Psychological Medicine, 2006, **36**, 441–454. © 2005 Cambridge University Press
doi:10.1017/S0033291705006264 First published online 6 October 2005. Printed in the United Kingdom

REVIEW ARTICLE

Brain reserve and dementia: a systematic review

MICHAEL J. VALENZUELA[1,2,3]* AND PERMINDER SACHDEV[1,2]

[1] *The Neuropsychiatric Institute, Prince of Wales Hospital*; [2] *School of Psychiatry, University of New South Wales*; [3] *The Black Dog Institute, Prince of Wales Hospital, Sydney, Australia*

ABSTRACT

Background. Behavioural brain reserve is a property of the central nervous system related to sustained and complex mental activity which can lead to differential expression of brain injury. Behavioural brain reserve has been assessed using autobiographical data such as education levels, occupational complexity and mentally stimulating lifestyle pursuits. So far there have been several epidemiological reports but no systematic review to put conflicting results into context. Our aim was to quantitatively review evidence for the effect of brain reserve on incident dementia.

Method. Cohort studies of the effects of education, occupation, premorbid IQ and mental activities on dementia risk 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. Twenty-two studies met inclusion criteria. Key information was extracted by both reviewers onto a standard template with a high level of agreement. Studies were combined through a quantitative random-effects meta-analysis.

Results. Higher brain reserve was associated with a lowered risk for incident dementia (summary odds ratio, 0·54; 95% confidence interval, 0·49–0·59). This effect was found over a median of 7·1 years follow-up and resulted from integrating data across more than 29 000 individuals. Notably, increased complex mental activity in late life was associated with lower dementia rates independent of other predictors; a dose–response relationship was also evident between extent of complex mental activities in late life and dementia risk.

Conclusions. This study demonstrates robust evidence that complex patterns of mental activity in the early, mid- and late-life stages is associated with a significant reduction in dementia incidence. Randomized control trials based on brain-reserve principles are now required.

INTRODUCTION

Brain reserve is a complex phenomenon with two major competing definitions. Neurological brain reserve argues that peak brain volume differentiates brain injury outcomes based on predominately hard-wired differences in structural neural characteristics such as neural numbers (Schofield, 1999), whilst behavioural brain reserve suggests complex mental activity across the lifespan allows flexible cognitive repertoires to be deployed in the face of underlying neural dysfunction (Stern, 2002). Neurological brain-reserve studies have so far used intracranial volume and head circumference to estimate peak brain volume (Schofield, 1999). This review will, however, focus on the behavioural interpretation – also referred to as cognitive

* Address for correspondence: Dr Michael J. Valenzuela, The Black Dog Institute, Prince of Wales Hospital, Randwick, NSW 2031, Australia.
(Email: michael@dancenetwork.com.au)

reserve – which in epidemiological studies has been estimated from autobiographical data such as education levels, occupational complexity and frequency of mentally stimulating lifestyle pursuits (Mortimer, 1997).

The specific link between brain reserve and dementia is of continuing interest and debate. It remains unexplained, for example, why between 10% and 40% of individuals who exceed pathological criteria for Alzheimer's disease (AD) at autopsy show no ante-mortem cognitive impairment (Mortimer, 1997). In one of few population-based autopsy series, the UK Medical Research Council Cognitive Function and Ageing Study (MRC CFAS) found that more than 30% of individuals with mild and severe AD pathology were non-demented. The group's conclusions with regard to the link between degenerative pathology and clinical status are worth reiteration in the context of discussion of brain reserve:

> If amyloid is a key determinant of cognitive decline, there must be other factors that determine whether a particular individual will develop cerebral decompensation in the face of a particular burden of amyloid plaque formation. Similar problems arise with all diagnostic schemes for Alzheimer's disease, including those based on the degree of tangle accumulation (e.g. Braak staging). Some individuals remain intellectually intact despite large burdens of neocortical and limbic Alzheimer-type pathology, whereas others become demented with very mild involvement. One consistent finding has been that higher educational attainment appears to protect from the presence and possibly development of dementia, with several possible underlying biological mechanisms … (Neuropathology Group, MRC CFAS, 2001, p. 174).

