does physical activity prevent cognitive decline and dementia?: A systematic review and meta-analysis of longitudinal studies. BMC Public Health 2014 May 27;14:510.
5. Öhman H, Savikko N, Strandberg TE, Pitkälä KH: Effect of physical exercise on cognitive performance in older adults with mild cognitive impairment or dementia: a systematic review. Dement Geriatr Cogn Disord 2014 Jan;38:347–65.
6. Denkinger MD, Nikolaus T, Denkinger C, Lukas A: Physical activity for the prevention of cognitive decline: current evidence from observational and controlled studies. Zeitschrift für Gerontol und Geriatr 2012 Jan;45:11–6.
7. Rogers RL, Meyer JS, Mortel KF: After reaching retirement age physical activity sustains cerebral perfusion and cognition. J Am Geriatr Soc 1990 Mar;38:123–8.
8. Colcombe SJ, Erickson KI, Scalf PE, Kim JS, Prakash R, McAuley E, et al.: Aerobic exercise training increases brain volume in aging humans. J Gerontol A Biol Sci Med Sci 2006 Nov;61:1166–70.
9. Kramer AF, Erickson KI: Capitalizing on cortical plasticity: influence of physical activity on cognition and brain function. Trends Cogn Sci 2007 Aug;11:342–8.

10. Hogervorst E: Exercise to Prevent Cognitive Decline and Alzheimer's disease: For Whom, When, What, and (most importantly) How Much? J Alzheimer's Dis Park 2012 Feb 2;02. DOI: 10.4172/2161-0460.1000e117
11. Miller DI, Taler V, Davidson PSR, Messier C: Measuring the impact of exercise on cognitive aging: methodological issues. Neurobiol Aging 2012 Mar;33:622.e29–43.
12. Snowden M, Steinman L, Mochan K, Grodstein F, Prohaska TR, Thurman DJ, et al.: Effect of exercise on cognitive performance in community-dwelling older adults: review of intervention trials and recommendations for public health practice and research. J Am Geriatr Soc 2011 Apr;59:704–16.
13. Steptoe A, Breeze E, Banks J, Nazroo J: Cohort Profile: The English Longitudinal Study of Ageing. Int J Epidemiol 2013;42:1640–1648.
14. Marmot MG, Smith GD, Stansfeld S, Patel C, North F, Head J, et al.: Health inequalities among British civil servants: the Whitehall II study. Lancet (London, England) 1991 Jun 8;337:1387–93.
15. McMunn A, Hyde M, Janevic M, Kumari M: Health; in Marmot M, Banks J, Blundell R, Lessof C, Nazroo J (eds): Health, wealth and lifestyles of the older population in England: the 2002 English Longitudinal Study of Ageing. London, 2004, p 208.
16. Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, et al.: Compendium of physical activities: an update of activity codes and MET intensities. Med Sci Sports Exerc 2000 Sep;32:S498–504.
17. Jorm AF, Jacomb PA: The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): socio-demographic correlates, reliability, validity and some norms. Psychol Med 1989 Nov;19:1015–22.
18. Jorm AF: The Informant Questionnaire on cognitive decline in the elderly (IQCODE): a review. Int Psychogeriatr 2004 Sep;16:275–93.

19. Folstein MF, Folstein SE, McHugh PR: “Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975 Nov;12:189–98.

20. Hamer M, Lavoie KL, Bacon SL: Taking up physical activity in later life and healthy ageing: the English longitudinal study of ageing. Br J Sports Med 2014 Mar 1;48:239–43.

21. Karim J, Weisz R, Bibi Z, Rehman S: Validation of the eight-item centre for epidemiologic studies depression scale (CES-D) among older adults. Curr Psychol 2014; DOI: 10.1007/s12144-014-9281-y

22. Whitehead PJ, Drummond AEE, Walker MF, Parry RH: Interventions to reduce dependency in personal activities of daily living in community-dwelling adults who use homecare services: protocol for a systematic review. Syst Rev 2013 Jan;2:49.

