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The effects of cognitive reserve and lifestyle on cognition and dementia in Parkinson's disease – a longitudinal cohort study.

Running heading- Cognitive reserve in Parkinson's.

Key words- Parkinson's disease, Dementia, Cognition, Cognitive reserve, Lifestyle

Key points-

- Cognitive reserve may help explain the mismatch between brain pathology and clinical manifestations in PD.
- An active cognitive lifestyle may promote better global cognition in PD.
- Higher educational level may reduce global cognitive decline in PD.
- Increasing age combined with low social engagement may be associated with an increased risk of dementia in PD.

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Abstract

Objective

Cognitive reserve theory seeks to explain the observed mismatch between the degree of brain pathology and clinical manifestations. Early-life education, midlife social and occupational activity and later-life cognitive and social interaction are associated with a more favourable cognitive trajectory in older people. Previous studies in Parkinson's disease (PD) have suggested a possible role for the effects of cognitive reserve but further research into different proxies for cognitive reserve and longitudinal studies are required. This study examined the effects of cognitive lifestyle on cross sectional and longitudinal measures of cognition and dementia severity in people with PD.

Methods

Baseline assessments of cognition, and of clinical, social and demographic information, were completed by 525 participants with PD. Cognitive assessments were completed by 323 participants at four year follow up. Cognition was assessed using the measures of global cognition dementia severity. Cross sectional and longitudinal serial analyses of covariance for cognition and binomial regression for dementia were performed.

Results

Higher educational level, socio-economic status and recent social engagement were associated with better cross-sectional global cognition. In those with normal cognition at baseline, higher educational level was associated with better global cognition after four years. Increasing age and low levels of a measure of recent social engagement were associated with an increased risk of dementia.

Conclusions

Higher cognitive reserve has a beneficial effect on performance on cognitive tests and a limited effect on cognitive decline and dementia risk in PD.

Introduction

Parkinson's disease (PD) is an age-related neurodegenerative condition which is associated with cognitive impairment and the development of dementia, in addition to its more obvious motor features (Hindle, 2010). There has been recent interest in the theoretical beneficial effects of enhanced cognitive reserve in delaying cognitive impairment and dementia in PD (Muslimovic, Schmand, Speelman, & de Haan, 2007, Poletti, Emre, & Bonuccelli, 2011) although the evidence thus far is limited (Hindle, Martyr, & Clare, 2014).

Cognition in Parkinson's disease

Up to 25% of newly-diagnosed people with PD, and up to 90% of people with PD at any stage, experience mild cognitive impairment (MCI) (Pirozzolo, Hansch, Mortimer, Webster, & Kuskowski, 1982), with an increased risk of developing PD dementia (PDD) (Aarsland et al., 2010). Cognitive impairment in PD is manifested particularly in abnormalities of executive function (EF) (Kudlicka, Clare, & Hindle, 2011), visuospatial function, attention and memory. Executive dysfunction in PD may contribute to impaired quality of life, reduced health status, increased carer burden (Kudlicka, Clare, & Hindle, 2013b) and lack of awareness of functional limitations (Kudlicka, Clare, & Hindle, 2013a). PD dementia most commonly occurs after the age of 70 years and may ultimately affect at least 80% of people with PD (Reid, Hely, Morris, Loy, & Halliday, 2011). PD dementia is related to the spread of PD pathology either with or without Alzheimer's disease (AD) pathology (Hindle, 2010). The main risk factor for PDD is current age, but the early presence of posterior cortical deficits in visuospatial function, memory and language (Kehagia, Barker, & Robbins, 2010; Morley et al., 2012; Williams-Gray et al., 2009), more severe motor symptoms, postural

instability with gait disorder, MCI, a family history of dementia, and depression are also important (Janvin, Larsen, Aarsland, & Hugdahl, 2006).

Brain compensatory mechanisms in PD.

Compensatory mechanisms in the brain maintain apparently normal motor and cognitive function over many years from the onset of pathological change to subsequent clinical diagnosis (Hindle, 2010). With increasing age, polygenic influences and the accumulation of other insults and pathology, there is an increased likelihood of failure of these mechanisms leading to the development of or the acceleration of PD and cognitive impairment (Hindle, 2010). Cognitive reserve is one mechanism postulated which may increase compensatory mechanisms and delay cognitive progression which helps explain the observed mismatch between the degree of pathological change and inter-individual rates of cognitive decline (Tucker & Stern, 2011) and the development of dementias such as AD (Stern, 2009). Higher cognitive reserve is proposed to be associated with less cognitive decline with age (Valenzuela & Sachdev, 2006).