Pioneering work by Katman and colleagues showed that those individuals with significant pathological burden yet preserved cognition may have benefited from larger pyramidal neurons, or heavier brain weight than the norm, and had performed at the highest levels on neuropsychological tests premorbidly (Katzman *et al*. 1988). More recent commentators (Albert, 1995; Mayeux, 2000), however, have highlighted conflicting findings in epidemiological studies of brain reserve, particularly those focused on the link between education and dementia (Gilleard, 1997).

In order to provide a more accurate and meaningful appraisal of evidence for the importance of brain reserve for neurodegenerative disease, we conducted a systematic quantitative review of the medical literature regarding the association between brain reserve and incident dementia.

METHOD

Brain-reserve search strategy

We searched MEDLINE (1966 to March, week 5, 2004), PsychINFO (1984 to March, week 5, 2004), CURRENT CONTENTS (to March 2004) and Cochrane Library databases for original research articles in any language. For this review, we searched for: (*a*) '*brain reserve*' or '*cognitive reserve*' or '*education*' or '*occupation*' or '*IQ*' or '*intelligence*' or '*leisure*' or '*activity*'. The results of this search were cross-matched with (*b*) '*dementia*' or '*Alzheimer's disease*' plus '*incidence*' or '*longitudinal*' or '*cohort*'. This search produced 629 studies. This list was supplemented by manual checking through reference lists of published reports and contact with several 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 one author (M.V.; approximately 250 studies). The next most common reason for exclusion was reporting on prevalence, dementia progression or cross-sectional cognition, rather than longitudinal assessment. Studies with total number of follow-up participants <100 were also excluded. Authors of studies where raw numbers of incident dementia cases and non-cases were not reported were contacted ($n=11$). In the absence of a response, the study was also excluded from quantitative integration ($n=4$).

Longitudinal cohort studies of dementia incidence were selected because amongst observational study types, the cohort design provides the highest quality data by enabling greater control of baseline characteristics (Levine *et al*. 1994). Since education and other brain-reserve indicators correlate with test performance (Kittner *et al*. 1986; Fillenbaum *et al*. 1988; Jorm *et al*. 1988; Liu *et al*. 1994), the need for evaluation of clinical *change* rather than *status* was paramount. A total of 22 brain-reserve-related

cohort studies were entered for this meta-analysis.

Quantitative meta-analysis

A quantitative meta-analytical approach was used for studies of dementia incidence because outcome was typically reported as an odds ratio (OR) or relative risk (which could be converted to an OR). Twenty-two studies met inclusion criteria as detailed in the search strategy above, yielding 33 datasets (see Table 1). Data extraction was done by two different researchers onto a standard template, with 74% agreement. Differences were resolved by consensus. Review Manager (Version 4.1.1, The Cochrane Collaboration, 2000) was used for quantitative integration with random effects modelling. Fixed effects modelling did not substantively change the results and are not reported. 'High' *versus* 'low' brain-reserve groups were defined based on the dichotomization technique used in the source study (see Table 1). Sensitivity analysis was conducted using a funnel plot and by detailed examination of individual studies for potential sources of heterogeneity. Whereas the combined summary OR reflects unadjusted differential risk, Table 1 also shows individual studies' adjusted ORs.

Definition of incident dementia

For the purposes of this review, an 'incidence' of dementia was equivalent to the definition utilized by researchers in their source publications. 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. An incident dementia case was defined as any individual who subsequently met DSM-III-R, DSM-IV or NINDS-ADRDA criteria for AD or dementia (depending on the classification scheme used in the source study).

