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REVIEW ARTICLE

Brain reserve and cognitive decline: a non-parametric systematic review

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ABSTRACT

Background. A previous companion paper to this report (Valenzuela & Sachdev, *Psychological Medicine* 2006, **36**, 441–454) suggests a link between behavioural brain reserve and incident dementia; however, the issues of covariate control and ascertainment bias were not directly addressed. Our aim was to quantitatively review an independent set of longitudinal studies of cognitive change in order to clarify these factors.

Method. Cohort studies of the effects of education, occupation, and mental activities on cognitive decline were of interest. Abstracts were identified in MEDLINE (1966–September 2004), CURRENT CONTENTS (to September 2004), PsychINFO (1984–September 2004), Cochrane Library Databases and reference lists from relevant articles. Eighteen studies met inclusion criteria. Key information was extracted by both reviewers onto a standard template with a high level of agreement. Cognitive decline studies were integrated using a non-parametric method after converting outcome data onto a common effect size metric.

Results. Higher behavioural brain reserve was related to decreased longitudinal cognitive decline after control for covariates in source studies ($\phi = 1{\cdot}70$, $p < 0{\cdot}001$). This effect was robust to correction for both multiple predictors and multiple outcome measures and was the result of integrating data derived from more than 47 000 individuals.

Conclusions. This study affirms that the link between behavioural brain reserve and incident dementia is most likely due to fundamentally different cognitive trajectories rather than confound factors.

INTRODUCTION

In a previous report we define behavioural brain reserve as a multifaceted CNS phenomena related to complex mental activity which allows for preserved cognitive performance in spite of underlying brain disease (Valenzuela & Sachdev, 2006). In that report, behavioural measures of brain reserve such as education, occupational complexity and late-life mental activities were studied in a parametric meta-analysis of 22 cohort studies, finding that higher brain reserve was associated with a 46% reduction in dementia incidence. This finding may therefore explain why up to 30% of individuals who have moderate-to-severe levels of neurodegenerative pathology at autopsy show no signs of cognitive dysfunction at ante-mortem test (MRC CFAS, 2001). Multi-scalar neurobiological processes are suggested to underlie the link between complex mental activity and dementia, including neuro- and synapto-genesis at the

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microscopic scale and functional reorganization at the scale of cortical connectivity.

The objective of our dementia incidence meta-analysis had been to put conflicting reports into context, however, a major limitation was reliance on a univariate integration of identified source studies. Although most studies controlled for covariates themselves, we could not do so given that summary data was used. The salient impact of covariates such as age, cerebrovascular disease and baseline cognition (Trollor & Valenzuela, 2001), for example, could not be systematically accounted for.

Another critique of reports which have linked behavioural brain-reserve variables and dementia incidence is the impact of ascertainment bias (Tuokko *et al*. 2003). In this scenario, subjects who have low brain reserve at baseline are likely to be near the 'threshold for dementia' on neuropsychological tests, therefore making incident dementia more likely at follow-up.

There have now been a number of longitudinal studies of *cognitive change*, rather than dementia incidence, and its relationship with behavioural brain-reserve variables (see Table A in the Appendix). Notably, these studies are wholly independent to the studies reviewed in our previous dementia incidence report (Valenzuela & Sachdev, 2006). These studies, therefore, provide an important opportunity for further insight into the brain-reserve effect by clarifying the issues of covariance and ascertainment bias.

Complicating parametric integration of this database, however, is the disparity in cognitive assessment and outcome measures which have been applied. Methods for conversion of different outcome measures to a common and continuous metric are the subject of some debate and require many assumptions about the data (Glass *et al*. 1981; McGraw & Wong, 1992). A less onerous and more transparent conversion entails recoding of effect sizes into common language terms such as nil, small, moderate and large (Cohen, 1988). Non-parametric integration of such converted data is subsequently relatively straightforward.

The objective of this report was, therefore, to systematically integrate independent cohort studies of cognitive change in order to clarify the relationship with behavioural brain reserve.