Childhood intelligence, education and level of occupation contribute to cognitive reserve, influencing cognitive ageing and decline (Tucker & Stern, 2011, Whalley, Deary, Appleton, & Starr, 2004). The effects of cognitive reserve may be enhanced in people with a protective genotype for AD (Pettigrew et al., 2013). The presence of well-connected structural brain networks protecting against age-related network degeneration may underlie cognitive reserve (Fischer, Wolf, Scheurich, & Fellgiebel, 2014). Cognitive reserve may reduce the rate of conversion from MCI to dementia, and the decline in executive function, attenuating the effects of brain atrophy (Reed et al., 2010) and protecting against amyloid-related cognitive impairment (Rentz et al., 2010). There may be particular role for the right prefrontal and parietal cortex in the promotion of the effects of cognitive reserve (Robertson, 2013).

In the absence of a single direct cognitive, functional, neuronal or structural measure of cognitive reserve a number of psychosocial, clinical and demographic variables are used as proxies. The most commonly used proxy measures for cognitive reserve are education, occupation and social class, and engagement with leisure and cognitive activities (Barnett, Salmond, Jones, & Sahakian, 2006; Stern, 2009; Tucker & Stern, 2011). Less commonly used proxies include height, head and brain size (Staff, 2012) and bilingualism (Craik, Bialystok, & Freedman, 2010). Psychosocial factors, including lifelong level of cognitive, social and physical activity and the size and complexity of social networks, are also known to contribute to delaying the onset of cognitive disability in later life (Fratiglioni, Paillard-Borg, & Winblad, 2004; Fratiglioni, Wang, Ericsson, Maytan, & Winblad, 2000; Wilson et al., 2002). Some of the proxies have been combined into a Cognitive Lifestyle Score, developed as an abbreviated form of the extensive Life Experiences Questionnaire which encompasses early life education, midlife social and occupational activity and later life cognitive and social interaction (Valenzuela & Sachdev, 2007). A higher Cognitive Lifestyle Score is associated with a more favourable cognitive trajectory in older people (Marioni, van den Hout, Valenzuela, Brayne, & Matthews, 2012, Valenzuela, Brayne, Sachdev, Wilcock, & Matthews, 2011), providing protection from cerebrovascular disease and neurotropic changes (Bennett, Arnold, Valenzuela, Brayne, & Schneider, 2014). Cognitive lifestyle is seen as serving a general protective function mediated through a number of mechanisms (Valenzuela et al., 2012), and is not specifically associated with any given disease or condition.

Cognitive reserve has been shown in systematic reviews to enhance performance on some cognitive tests in PD in cross-sectional studies and possibly also slow the progression of global cognitive decline (Hindle, et al., 2014, Muslimovic, et al., 2007) although there is a

need for more evidence from cross sectional and particularly longitudinal studies, using other proxies for cognitive reserve (Hindle, et al., 2014, Muslimovic, et al., 2007) .

This study aims to examine the effects of cognitive reserve on cognition and cognitive decline in PD by using early life, mid-life and later life factors which contribute to cognitive lifestyle as proxies for cognitive reserve. It was hypothesised that higher scores on cognitive lifestyle measures as proxy measures for cognitive reserve would be associated with better cross sectional performance on cognitive tests and a lower rate of cognitive decline and development of dementia in people with PD.

Methods

Participants

This study was part of the Prospective Study of Mood States in Parkinson's disease (PROMS)-PD study (ethics ref 07/MRE01/9) (Brown et al., 2011). People with PD were recruited over a 12-month period from specialist movement disorder clinics within four locations within the UK, Greater London, Merseyside, North West Wales, and the North East of England. Inclusion criteria were: a diagnosis of idiopathic PD according to UK Parkinson's disease Society Brain Bank criteria (Hughes, Daniel, Kilford, & Lees, 1992), the ability to give informed consent and living within two hours travel from recruiting clinics. People were excluded if they had insufficient English to participate in the study or had prohibitive communication difficulties. People with cognitive impairment were only excluded where they lacked capacity to give informed consent. The study received national ethical approval and complied fully with the declaration of Helsinki (Ethics ref 07/MRE01/9).