Dementia rates across source studies

In order to facilitate comparison of dementia incidence rates across the different source studies, a per annum (p.a.) dementia rate measure was calculated for each study as a whole. Dementia rates (% p.a.) were calculated on the following formula:

$$\frac{\left(\begin{array}{c}\text{no. incident}\\ \text{dementia cases}\end{array} \Big/ \begin{array}{c}\text{no. baseline}\\ \text{cohort}\end{array}\right) \times 100}{\text{no. years follow-up}}.$$

RESULTS

Effect of education

As shown in Table 1, the majority of brain-reserve studies have used education as a brain-reserve measure (Hebert *et al.* 1992; Bickel & Cooper, 1994; Paykel *et al.* 1994; Stern *et al.* 1994; Cobb *et al.* 1995; Yoshitake *et al.* 1995; Persson & Skoog, 1996; Evans *et al.* 1997; Schmand *et al.* 1997; Ott *et al.* 1999; Elias *et al.* 2000; Ganguli *et al.* 2000; Qiu *et al.* 2001; Scarmeas *et al.* 2001; Anttila *et al.* 2002; Wilson *et al.* 2002; Tuokko *et al.* 2003; Fitzpatrick *et al.* 2004). The combined OR for incident dementia for individuals with high education compared to low was 0·53 (95% CI 0·45–0·62, $p<0·0001$), indicating a decreased risk of 47%. Five out of 15 studies showed no significant effect, while 10 out of 15 demonstrated a significant protective effect. Heterogeneity in this analysis was significant ($\chi^2=30·61$, $p=0·0063$).

Effect of occupation

The combined OR for incident dementia for individuals with history of high occupational status compared to low was 0·56 (95% CI 0·49–0·65, $p<0·0001$), indicating a decreased risk of 44%. Three out of 12 studies showed no significant effect, while 9 out of 12 demonstrated a significant protective effect (Bickel & Cooper, 1994; Paykel *et al.* 1994; Stern *et al.* 1994; Evans *et al.* 1997; Schmand *et al.* 1997; Jorm *et al.* 1998; Elias *et al.* 2000; Helmer *et al.* 2001; Scarmeas *et al.* 2001; Karp *et al.* 2004). Many studies with a significant result from the unadjusted analysis also demonstrated a significant protective effect after controlling for covariates, *including age and education* (Table 1). Heterogeneity in this analysis was non-significant ($\chi^2=18·95$, $p=0·062$). A single study made the distinction between occupational status and managerial history (Schmand *et al.* 1997), finding that being in charge of a number of people in one's life was independently protective against dementia rather than job status *per se*.

Table 1. *Details of eligible cohort studies of brain reserve and dementia incidence*