23. Erickson KI, Hillman CH, Kramer AF: Physical activity, brain, and cognition. Curr Opin Behav Sci 2015 Aug;4:27–32.

24. Aguiar AS, Castro AA, Moreira EL, Glaser V, Santos ARS, Tasca CI, et al.: Short bouts of mild-intensity physical exercise improve spatial learning and memory in aging rats: involvement of hippocampal plasticity via AKT, CREB and BDNF signaling. Mech Ageing Dev Jan;132:560–7.

25. Leckie RL, Oberlin LE, Voss MW, Prakash RS, Szabo-Reed A, Chaddock-Heyman L, et al.: BDNF mediates improvements in executive function following a 1-year exercise intervention. Front Hum Neurosci 2014 Jan;8:985.

26. Stern Y: Cognitive reserve in ageing and Alzheimer’s disease. Lancet Neurol 2012 Nov;11:1006–12.

27. Phillips C, Baktir MA, Das D, Lin B, Salehi A: The Link Between Physical Activity and Cognitive Dysfunction in Alzheimer Disease. Phys Ther 2015 Jul;95:1046–60.

28. Middleton LE, Manini TM, Simonsick EM, Harris TB, Barnes DE, Tylavsky F, et al.: Activity energy expenditure and incident cognitive impairment in older adults. Arch Intern Med 2011 Jul 25;171:1251–7.

TABLES

Table 1. Characteristics of the population at baseline

	No incident dementia	**Incident dementia**	**Sig.**
Age; years	**N = 10,746** 64.80 ± 0.09	**N = 388** 75.59 ± 0.45	<0.001
Gender	**N = 10,746**	**N = 388**	0.16
Male	46	42	
Female	54	58	
Education	**N = 10,722**	**N = 385**	<0.001
Degree or equivalent	11	7	
Below degree	47	35	
No qualification	42	58	
Verbal Fluency	**N = 10,489** 19.36 ± 0.06	**N = 367** 15.25 ± 0.29	<0.001
Immediate Recall	**N = 10,487** 5.47 ± 0.02	**N = 370** 4.07 ± 0.09	<0.001
Walking speed; seconds	**N = 10,746** 1.39 ± 0.11	**N = 388** 2.73 ± 0.87	0.03
Baseline PA	**N = 10,647**	**N = 378**	<0.001
Moderate/vigorous >1x per wk	60	42	
Moderate/vigorous 1x per wk	15	16	
Mild 1x per wk	15	22	
PA < 1x per wk	10	20	
Wealth; quintiles	**N = 10,551**	**N = 386**	<0.001
<3rd	59	69	
4th or 5th	41	31	
Smoking status	**N = 10,654**	**N = 378**	0.02
Current	18	12	
Previous	47	50	
Never	35	38	
Alcohol consumption	**N = 10,652**	**N = 377**	0.003
>1x daily	4	4	
Daily	24	19	
1-2x per wk	31	26	
<1x per wk	41	51	
Depression	**N = 10,746**	**N = 388**	0.29
Yes	5	4	
No	95	96	

Mood problem	**N = 10,746**	**N = 388**	0.23
Yes	5	3	
No	95	97	
Cardiovascular condition	**N = 10,744**	**N = 388**	<0.001
Yes	50	71	
No	50	29	
Chronic disease	**N = 10,746**	**N = 388**	0.003
Yes	50	58	
No	50	42	

*For categorical data crosstabs indicate percentages for each category. For continuous data mean (± SEM) is included. The cohort is divided into those with and without dementia diagnosis between ELSA waves 2-6.