Measures

Baseline assessments took place over two occasions, usually in the participant's home. The initial assessment and subsequent follow-up in year four were undertaken by trained researchers. Researchers were trained together centrally and assessed for inter-rater reliability on all measures.

Proxy measures of cognitive reserve

Early Life

Education was used as an early life proxy measure of cognitive reserve. Since there is no agreed method of measuring education as a proxy for cognitive reserve, a classification which encompasses all possible categories of educational achievement was devised specifically for this study. A ten point categorisation of educational achievement was calculated by summating (a) self-report of years of education at school (before 14yrs=1, 14-15yrs=2, 16-18yrs=3), (b) whether or not they had higher education (no=0, yes=1) and (c) the maximum level of higher educational qualification achieved (other=2, diploma= 3, degree =4, masters degree =5, doctorate or equivalent= 6) .

Midlife

Socio-occupational status was assessed using the National Statistics Socio-economic Classification five class version (Office for National Statistics) (managerial and professional=1, intermediate=2, small employers and own account worker=3, lower supervisory and technical=4, semi-routine and routine=5).

Late Life

Current social engagement was assessed using screening questions designed specifically for the PROMS-PD study which gave categories for the number of people participants know well enough to visit (no people=1, 1-2=2, 3-4=3, 5 or more=4), the number of actual visits in the

last week (none=1, 2=1-6, 3=7or more) and the amount of telephone use in the last week (no telephone use=1, 1-6=2, 7 or more=3).

Cognition

Global cognition was assessed using the Mini-mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) with a maximum score of 30. The Addenbrooke's Cognitive Examination-Revised (ACE-R) (Mioshi *et al.*, 2006) assesses five cognitive domains: attention/orientation, memory, fluency, language and visuospatial. Higher scores indicate better functioning. The ACE-R has demonstrated reliability in a PD population (Reyes *et al.*, 2009). A score of less than 83 suggests clinically significant cognitive impairment and possible dementia (Mioshi *et al.*, 2006). Patients with higher scores may be cognitively intact or show mild cognitive impairment. The Clinical Dementia Rating (CDR) (Morris, 1993) is a clinician rated global measure of dementia. Ratings range from 0- healthy to 3 – severe dementia.

Disease Severity

The Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn et al., 1987) was used to assess severity of Parkinson's disease motor symptoms. Hoehn and Yahr (H&Y) staging provided an overall rating of disease severity.

Mood

The Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983) is a 14 item self-report measure of anxiety and depression. Subscale scores can be computed for depression and anxiety, scores of 8-10 indicate 'possible' depression or anxiety, and 11+ a 'definite' problem. The HADS has been validated for use in PD (Marinus et al., 2002, Mondolo et al., 2006).

Planned Analysis

All statistical analyses were performed using SPSS v 20 (IBM Corporation, NY, USA). The general linear model univariate tab was used to complete a series of ANCOVAs without the interaction term, using the type I (regression) sum of squares. In all analyses the potential confounding effects of age, motor severity and mood were accounted for by inclusion as covariates.

For baseline cross-sectional data the score for each cognitive test was used as a dependent variable with H&Y and the proxy for cognitive reserve (one of early life education, mid-life socio-occupational status, late-life number of people to visit category or telephone-use category) as factors. Age, UPDRS and HADS depression were included as covariates. The order in the model for score at baseline as dependent variable was H&Y followed by age, UPDRS motor severity, HADS depression and then each proxy for cognitive reserve in separate analyses.

For year four data the scores in year four for each cognitive test were controlled for by including the scores at year one as a covariate. The cognitive score at year four was used as a dependent variable with H&Y followed by each proxy for cognitive reserve as factors in separate analyses. The score at baseline for each cognitive test, age, UPDRS and HADS depression were included as covariates. The order in the model for the score at 4 years for each cognitive test as dependent variable was the score at baseline for each cognitive test followed by H&Y, age, UPDRS motor severity, HADS depression and then the proxy for cognitive reserve. In order to clarify whether the effect of cognitive reserve is best seen in those with normal baseline cognition an additional analysis was performed for participants who did not have baseline significant cognitive impairment (ACE-R of 83 or more). The significance of results was corrected using the Holm-Bonferroni correction for multiple comparisons (Holm, 1979).