Study (first-named author)	Predictor definition	Cohort age	Education level	% Drop-out	F/U (yr)	*N*	Dementia rate (% p.a.)	Unadjusted OR	95% CI	Covariates in model	Adjusted risk	95% CI
Education												
Cobb (1995)	<Grade school, >HS, ⩾HS	*x*=68 55–88 yr	8%<GS, 62% ⩾HS	**0**	17	3300	0·5	0·45*	0·31–0·67	Age	0·76	0·52–1·11
Schmand (1997)	⩽8 yr, >8 yr	*x*∼75 65–84 yr	*x*=8·9 yr	54·4	4	2063	1·9	0·73*	0·52–1·02	Age, gender, DART-IQ, occupation, managerial experience, co-morbid disease, family medical history	0·86	0·57–1·31
Qui (2001)	<8 yr, ⩾8 yr	*x*=81·5 75+ yr	59%<8 yr	12	2·8	1296	4·1	0·44*	0·30–0·65	Age, gender	0·48*	0·29–0·77
Stern (1994)	<8 yr, ⩾8 yr	*x*∼74 60–99 yr	*x*∼9 yr	26	2·0	593	8·9	0·36*	0·23–0·56	Age, gender	0·50*	0·33–0·75
Elias (2000)	⩽8 yr, >8 yr	*x*∼73 65–94 yr	7·7%⩽8 yr	8·5	22	1076	0·5	0·91	0·61–1·36	Age, gender, occupation	N.S.	N.S.
Ott (1999)	Primary, 7–10 yr, >10 yr	*x*∼70 55+ yr	38% Primary	0	2·1	6827	1	0·51*	0·33–0·77	Age	0·48*	0·26–0·91
Evans (1997)	⩽8 yr, >8 yr	*x*∼72 65+ yr	32%<8 yr	20·4	4·3	642	3·4	0·30*	0·19–0·50	Age, interval time, gender, occupational prestige, income	0·78*	0·69–0·89
Wilson (2002)	Years	*x*∼76 65+ yr	*x*=18 yr		4·5	801	3·5	Data unavailable		Age, sex, physical activity, cognitive activity	1·01	0·95–1·07
Ganguli (2000)	⩽HS, >HS	*x*=72·6 65+ yr	57%>HS	0	10	1298	1·5	0·54*	0·40–0·73	Age, gender	0·65*	0·49–0·87
Yoshitake (1995)	⩽6 yr, >6 yr	*x*=73 65–92 yr	23%<6 yr	0	7	828	1·7	Data unavailable		Multiple	0·85	0·44–1·64
Scarmeas (2001)	⩽8 yr, >8 yr	*x*∼76 64+ yr	*x*∼8 yr	1·5	2·9	1772	1·7	0·64*	0·48–0·85	Age, ethnicity, occupation, leisure activities	0·81	0·58–1·12
Paykel (1994)	⩽14 yr, >14 yr	*x*=80·8 75+ yr	68%<14 yr	18·9	2·4	1195	1·7	0·74	0·39–1·42	Age, gender, social class	N.S.	N.S.
Hebert (1992)	⩽7 yr, >7 yr	∼72 yr	29%⩽7 yr	22	4·7	513	3·2	0·26*	0·16–0·44	Age, smoking, alcohol use, gender	0·5*	0·3–0·7
Persson (1996)	No vocational education, vocational education	All 70 yr at baseline	27% vocational education	7	9	374	1·1	0·70	0·31–1·60	Not reported		
Bickel (1994)	Elementary, >elementary	*x*=73·8 65–92 yr	73·2% elementary	3·5	7·8	314	1·4	0·68	0·29–1·63	Age	0·68	0·29–1·67
Fitzpatrick (2004)	<HS graduate, ⩾HS graduate	65+ yr	29% HS graduate	1·4	5·4	3608	2·5	0·56*	0·46–0·69	Not reported		
Tuokko (2003)	<7 yr, ⩾11 yr	65+ yr	*x*=8·8 yr	49·9	5	840	2·7	0·54*	0·37–0·80	Age, occupation, gender	1·11	1·04–1·18
Occupation												
Bickel (1994)	Occupational category: high (self-employed, professional, skilled gainful) *versus* low (unskilled, semi-skilled, housewife)	*x*=73·8 65–92 yr	*73·2% elementary*	3·5	7·8	314	1·4	0·39*	0·18–0·85	Age	0·41*	0·2–0·9
Schmand (1997)	Occupational category: high (self-employed, professional, skilled gainful) *versus* low (unskilled, semi-skilled, housewife)	*x*∼75 65–84 yr	*x*=8·9 yr	54·4	4	2063	1·9	0·44*	0·29–0·67	Age, gender, DART-IQ, education, managerial experience, co-morbid disease, family medical history	1·05	0·66–1·68