METHOD

Behavioural brain-reserve search strategy

MEDLINE (1966 to March week 5, 2004), PsychINFO (1984 to March week 5, 2004), CURRENT CONTENTS (to March 2004) and Cochrane Library databases were searched for original research with the following strategy: (*a*) 'brain reserve' or 'cognitive reserve' or 'education' or 'occupation' or 'IQ' or 'intelligence' or 'leisure' or 'activity'. The results of this search was cross-matched with (*b*) 'cognition' or 'cognitive' or 'neuropsychological' plus 'decline' and 'incidence' or plus 'longitudinal' or 'cohort'. This search produced 404 studies. The search was supplemented by manual checking through reference lists of published reports and contact with leading research groups.

A large number of these studies were excluded on grounds of irrelevance to the brain reserve topic as determined by published abstract read by M.V. (approximately 300 studies). The next most common reason for exclusion was reporting on cross-sectional data, or progression of cognitive decline in demented subjects. Studies with total number of follow-up participants less than 100 or follow-up less than 1 year were also excluded. There were no exclusion criteria based on drop-out or mortality rates. Studies which had been used in the previously reported quantitative dementia incidence meta-analysis were also excluded in order to draw conclusions from an independent database. A total of 18 cohort studies met inclusion criteria for this review.

Data extraction was done by two different researchers onto a standard template, with 74% agreement. Differences were resolved by consensus.

Non-parametric integration of cognitive decline studies

A systematic integration of cognitive decline using a non-parametric method was performed because effect size was often reported in a number of different ways (see Table A in the Appendix). Heterogeneity in the cognitive tests used also made conversion into a continuous metric impractical. Using published guidelines for classifying effect sizes (Glass *et al*. 1981; Cohen, 1988; McGraw & Wong, 1992), study results were converted into a 4-point ordinal

Table 1. *Conversion criteria for different types of effect sizes in longitudinal studies of cognitive decline*

	Cohen effect size (*d*)	*r*	r^2	Odds ratio[a]	β value[b]	χ^2[c] ϕ
Nil (0)	0	0	0	1·0	N.S.	0·0
Small (1)	0·2	0·10	0·01	0·71	<50% age effect	0·1
Moderate (2)	0·5	0·24	0·06	0·45	~age effect	0·3
Large (3)	>0·8	>0·37	>0·14	<0·32	>150% age effect	>0·5

[a] What is considered a 'small', 'moderate' or 'large' odds ratio will differ depending on the control or baseline event rate. These odds ratio conversions assume a control event rate of 10% and uses the Probit transformation for differences in the experimental event rate.

[b] When only β coefficients were reported, effect size was graded with respect to the age predictor coefficient: equivalent β values were graded 'moderate', >150% of the age coefficient was graded 'large', and <50% of the age coefficient was graded 'small'.

[c] The effect size estimate chosen for the χ^2 procedure was phi, $\phi = \sqrt{(\chi^2/n)}$, where n = number of studies integrated.

scale: 0, no effect; 1, minor effect; 2, moderate effect; 3, strong effect (see below for more details). Effect size conversions were made using the multivariate-adjusted results from the source studies. Study results were then graphically displayed and tested for deviance from a null hypothesis using the χ^2 procedure and then corrected for study sample size via the phi (ϕ) procedure (see Table 1).

Standard effect size metric

Effect size is a statistical estimate of the magnitude of the experimental effect, or the 'degree to which the null hypothesis is false', as opposed to its significance level. It can take many forms, usually dependent on the nature of the experiment. Examples include a simple *t* test value, *F* test value, correlation coefficient, β value, odds ratio or relative risk (Cohen, 1988). Cohen's (1988) book on the topic emphasizes that cut-offs for these decisions should primarily be guided by one's knowledge of the field in question. In the absence of such knowledge, Cohen proposed several criteria. Table 1 summarizes cut-off criteria for conversion of several types of effect sizes into a simple common-language ordinal scale.