Binomial logistic regression was used to predict the probability of participants developing dementia of any severity using CDR score over 4 years. Participants with no clinical dementia (CDR=0) at baseline were selected and dichotomised at 4 years into CDR groups, those who had no dementia and those who were rated as having any evidence of any severity of dementia (CDR 0.5 or more). These groups were then compared using ANOVA for age, UPDRS, and HADS depression, and using Chi Squared for Hoehn and Yahr, education, social class, number of visits, number of people to visit and telephone use categories. Predictor variables which showed significant differences between groups were then used in order of significance of the p value in a series of block steps to build regression models until the differences between the newest model and the previous model were not significant using the CDR groups at four years as the outcome variable. Continuous variables were checked for linearity using the Box Tidwell test. The strength of the model was tested using the Hosmer-Lemeshow test.

Results

Sample characteristics

The cohort comprised 525 people with PD (340 male, 185 female) with a median age of 69 and median Hoehn and Yahr status of 2. Complete data was available for 490 participants at baseline and 323 for the year 4 longitudinal analysis. Those lost to follow-up were older ($p<.001$), had later stage PD ($p<.001$) with greater motor severity ($p<.001$), were more depressed ($p=.002$) and had knew fewer people well enough to visit ($p=.001$). See Table 1.

[Insert Table 1 about here]

Baseline analysis

Higher levels of education were associated with higher scores on MMSE, total ACE-R, measures of verbal fluency and visuospatial function, with the result for language not quite reaching significance after correction for multiple comparisons. Higher social class was robustly associated with higher scores on MMSE, ACE-R total and all components of the ACE-R (attention/orientation, memory, verbal fluency, language and visuospatial). The level of social engagement using number of people known well enough to visit (p=.032) was not significant after Holm-Bonferroni correction and the number of visits categories was not associated with any measure of cognition. A higher level of recent telephone use however was associated with higher scores on MMSE, ACE-R total and all components of ACE-R except language (attention/orientation, memory, verbal fluency, and visuospatial). See Table 2.

[Insert table 2 about here]

Year four analysis

For the whole cohort there were no significant associations between any year four cognitive score and educational level, social class or any measure of social engagement after covarying for the scores at baseline (table 3). For those in whom the baseline ACE-R score was over 83 (maximum of 258 participants in the analysis) higher educational levels were associated with a statistically significantly higher longitudinal score on MMSE with the results for longitudinal scores on attention/orientation and total ACE-R score not quite reaching significance after correction for multiple comparisons. Social class and measures of social engagement were not associated with year four scores on any cognitive measure. See Table 4.

[Insert tables 3 and 4 about here]

Dementia

The majority of participants without clinical dementia (CDR=0) at baseline (n=283) still did not have clinical evidence of dementia at 4 years (n=222). Some participants developed very mild dementia at 4 years (n=52 CDR=.05) with a small number developing mild dementia (n=9 CDR=1). Those who changed from no dementia to very mild or mild dementia at 4 years were older (p<.001), had higher motor severity (p=.007), and used the telephone less (p=.001) at baseline (Table 5). Age, telephone use and motor severity (UPDRS) were used in the regression modelling. Although the result for education was not quite significant after correction for multiple comparisons, for completeness it was also added in the regression, but was found not to add significantly to any model. UPDRS did not add significantly to the model after age and telephone use. Age alone gave a very high sensitivity (100%) but very poor specificity (1.6%), but the addition of telephone use gave a significant improvement in the model (difference on –2 Log Likelihood χ^2 7.042 (2,281) p=.030 and total model χ^2 20.454 (3,281) p<.001) increasing the prediction of dementia (sensitivity 98.6%, specificity 11.5%). The model was able to correctly identify about 80% of cases and the strength was confirmed (Hosmer and Lemeshow χ^2 5.517 df 8 p=.701) (Table 6).

[Insert tables 5 and 6 about here]

Discussion

This is the largest individual study to date of the effects of cognitive reserve on cognition and cognitive decline in PD. It is the first study to use more than one proxy for cognitive reserve in PD in order to examine the effects of early life (educational level), midlife (socio-occupational class) and later life (recent social engagement) categories on cross-sectional and longitudinal measures of cognition.

Higher levels of education were significantly associated with baseline cross-sectional performance on cognitive tests, and there was a significant association with year four

performance of the MMSE in those with normal cognition at baseline. It could be argued that there may be a ceiling effect with those who had high levels of education and ACE-R managing to continue perform well on MMSE despite some cognitive decline. The results do however support the meta-analysis findings which showed that education was associated with significant differences on cross-sectional performance on the MMSE and with decline in MMSE scores (Hindle, et al., 2014) but had no effect on long-term dementia diagnosis.