Schmand (1997)	Managerial experience: nil *versus* any	*x* ~ 75 65–84 yr	*x* = 8·9 yr	54·4	4	2063	1·9	0·55*	0·37–0·81	Age, gender, DART-IQ, occupation, education, co-morbid disease, family medical history	0·58*	0·38–0·91
Stern (1994)	Low occupational category (unskilled, semi-skilled, skilled trade, clerical), high (managerial, professional, technical)	*x* ~ 74 60–99 yr	*x* ~ 9 yr	26	2·0	593	8·9	0·33*	0·19–0·58	Age, gender	0·44*	0·26–0·75
Evans (1997)	Low occupational prestige score (<12), high (⩾12)	*x* ~ 72 65+ yr	32% <8 yr	20·4	4·3	642	3·4	0·46*	0·27–0·79	Age, interval time, gender, education, income	0·97	0·94–1·01
Elias (2000)	Low (unskilled, semi-skilled, clerical, skilled manual), high (administration, managerial, professional)	*x* ~ 73 65–94 yr	7·7% ⩽8 yr	8·5	22	1076	0·5	0·94	0·63–1·41	Not reported		
Paykel (1994)	Classes I to IIIa, Classes IIIb to IV	*x* = *80·8* 75+ yr	*68% <14 yr*	18·9	2·4	1195	1·7	0·74	0·39–1·42	Not reported		
Jorm (1998)	John Holland occupational categories: realistic, non-realistic	70+ yr	60% <12 yr	38·0	12	756	1·1	1·08	0·60–1·94	Not reported		
Scarmeas (2001)	Low (unskilled, trade, clerical) high (managerial, professional, technical)	*x* ~ *76* 64+ yr	*x* ~ *8 yr*	1·5	2·9	1772	1·7	0·67*	0·46–0·99	Not reported		
Anttila (2002)	Physical (farming, cooking, construction, mining), sedentary (office, professional, service)	*x* ~ *72* *65–79 yr*	*x* ~ *8 yr*	27	21	1449	0·2	0·48*	0·27–0·87	Age, ApoE4	0·42*	0·23–0·78
Helmer (2001)	Low occupational category (house duties, farmers, domestic, blue collar), high (managerial, professional)	*x* ~ *74*	*31% <primary, 35% >HS*	21·9	10	2950	1·3	0·44*	0·27–0·69	Gender, education, wine consumption, smoking, income, vascular factors	N.S.	N.S.
Karp (2004)	Main lifetime occupation coded on socio-economic classification	*x* = 81·5 75+ yr	59% <8 yr	7·4	5	1473	2·2	0·59*	0·39–0·89	Age, gender, vascular disease, alcohol	1·1	0·7–1·7
Premorbid IQ												
Schmand (1997)	DART-IQ (high *versus* low by median split)	*x* ~ 75 65–84 yr	*x* = 8·9 yr	54·4	4	2063	1·9	0·60*	0·43–0·84	Age, gender, occupation, education, managerial experience, co-morbid disease, family medical history	0·61*	0·41–0·91
Elias (2000)	Pre-morbid memory score	*x* ~ 73 65–94 yr	7·7% ⩽8 yr	8·5	22	1076	0·5	0·54*	0·31–0·92	Age, education, occupation, gender	0·72*	0·58–0·92

[*continued overleaf*

Table 1 (*cont.*)

Study (first-named author)	Predictor definition	Cohort age	Education level	% Drop-out	F/U (yr)	*N*	Dementia rate (% p.a.)	Unadjusted OR	95% CI	Covariates in model	Adjusted risk	95% CI
Mental activities												
Wang (2002)	Frequency and type of activities in mental, physical, social, productive and recreational domains	*x*=81·1 75+ yr	47·1 >7 yr	**5·7**	6	776	2·6	0·44	0·29–0·67	Age, gender, education, baseline cognition, co-morbidity, physical functioning, depressive symptoms plus controlling for other mental activity domains	Mental 0·59* Social 0·60* Productive 0·61*	0·37–0·96 0·38–0·94 0·39–0·95
Fratiglioni (2000)	Social network summary scale – based on structure and adequacy of social network related to marital/living arrangements, children and close social ties	x ~ 80 75+ yr	57% <8 yr	**12·5**	3	1203	4·9	0·63*	0·44–0·91	Age, gender, baseline cognition, physical function, vascular disease, depression	0·63*	0·48–0·83
Scarmeas (2001)	Participation in past month in a list of 13 intellectual and social activities	*x ~ 76* 64+ yr	*x ~ 8 yr*	1·5	2·9	1772	4·0	0·55*	0·41–0·74	Age, ethnicity, education, occupation, health limitations, depression, cardiac disease, HT, DM, stroke	0·62*	0·46–0·83
Wilson (2002)	Composite measure of cognitive activity frequency – time spent in 7 common activities	*x ~ 76 65+ yr*	*x*=18 yr	8·5	4·5	801	3·5	Data unavailable		Age, gender, education, baseline cognition, depression, co-morbidity, APOE	0·67*	0·49–0·92
Fabrigoule (1995)	Social and leisure activities – participation and difficulty experienced in 10 common activities. Summarized by number of activities practised without difficulty	*x ~ 76 65+ yr*	Not given	25·0	2	2040	2·1	Data unavailable		Age, cognitive performance, physical activity, occupation	0·41*	0·18–0·90
Verghese (2003)	Activity-days in cognitive tasks (reading, writing, crosswords, playing cards, group discussions, music)	75–85 yr	77% ⩽HS	3·9	5·1	469	5·2	0·33*	0·20–0·54	Age, gender, education, chronic medical disease, baseline cognition	0·48*	0·29–0·74