Table 2. Cox proportional hazards regression to predict dementia risk from baseline PA (N=10,663)

	STEP 1			STEP 2		
	HR	**95% CI**	**Sig.**	**HR**	**95% CI**	**Sig.**
Baseline PA						
Moderate/vigorous >1x per wk	0.50	0.37-0.67	<0.001	0.51	0.38-0.70	<0.001
Moderate/vigorous 1x per wk	0.66	0.46-0.94	0.02	0.66	0.46-0.94	0.02
Mild 1x per wk	0.69	0.50-0.95	0.02	0.67	0.49-0.93	0.02
PA < 1x per wk	[Ref]			[Ref]		
Age; years	1.11	1.10-1.12	<0.001	1.11	1.10-1.13	<0.001
Gender						
Male	1.13	0.91-1.40	0.29	1.10	0.87-1.39	0.41
Female	[Ref]			[Ref]		
Education						
Degree or equivalent	1.15	0.72-1.85	0.56	1.18	0.73-1.90	0.50
Below degree	1.01	0.80-1.27	0.95	1.01	0.80-1.27	0.94
No qualification	[Ref]			[Ref]		
Wealth; quintiles						
<3rd	1.14	0.90-1.46	0.28	1.09	0.84-1.40	0.53
4th or 5th	[Ref]			[Ref]		
Verbal fluency	0.95	0.93-0.97	<0.001	0.95	0.93-0.97	<0.001
Immediate recall	0.78	0.73-0.84	<0.001	0.78	0.73-0.83	<0.001
Physical function	1.00	0.99-1.01	0.80	1.00	0.99-1.01	0.76

STEP 1: Adjusted for baseline PA, age, gender, education, wealth, cognitive function, physical function

STEP 2: Adjusted for baseline PA, age, gender, education, wealth, cognitive function, physical function, smoking status, alcohol consumption, depression, mood problems, cardiovascular conditions and chronic disease

Table 3. Cox proportional hazards regression to predict dementia risk from average PA levels across the follow-up (N=10,667)

	STEP 1			STEP 2		
	HR	**95% CI**	**Sig.**	**HR**	**95% CI**	**Sig.**
Average PA*	0.79	0.69-0.90	<0.001	0.82	0.72-0.94	0.01
Age; years	1.11	1.10-1.12	<0.001	1.11	1.10-1.12	<0.001
Gender						
Male	1.15	0.92-1.43	0.21	1.12	0.89-1.42	0.33
Female	[Ref]			[Ref]		
Education						
Degree or equivalent	1.15	0.72-1.85	0.56	1.17	0.73-1.88	0.52
Below degree	1.01	0.80-1.28	0.92	1.01	0.80-1.27	0.93
No qualification	[Ref]			[Ref]		
Wealth; quintiles						
<3rd	1.13	0.88-1.45	0.33	1.08	0.84-1.39	0.54
4th or 5th	[Ref]			[Ref]		
Verbal fluency	0.95	0.93-0.97	<0.001	0.95	0.93-0.97	<0.001
Immediate recall	0.78	0.73-0.84	<0.001	0.78	0.73-0.83	<0.001
Physical function	1.00	0.99-1.01	0.71	1.00	0.99-1.01	0.69

* In those with dementia diagnosis, average PA is calculated using only waves prior to diagnosis

STEP 1: Adjusted for average PA, age, gender, education, wealth, cognitive function, physical function

STEP 2: Adjusted for average PA, age, gender, education, wealth, cognitive function, physical function, smoking status, alcohol consumption, depression, mood problems, cardiovascular conditions and chronic disease

Table 4. Multiple regression to predict scores on immediate recall and verbal fluency measures. Coefficients (ß) and significance values (sig.) are reported

	Cognitive outcome			
	Δ Immediate recall (N=127)		**Δ Verbal fluency (N=67)**	
	ß	**Sig**	**ß**	**Sig**
Δ Physical activity	0.51	<0.001	0.94	0.08
Δ Physical function	0.19	<0.001	-0.06	0.82
Age	0.03	0.19	-0.01	0.91
Gender	-0.15	0.64	0.93	0.44
Education	0.58	0.02	1.69	0.09

Δ = Delta change score (post- minus pre-diagnosis value)