The present study showed that, of those who did not have dementia at baseline, those who developed very mild or mild dementia at 4 years were older, with more severe motor symptoms and had less frequent use of the telephone at baseline. The regression modelling showed that higher age and lack of telephone use but not lower education or higher UPDRS gave the best model for predicting a change from no dementia to very mild or mild dementia over 4 years. This result for education contrasts with recent studies which showed an effect of education on dementia risk in the general population (Huang & Zhou, 2013). Other studies have used combinations of measures including education to define cognitive reserve and shown that it has a protective effect in relation to memory and executive function (Giogkaraki, Michaelides, & Constantinidou, 2013).

Socio-occupational class was associated with significant differences in cross-sectional cognitive performance but had no effect on longitudinal performance even in those with normal cognition at baseline. Education is already taken into account in interpreting some tests such as the Montreal Cognitive Assessment (MOCA) (Nasreddine et al., 2005) but social class may be an additional factor to consider later in life. Occupational complexity may be associated with better cognitive performance in old age in cross-sectional studies (Correa Ribeiro, Lopes, & Lourenco, 2013) and this study confirms this effect in PD but does not confirm a longitudinal protective effect.

Recent social engagement and telephone use were associated with significant differences on several measures of cognition but had no effect on longitudinal measures of cognition, although those who developed very mild or mild dementia had less frequent telephone use. Lack of recent telephone use was also predictive of the development of very mild or mild dementia over 4 years. Frequent telephone use may be a feature of an active cognitive lifestyle which is associated with a favourable cognitive trajectory as people age (Marioni, et al., 2012). Studies in healthy individuals have shown that, in addition to years of education, further stimulatory experiences in either midlife or late life are necessary for protective effect against dementia (Valenzuela, et al., 2011). Cognitive lifestyle, which includes factors in early, middle and later life, has been shown to have a protective effect on cognition, cognitive decline and dementia (Marioni, et al., 2012). One difficulty with later life recent cognitive lifestyle and engagement measures such as telephone use however is that the extent of social engagement may be the consequence of, rather than a contributory protective factor against, cognitive impairment. These issues of the relative benefits of early, middle and later life cognitive lifestyle require further clarification in PD.

There were no pathological or imaging correlates for the effects of cognitive reserve included in this study. Structural and functional imaging is used increasingly to explore the relationship between cognitive reserve, brain structure and function, and cognitive decline (Staff, 2012) and this would be important to include in future studies in PD. The proxies of education and linguistic ability have been shown to protect against hippocampal atrophy in AD (Schweizer, Ware, Fischer, Craik, & Bialystok, 2012; Shpanskaya et al., 2014) with other proxies being associated with protection against cerebrovascular disease (Bennett, et al., 2014). To date there are no neuropathological or imaging studies of standard proxies for cognitive reserve in PD. One recent study assessed grey matter volume, cognitive function and olfactory function but the results were difficult to interpret. The study found cortical

areas associated with olfaction to be more atrophic in those with better performance on olfactory tests and that this was also associated with better cognitive performance (Lee et al., 2014).

There are some potential limitations of this study. The study had four year follow-up and the full effect of cognitive reserve may be best seen over a longer follow-up period. Neuropathological and/ imaging were not performed but would provide additional information in future studies. All proxies of cognitive reserve are potentially limited by their indirect nature. We utilised available factors for proxies of recent cognitive engagement which may be subject to many external factors, and specific tools such as the Life Experiences Questionnaire (LEQ) may be more appropriate in future studies (Valenzuela & Sachdev, 2007).

Conclusions

Higher cognitive reserve has a beneficial effect on performance on cognitive tests and a limited effect on cognitive decline and dementia risk in PD.