Multiple predictors

Several reports examined the effect of different and potentially correlated brain-reserve predictors from the one study, thereby posing a potential bias towards homogeneity. The overall analysis was therefore repeated on a 'trimmed-down' dataset, where each study provided a single and unique dataset (i.e. number of datasets = number of studies = 18) and results were found to not significantly change ($\phi = 1{\cdot}10$, $p < 0{\cdot}0001$), thus, the more expansive results are reported. Where a study reported on more than one predictor, for the purposes of the 'trimmed-down' analysis, the more conservative result (closest to the null hypothesis) was utilized.

Multiple outcome measures

Another issue was multiple outcome measures (Wolf, 1986), as brain-reserve effects on global cognitive status as well as on a number of different cognitive domains were often reported. Therefore, the current approach was to compare the difference when using either all reported outcomes *versus* the 'most representational result' (MRR) for each study. The MRR was chosen on a simple counts basis, so that in a study with four outcomes, if three were graded as having an effect size of 2 and one was 0, the MRR was entered as 2. When outcomes within a study were evenly divided, then the more conservative result was entered. 39 datasets were identified from 18 studies for this analysis (Table A).

Definition of cognitive change

For the purposes of this review, 'cognitive change' was defined by the source publications (see Table A). Some studies dichotomized cognitive change by setting an arbitrary threshold on a cognitive outcome measure, however, most utilized cognitive outcome as a continuous variable. As a rule, the source studies began with community-acquired disease-free individuals (typically verified by a screening questionnaire or interview) who were then subjected to regular longitudinal medical, behavioural and cognitive

assessments for varying time periods. Studies which used stratified sampling techniques were analysed after collapsing across groups.

Definition of brain reserve

'High' *versus* 'low' brain-reserve groups were defined based on the dichotomization technique used in the source study (see Table A). Some studies utilized the predictor brain-reserve variable, that is, education, occupation or mental activities, in a continuous variable fashion.

RESULTS

We tested the pattern of effect sizes from cognitive decline studies of brain reserve against a standard null hypothesis (H_0) with the χ^2 procedure. The H_0 was derived from standard proportions found in a normal distribution divided into four equidistant groups along the ordinal. This produced a χ^2 measure of deviance that was transformed into a phi-statistic of effect size (ϕ) by correcting for sample size (n) being the number of cohort studies integrated (Cohen, 1988).

Effect of education

Thirteen studies have examined the relationship between education and longitudinal cognitive decline (Shichita *et al.* 1986; Colsher & Wallace, 1991; Evans *et al.* 1993; White *et al.* 1994; Albert *et al.* 1995; Farmer *et al.* 1995; Butler *et al.* 1996; Carmelli *et al.* 1997; Jacqmin-Gadda *et al.* 1997; Arkbuckle *et al.* 1998; Lyketsos *et al.* 1999; Christensen *et al.* 2001). Overall the effect is significant and large, with three studies showing no effect and 10 showing a significant effect (Fig. 1*b*).

Effect of occupation

Only four studies have examined the effect of occupation on cognitive decline (Evans *et al.* 1993; White *et al.* 1994; Arkbuckle *et al.* 1998; Verhaegen *et al.* 2003). One showed no significant effect and three showed small significant effects (Fig. 1*c*). The overall effect was non-significant.

Effect of mental activities

Six studies have examined the impact of leisure and social activities on prospective cognitive change (Gribbin *et al.* 1980; Shichita *et al.* 1986; Arkbuckle *et al.* 1998; Hultsch *et al.* 1999; Bassuk *et al.* 1999; Seeman *et al.* 2001). All but one found a significant effect (Fig. 1*d*). The effect size was moderate.