FIGURE 1

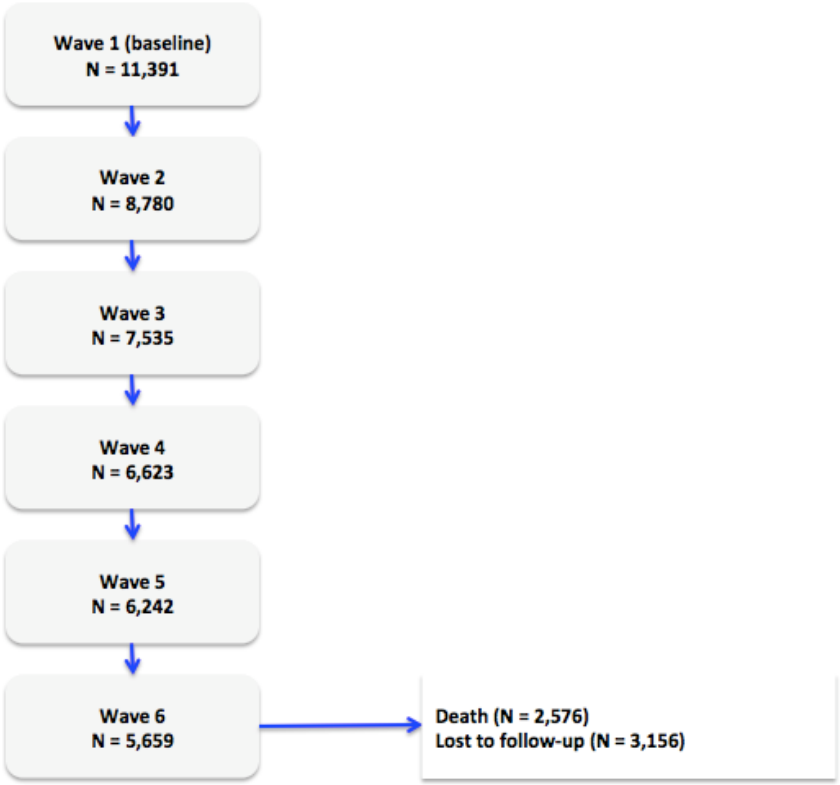


Figure 1. Flowchart of available data (N) in each wave

FIGURE 2

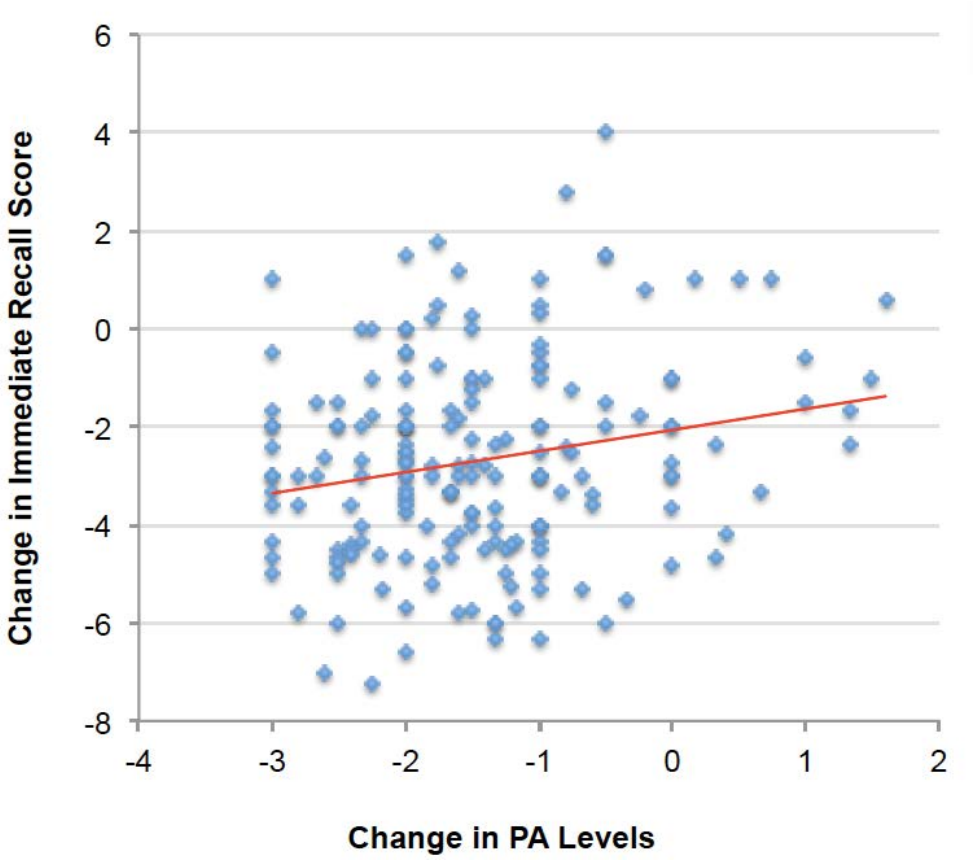
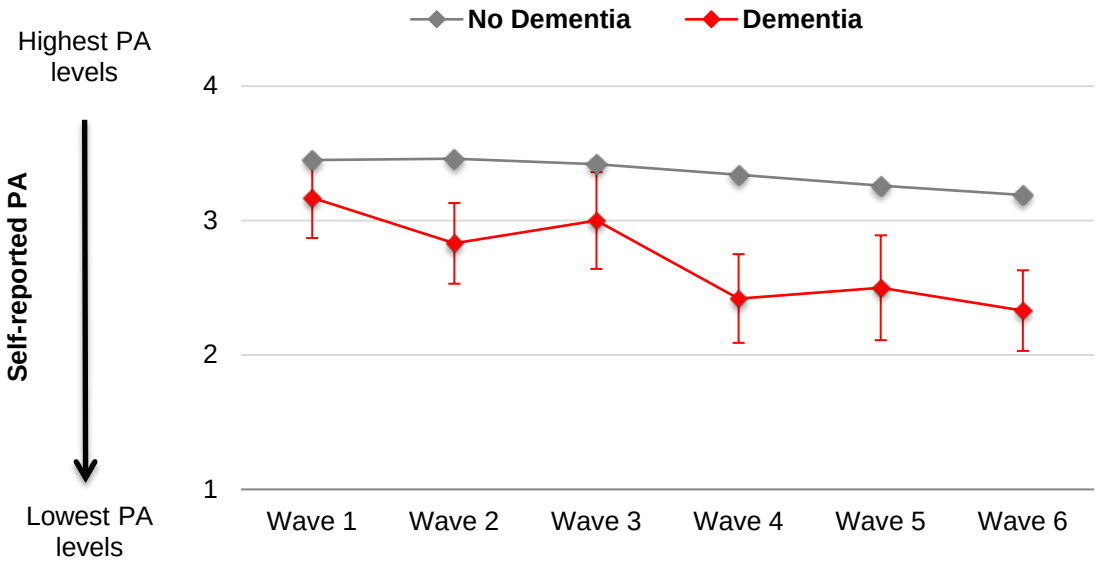


Figure 2. Changes in immediate recall score and PA levels from pre- to post-diagnosis. Negative values show a decrease, whereas positive values indicate an increase.

SUPPLEMENTARY DATA



Supplementary Figure 1. Mean category response for self-reported PA (± SEM) stratified by dementia diagnosis, at waves 1-6. PA categories: 1 = no PA at least once per week; 2 = mild PA once per week; 3 = moderate or vigorous PA once per week; 4 = moderate or vigorous PA two times per week or more.

Supplementary Table 1. Mean (±SEM) values for cognitive function, physical function and physical activity levels pre-diagnosis and post-diagnosis. These participants carried out moderate/vigorous PA at least 1x/wk prior to diagnosis (N=282)

	Dementia diagnosis		
	Pre	**Post**	**Sig.**
Verbal fluency	15.50 ± 0.49	10.13 ± 0.57	<0.001
Immediate recall	4.05 ± 0.11	1.79 ± 0.15	0.001
Physical function	4.64 ± 0.24	3.55 ± 0.32	0.001
Physical activity	2.64 ± 0.06	1.56 ± 0.05	<0.001