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Table 1 Participant characteristics at baseline

	Baseline n=525 (m 340, f 185)	Followed-up n=330 (m 212, f 118)	Lost to follow-up n= 195 (m 128 f 67)	ANOVA Follow-up vs Lost to Follow-up	Chi Square Follow-up vs Lost to Follow-up
	Mean (range, SD)	Mean (range, SD)	Mean (range, SD)		
Age (years)	68 (32-94, 10.3)	66.1 (36-91, 10.1)	71.5 (32-94, 10.0)	**F (1,524)= 30.7 p<.001**	
UPDRS motor	26.3 (4-78,12.0)	24.8 (5-75, 11.1)	29.0 (5-78, 12.8)	**F (1,522)= 15.7 p<.001**	
HADS- depression score	6.2 (0-17, 3.6)	5.9 (0-17, 3.5)	7 (0-17, 3.7)	**F (1,490)= 9.9 p=.002**	
	Median (range, interquartile range)	Median (range, interquartile range)	Median (range, interquartile range)		
Hoehn & Yahr	2 (1-5, 1)	2 (1-5, 1)	2 (1-5, 1)		**24.4 p<.001**
Educational level	3 (1-10, 3)	3 (1-10, 4)	3 (1-10, 3)		16.4 p=.058
Socio-occupational status (NE-SEC code)	2 (1-5, 3)	2 (1-5, 3)	1 (1-5, 3)		2.0 p=.725

People know well (1=none, 2=1-2, 3=3-4, 4=>5)	4 (1-4, 0)	4 (2-4, 0)	4 (1-4, 0)		**16.0 p=.001**
Number of visits (none=1, 2=1-6, 3=7or more)	2 (2-2,.51)	2 (2-2, .49)	2 (2-2, .54)		**2.823 p=.244**
Telephone use (1=none, 2=1-6, 3=7 or more)	3 (1-3, 1)	3 (1-3, 1)	3 (1-3, 1)		1.3 p=.50

Table 2 Associations between baseline cognitive performance and cognitive reserve proxies (N=490)

Cognitive test	Mean (range)	Early life	Midlife	Late life		
		Education	NS-SEC	People know well	Number of visits	Telephone use
MMSE	27.87 (16-30)	**F (9,486)=3.106 p<.001 ηp^2 =.056**	**F (4,480)=10.387 p<.001 ηp^2 = .082**	F (3,486) = .435 p =.728 ηp^2 = .003	F (2,488) =.094 p =.911 ηp^2 <.001	**F (2,488) = 8.434 p<.001 ηp^2 = .034**
ACE-R total	86.52 (46-100)	**F (9,487)= 4.014 p< .001 ηp^2 = .072**	**F (4,481)=10.726 p<.001 ηp^2 =.084**	F (3,487) =.734 p=.532 ηp^2 = .005	F (2,488) =.375 p=.687 ηp^2 = .002	**F (2,489) =11.084 p<.001 ηp^2 =.044**
Attention/orientation	17.20 (10-18)	F (9,487)=1.486 p=.150 ηp^2 =.028	**F (4,481)=5.222 p<.001 ηp^2 =.043**	F (3,487) =1.330 p=.264 ηp^2 =.008	F (2,489) =.554 p= .575 ηp^2 =.002	**F (2,489) = 4.718 p=.009 ηp^2 =.019**
Memory	20.74 (6-26)	F (9,487) = 1.980 p=.040 ηp^2 =.037	**F (4,481) =5.894 p<.001 ηp^2 =.048**	F (3,487)=1.536 p=.204 ηp^2 =.010	F (2,489) =.503 p=.605 ηp^2 =.002	**F (2,489)=7.936 p<.001 ηp^2 =.032**
Verbal fluency	10.08 (0-14)	**F (9, 487)= 3.842 p<.001 ηp^2 =.069**	**F (4,481)= 6.475 p<.001 ηp^2 =.052**	F (3,487)=2.063 p=.104 ηp^2 =.013	F (2,489) =.092 p=.912 ηp^2 =<.001	**F (2,489)= 8.792 p<.001 ηp^2 =.035**
Language	24.21 (13-26)	F (9,485)= 2.326 p=.014 ηp^2 =.043	**F (4,479)= 7.498 p<.001 ηp^2 =.060**	F (3,485)=2.949 p=.032 ηp^2 =.018	F (2,487) =.362 p=.697 ηp^2 =..002	F(2,487)=2.123 p=.121 ηp^2 =.009
Visuospatial	14.34 (2-16)	**F (9,486) =2.488 p=.009 ηp^2 =.046**	**F 4 (480) =6.006 p<.001 ηp^2 =.049**	F (3,486)=1.939 p=.122 ηp^2 =.012	F (2,488) =.948 p=.388 ηp^2 =.004	**F (2,488)=6.057 p=.003 ηp^2 =.025**