Overall effect is large and significant

A total of 39 outcomes, from 18 different studies, were combined, based on an integrated sample of 47 028 individuals. As shown in Fig. 1*a*, the overall effect of high brain reserve on cognitive decline diverged significantly from the null hypothesis. The magnitude of the deviation was large, supporting findings from the dementia incidence meta-analysis in our previous report. All studies with significant findings (effect size >0) showed a protective effect, that is, high brain reserve was associated with less cognitive decline. *Unlike the previous meta-analysis of dementia incidence, this combined summary effect was based on results from studies that had already adjusted for covariates.*

Both the significance level and magnitude of the overall effect were similar when either the MRR ($\phi = 1{\cdot}31$, $p < 0{\cdot}0001$) or all reported outcomes were analysed ($\phi = 1{\cdot}72$, $p < 0{\cdot}0001$). Trimming down the dataset for multiple predictors also did not significantly change the overall effect size ($\phi = 1{\cdot}10$, $p < 0{\cdot}0001$). There were no significant differences in sample sizes between negative and positive reports ($p = 0{\cdot}29$) and there was no significant Spearman correlation between years of follow-up and effect size ($r = -0{\cdot}01$, $p =$ N.S.).

DISCUSSION

The objective of this paper was to systematically integrate prospective studies which have examined the link between behavioural brain-reserve measures and longitudinal cognitive change. Overall, the results showed that behavioural brain reserve was significantly and robustly associated with attenuated cognitive decline in 18 independent studies, summed over a sample of over 47 000 individuals.

Meta-analysis issues

Cognitive ageing studies in the brain-reserve area have used a number of different neuropsychological outcome measures and effect-size estimates, making systematic integration a