Partial eta squared ηp^2, NS-SEC= Socio-occupational status.
Significant results in bold after Holm-Bonferroni correction for multiple comparisons within each column (significance for seven tests first p<.0071, second p<.0083, third p<.01, fourth p<.0125, fifth p<.016, sixth p<.025, seventh p<.05)

Table 3 Associations between cognitive performance at four year follow up and cognitive reserve proxies (whole cohort)

Cognitive test	Mean (range)	Early life	Midlife	Late life		
		Education	NS-SEC	People know well	Number of visits	Telephone use
MMSE	27.83 (13-30)	F (9,309) =2.523 p=.019 ηp^2 =.065	F (4,309) =.279 p=.892 ηp^2 =.004	F (3,310) =2.765 p=.065 ηp^2 =.018	F (2,311) =.325 p=.723 ηp^2 =.002	F (2,311) =2.315 p=.100 ηp^2 =.015
ACE-R total	87.57 (37-100)	F (9,309) =1.506 p=.145 ηp^2 =.044	F (4,309) =.721 p=.578 ηp^2 =.010	F (3,310) =1.252 p=.287 ηp^2 =.008	F (2,311) = .198 p=.821 ηp^2 =..001	F (2,311) =.209 p=.812 ηp^2 =.001
Attention/orientation	17.11 (8-18)	F (9,320) =2.072 p=.032 ηp^2 =.058	F (4,320) =.441 p=.779 ηp^2 =.006	F (3,321) =3.262 p=.040 ηp^2 =.021	F (2,322) =.302 p=.740 ηp^2 =..002	F (2,322) =2.460 p=.087 ηp^2 =.016
Memory	21.74 (3-26)	F (9,318) =.862 p=.560 ηp^2 =.025	F (4,318) =1.306 p=.268 ηp^2 =.017	F (3,319) =1.587 p=.206 ηp^2 =.010	F (2,320) =.365 p=.702 ηp^2 =.002	F (2,320) =.767 p=.465 ηp^2 =.005
Verbal fluency	10.02 (0-14)	F (9,320) =1.095 p=.366 ηp^2 =.032	F (4,320) =.655 p=.634 ηp^2 =.008	F (3,321) =1.298 p=.275 ηp^2 =.008	F (2,322) =.506 p=.603 ηp^2 =.003	F (2,322) =.754 p=.471 ηp^2 =.005
Language	24.20 (11-26)	F (9,315) =.660 p=.745 ηp^2 =.020	F (4,315) =.620 p=.648 ηp^2 =.008	F (3,316) =.307 p=.736 ηp^2 =.002	F (2,317) =2.793 p=.063 ηp^2 =..018	F (2,317) =.295 p=.745 ηp^2 =.002
Visuospatial	14.15 (4-16)	F (9,311) =1.349 p=.211 ηp^2 =.040	F (4,311) =.572 p=.683 ηp^2 =.008	F (2,312) =.294 p=.745 ηp^2 =.002	F (2.313) =.108 p=.898 ηp^2 =..001	F (2,313) =4.785 p=.009 ηp^2 =.031

Partial eta squared ηp^2, NS-SEC= Socio-occupational status.

No significant results after Holm-Bonferroni correction for multiple comparisons within each column (significance for seven tests first p<.0071, second p<.0083, third p<.01, fourth p<.0125, fifth p<.016, sixth p<.025, seventh p<.05)

Table 4 Associations between cognitive performance at four year follow up and cognitive reserve proxies for participants with ACE-R >83 at baseline