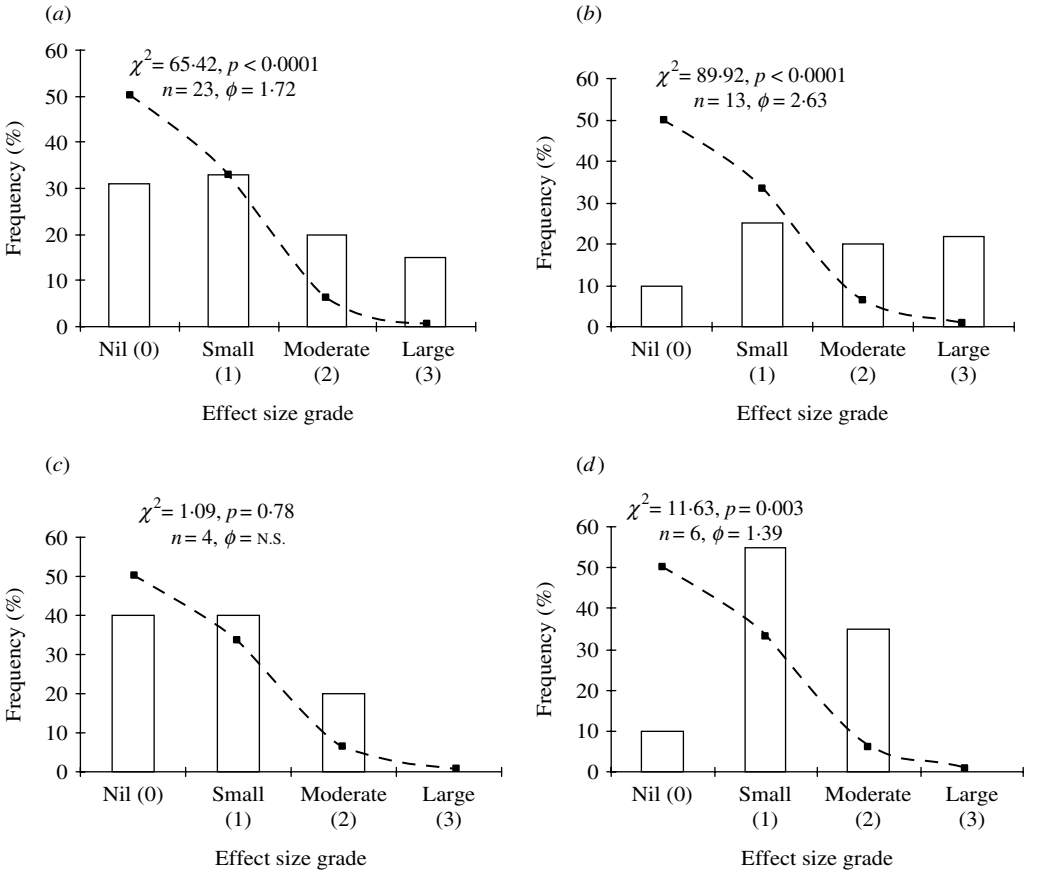

FIG. 1. Frequency distribution of individual studies' effect sizes compared to null hypothesis. (*a*) Overall effect of brain reserve on cognitive decline, (*b*) education alone, (*c*) occupation alone, and (*d*) complex mental activities alone. χ^2 value describes level of deviance from H_0; phi (ϕ) is the effect size estimate corrected for sample size, n, which is the number of studies integrated. □, Actual studies; ■----■, null hypothesis.

challenge. The non-parametric method used here entailed no opaque conversion formulae or exigent assumptions about the source data; instead we opted to use a common language approach which converted different effect estimates into an ordinal scale using standard criteria. This approach, therefore, benefits from a high degree of face validity and is approachable by non-statistically orientated clinicians.

As previously mentioned, simultaneous control of relevant covariates was not possible in the earlier report on brain reserve and dementia incidence (Valenzuela & Sachdev, 2006). Our approach to the cognitive decline literature was, therefore, particularly informative, as relevant covariates within the source studies, including age, were taken into account. The overall finding that increased mental activity was related to a slower rate of longitudinal cognitive decline was robust, with a summary ϕ of 1·72, well above Cohen's cut-off for a large effect of 0·5 (see Table 1). This result is, therefore, also consistent in magnitude with the summary odds ratio found in our previous paper, which showed a strong relationship between complex mental activity and a 46% decrease in risk for incidence dementia.

Another benefit of the present strategy was that the null hypothesis could be easily manipulated. The null hypothesis used here was conservative, that is, the distribution of effects from different brain-reserve studies was tested against one that allowed for several false positives as seen in Fig. 1. A conservative approach

was considered appropriate given the noted heterogeneity in outcomes measures.

Straightforward non-parametric integration, however, does suffer from being overly democratic. All studies are treated equally, as opposed to the differential weighting that studies attain in parametric integration based on sample size. A close look at those studies that produced a negative result suggests this factor was not an untoward bias in this analysis. The average sample size, for example, of negative studies was 990, non-significantly different from those that produced positive findings (average sample size = 2928, see Table A). Negative studies, therefore, tended to have smaller sample sizes, making the present findings, if anything, more compelling.

Another limiting factor was that integrated studies had a wide range of follow-up periods, from 1 to 45 years, even though the majority were in the 3- to 7-year range. In order to rule out that extreme follow-up periods were not artificially affecting our results, we tested for a correlation between follow-up period and effect size. No correlation or trend was evident and so disparity in this study characteristic is not likely to have imparted a significant confound on our results.

Bias in dementia incidence studies

Ascertainment bias has been identified as a major potential confounder in longitudinal Alzheimer's disease (AD) diagnosis, particularly in brain-reserve studies (Tuokko *et al.* 2003). The great majority of cognitive change reports reviewed here utilized neuropsychological scores in a continuous variable fashion, in effect nullifying this issue. This paper, therefore, shows a strong and robust link between behavioural brain-reserve variables and decreased rate of cognitive decline.

The potential interaction between the AD process and brain-reserve variables, for example drop-off of mental activities, also deserves comment. Here, five out of six studies which examined the link between mental activities and behavioural brain reserve showed significant effects after controlling for relevant covariates. Moreover, subjects were disease-free as determined from screening examination and four of the studies controlled for baseline cognitive function. In our opinion, there is a low likelihood that 'preclinical AD' was affecting the mental activity patterns of healthy subjects in these studies, particularly in a fashion that was independent to their initial neuropsychological status.

The link between high behavioural brain reserve and decreased dementia incidence found in our previous report (Valenzuela & Sachdev, 2006), hence receives considerable and complementary support from this review of cognitive change in healthy individuals. Our finding supports the view that attenuated cognitive decline in those with higher behavioural brain reserve is most likely the fundamental reason for this association.

CONCLUSIONS

A non-parametric quantitative integration of the brain-reserve literature was completed in relation to longitudinal studies of cognitive change. A robust result was found showing decreased cognitive decline in high behavioural brain-reserve individuals, based on a systematic review of over 47 000 subjects and after controlling for relevant covariates in the source studies. This report, therefore, complements and supports the finding of our previous paper, suggesting that the link between behavioural brain reserve and dementia is more than likely based on fundamentally attenuated rates of cognitive decline rather than confounding factors.

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DECLARATION OF INTEREST

None.

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APPENDIX

Table A. *Details of all eligible cohort studies of brain reserve and cognitive decline*

Study (first-named author)	Predictor definition	Cohort age	Education level	F/U (yr)	*n*	Cognitive outcome	Covariates in model	OR	CI	*β* coeff.	*p* value	Effect size grading (0, 1, 2, 3)
Education												
White (1994) Boston sample	⩽8 yr *v.* >12	65+, 6% >85	40% <9 yr 5% >12 yr	6	2658	SPMSQ: decline = moving from unimpaired to impaired (⩾3)	Age, gender, stroke hx, baseline SPMSQ	2·3	1·6–3·4			2
New Haven sample				6	2153			1·8	1·7–1·8			1
Iowa sample				6	2839			1·7	1·3–2·3			1
Pooled sample				6	7643		Plus occupation	1·7	1·4–2·0			1
Farmer (1995)	Years	18+, 29% >65	28% <10 yr, 31·9% college	1	14 883	MMSE: baseline stratified by ⩽23; decline dichotomized by whether or not decline ⩾3 points	Residential status, income, substance abuse, age, gender, baseline MMSE	0·3	0·2–0·4			3
Evans (1993)	Years formal schooling	65+, 8% >85	25% <7 yr, 24% >12 yr	3	2273	Immediate memory change scores: normalized	Age, gender, occupational prestige, income, birthplace, language			0·048	*<0·0001*	3
						Mental state change scores: normalized				0·023	*0·001*	2
Albert (1995)	Years	70–79	Top 1/3 of population on a screening instrument	2·5	1192	Battery of 5 tests combined	Multiple (pathway analysis). Physical activity, peak pulmonary function, self-efficacy were main other predictors			$t = 5·6$	*<0·01*	3
Christensen (2001)	Years and <10 yr, 10–12 yr, ⩾12 yr	70–93	23% <10 yr, 33% >12 yr	7	887	MMSE change	Health, stroke hx				*>0·05*	0
						CIQ (NART, similarities, vocab), Memory (Word recognition, recall, address recall) Speed (Symbol digit)				0·08	*>0·05*	0
										0·01	*>0·05*	0
										−0·09	*>0·05*	0
Winnock (2001)	Primary school with diploma *v.* no school or no diploma	73·7	73% primary school diploma	7	600	MMSE	Age, gender, time, age × time, ApoE4			−0·56	*0·0001*	3
Jacqmin-Gadda (1997)	<primary, >primary, ⩾high school	65+, $x = 74·4$	31% <primary, 35% ⩾HS	5	2537	MMSE	Age, gender, baseline MMSE, time, age × time			0·028	*<0·001*	2
Lyketsos (1999)	Years	18 yr+, 45% >50, 15% >70	27% <9 yr, 7% >15 yr	12	1488	MMSE	Age, gender, race, baseline MMSE			−0·64	*<0·05*	1
Butler (1996)	Bachelor degree *v.* not	75–102 $x = 84$		1·6	575	MMSE – annualized decline	Age stratification				*<0·05*	1
Shichita (1986)	Nil, up to HS, finish HS, post HS	69–71		5	302	Benton Visual Retention Test	Baseline score, baseline × education, activity, gender			0·574		3
Arkbuckle (1998)	Years	65	x = grade 9	4·5	132	Verbal Factor subtests	Multiple (pathway analysis)			0·2		2
						Non-verbal factor subtests				N.S.		0
Colsher (1991)	<9 yr, 9–12 yr, >12 yr	$x = 72·8$	$x = 10·75$ yr	6	1953	SPMSQ	Age				*<0·05*	1
						Memory tests	Age				*>0·05*	0