Cognitive test	Mean (range)	Early life	Midlife	Late life		
		Education	NS-SEC	People know well	Number of visits	Telephone use
MMSE	**28.57 (18-30)**	**F (9,251) =2.710 p=.005 ηp^2 =.095**	F (4,252) =2.493 p=.044 ηp^2 =.040	F (3,253) =3.894 p=.022 ηp^2 =.031	F (2,253) =1.103p=.358 ηp^2 =.008	F (2,253 =1.735 p=.179 ηp^2 =.014
ACE-R total	98.11 (58-100)	F (9,251) =2.495 p=.010 ηp^2 =.088	F (4,252) =1.065 p=.375 ηp^2 =.017	F (3,253) =1.634 p=.197 ηp^2 =.013	F (2,253) =.383 p=.682 ηp^2 =.003	F (2,253) =2.266 p=.106 ηp^2 =.018
Attention/orientation	17.52 (10-18)	F (9,255) =2.440 p=.011 ηp^2 =.085	F (2,256) =1.847 p=.120 ηp^2 =.030	F (3,257) =4.574 p=.011 ηp^2 =.036	F (2,257) =.581 p=.560 ηp^2 =.005	F (2,257) =1.222 p=.297 ηp^2 =.010
Memory	23.07 ((10-26)	F (9,253) = 1.200 p=.296 ηp^2 =.044	F (4,254) = 1.824 p=.125 ηp^2 =.029	F (3,255) =1.409 p=.246 ηp^2 =.011	F (2,255) .089 p=.915 ηp^2 =.001	F (2,255) =.979 p=.377 ηp^2 =.008
Verbal fluency	10.95 (1-14)	F (9,255) =1.698 p=.090 ηp^2 =.061	F (4,256) =.839 p=.502 ηp^2 =.014	F (3,257) =1.619 p=.200 ηp^2 =.013	F (2,257) =.122 p=.885 ηp^2 =.001	F (2,257) =2.393 p=.094 ηp^2 =.019
Language	24.83 (19-26)	F (9,253) =1.499 p=.149 ηp^2 =.149	F (4,254) =1.299 p=.271 ηp^2 =.021	F (3,255) =.262 p=.769 ηp^2 =.002	F (2,255) =.345 p=.708 ηp^2 =.003	F (2,255) =1.266 p=.284 ηp^2 =.010
Visuospatial	14.65 (10-16)	F (9,252) =1.418 p=.181 ηp^2 =.052	F (4,253) =.384 p=.820 ηp^2 =.006	F (3,254) = 1.028 p=.359 ηp^2 =.008	F (2,254) =1.327 p=.267 ηp^2 =.011	F (2,254) =2.130 p=.121 ηp^2 =.017

Partial eta squared ηp^2 , NS-SEC= Socio-occupational status.

Significant results in bold after Holm-Bonferroni correction for multiple comparisons within each column (significance for seven tests first p<.0071, second p<.0083, third p<.01, fourth p<.0125, fifth p<.016, sixth p<.025, seventh p<.05)

Table 5. Baseline characteristics of participants with no dementia at baseline- comparison between those with no change and those with deterioration at 4 years

	CDR= 0 baseline and 4 years n=222	Change in CDR at 4 years 0 to 0.5 n=52 0 to 1.0 n=9	ANOVA Follow-up vs Lost to Follow-up	Chi Square Follow-up vs Lost to Follow-up
	Mean (SD)	Mean (SD)		
Age (years)	64.8 (9.8)	70.21 (10.4)	**F (1,282)= 13.8** **p<0.001**	
UPDRS motor	23.3 (10.6)	27.7 (11.8)	**F (1,282)= 7.4** **p=.007**	
HADS- depression score	5.6 (3.6)	6.1 (2.8)	F (1,282)= .629 p=.428	
	Median (range, interquartile range)	Median (range, interquartile range)		
Hoehn & Yahr	2 (1-5, 1)	2 (1-5, 1)		7.16 p=.127

Educational level	3 (1-10, 4)	3 (1-10, 3)		**19.48 p=.021**
Socio-occupational status (NE-SEC code)	2 (1-5, 3)	1 (1-5, 3)		2.85 p=.582
People know well (1=none, 2=1-2, 3=3-4, 4=>5)	4 (2-4, 0)	4 (2-4, 0)		.012 p=.994
Number of visits (none=1, 2=1-6, 3=7or more)	2 (2-2, .49)	2 (2-2, .49)		.424 p=.809
Telephone use (1=none, 2=1-6, 3=7 or more)	3 (1-3, 1)	3 (1-3, 1)		**13.37 p=.001**

Table 6.Binomial logistic regression model predicting development of very mild or mild dementia over four years

	B	S.E.	Wald	df	Sig	Exp(B)	95% C.I. for Exp(B)	
							Lower	Higher
Age	.047	.016	8.785	1	**.003**	**1.048**	1.016	1.082
Telephone use			6.783	2	**.034**			
Telephone use 1 (none)	1.755	.678	6.703	1	**.010**	**5.785**	1.532	21.844
Telephone use 2 (1-6)	.254	.327	.604	1	.437	1.290	.679	2.449
Constant	-4.648	1.091	18.165	1	.000	.010		