Carmelli (1997)	Ranked from 1 (<HS) to 7 (postgraduate)	$x = 70{\cdot}7$	x rank = 4·5	6	566	Benton Visual Retention Test: change in quartile rank	Nil				0
						COWAT: change in quartile rank					0
						Digit Symbol Substitution: change in quartile rank					0
Occupation											
Evans (1993)	Perceived prestige rank	65+, 8% >85	25% <7 yr, 24% >12 yr	3	2273	Immediate memory change scores: normalized	Age, gender, education, income, birthplace, language			0·004	*0·02*	1
						Mental state change scores: normalized				0·001	*N.S.*	0
White (1994) Pooled sample	Occupational groups 1 (professional, clerical) to 5 (equipment operators, labourers)	>65, ~6% >85	~40% <9 yr, 5% >12 yr	6	7643	Incident case means moving from unimpaired to impaired (>=3) on SPMSQ	Age, gender, education, stroke hx, baseline SPMSQ	1·4	1·1–1·7			1
Arkbuckle (1998)	Occupational prestige		x = grade 9	4·5	132	Verbal subtests decline	Multiple (pathway analysis)			0·24	*<0·05*	2
						Non-verbal subtests decline				N.S.	*N.S.*	0
Verhaegen (2003)	Socio-economic Score based on income, occupation, education & social status	$x = 81$	$x = 10{\cdot}8$	4	206	General IQ	Age, gender, diabetes, chronic heart disease, heart failure			−0·10	*<0·05*	1
Mental activity												
Shichita (1986)	Maeda's Activity scale: frequency and level of activity at home, outing, sports, hobbies, reading socializing (0–39)	69–71		5	302	Benton Visual Retention Test	Baseline score, baseline × education, education, gender			0·063		1
Arkbuckle (1998)	Engagement: occupation, post-war education, activity levels	65	x = grade 9	45	132	Verbal Factor decline	Multiple (pathway analysis)			0·2	*<0·05*	2
Hultsch (1999)	Activity levels: 70 activities rated for frequency on 9 point scale. Novel information processing activities as a separate scale	55–86	83% >11 yr, $x = 13{\cdot}42$	6	250	Non-verbal factor decline 9 latent variables – main one in structural models was working memory	Age, self reported health, personality			0·15 0·21	*<0·05*	1 2
Gribbin (1980)	Life Complexity Scale: 29 page questionnaire	40–88		14	140	Word Fluency	Baseline cognitive function				*N.S.*	0
						Intellectual ability					*p <0·001*	2
						Psychomotor speed					*p <0·001*	1
Bassuk (1999)	Social engagement: 6 domains – spouse, contact with family, friends visual, friends non-visual, meetings and recreation	65+, 38% >75 yr	60% <12 yr	12	756	SPMSQ – categorized into 3 levels and decline defined as transition into lower level	Gender, SPMSQ at baseline, ethnicity, education, income, housing, health, CVD, sensory impairment, depression, moking, ETOH, exercise	1·33	1·03–1·72		*0·03*	1
Seeman (2001)	Various quantitative and qualitative summary measures based on social domains such as spouse, children, friends/relatives, group interactions	70–79	Top 1/3 of population	7·5	722	Composite score of battery covering 6 different cognitive domains	Age, education, income, ethnicity, chronic conditions, lung function, exercise, depression, self-efficacy			1·2	*0·05*	1

Operational definition of predictor, along with other cohort descriptors. Median education level as reported by source study. F/U, median follow-up time in years reported by source study. Specific cognitive outcomes are shown. All effect sizes are reported after covariate adjustment. 0, Non-significant effect; 1, Small effect; 2, Moderate effect; 3, Large effect.