Operational definition of predictor is given, along with other cohort descriptors. % Drop-out signifies percentage of people that agreed to begin study and were subsequently lost to follow-up. F/U, follow-up time in years. HS, High school. Dementia rate is calculated as: (no. of incident dementia cases/total no. of subjects in sample at follow up/no. of years of follow-up x 100) %. Method of predictor dichotomization is as per source study. Adjusted risk refers to the relative risk or odds ratio figure quoted in the source study after adjusting for the covariates in the model. Cohort age gives a mean age if reported (*x*=), estimated mean from cohort breakdown (*x* ~) and age range where reported.

Effect of premorbid IQ

A limited number of studies have reported on the effect of high premorbid intelligence on the likelihood of developing dementia ($n=2$). Overall, the combined OR for individuals with high pre-dementia IQ compared to low was 0·58 (95% CI 0·44–0·77) – a decreased risk of ~42% (Schmand *et al.* 1997; Elias *et al.* 2000). Neither study reported non-significant effects. Heterogeneity in this analysis was non-significant ($\chi^2=0{\cdot}12$, $p=0{\cdot}73$).

Effect of mentally stimulating leisure activities

A recent set of studies has examined the effect of current leisure and mental activity on incident dementia (Fabrigoule *et al.* 1995; Fratiglioni *et al.* 2000; Scarmeas *et al.* 2001; Wang *et al.* 2002; Wilson *et al.* 2002; Verghese *et al.* 2003). All have found a significant protective effect, both before (combined OR 0·50, 95% CI 0·42–0·61, $p<0{\cdot}0001$) and after controlling for a number of relevant covariates, including age, general health, education and occupation (see Table 1). Heterogeneity in this analysis was non-significant ($\chi^2=4{\cdot}98$, $p=0{\cdot}17$).

Overall effect is large

The summary OR of incident dementia for individuals with high brain reserve compared to low was 0·54 (95% CI 0·49–0·59, $p<0{\cdot}0001$) – a decreased risk of 46% (see Fig. 1). Eight out of 33 datasets showed no significant effect, while 25 out of 33 demonstrated a significant protective effect. Heterogeneity in this analysis was significant ($\chi^2=55{\cdot}62$, $p=0{\cdot}006$). This analysis was based on an integrated total of 29 279 individuals from 22 studies. The median follow-up was 7·1 years.

Adjusting for multiple predictors and co-linearity

As several reports examined the effect of different and potentially correlated brain-reserve predictors *from the one study*, a potential bias towards homogeneity is present. 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 = 22). The overall effect was not significantly changed: summary OR 0·50 (95% CI 0·45–0·54, $p<0{\cdot}0001$).

Adjusting for confounds

This meta-analysis relied on comparing non-adjusted differential dementia risk in high and low brain-reserve groups, since source studies provided summary data rather than raw data. However, as can be seen in Table 1, a majority of the individual source studies were able to control for relevant covariates *including age and other brain-reserve measures*. From the pattern of results, it is evident that mentally stimulating leisure activity is the most robust brain-reserve measure, since all these studies showed a significant protective effect even after controlling for age, education, occupation and other potential confounds.

Sensitivity analyses

If the studies that examined education are removed from the overall analysis, heterogeneity is non-significant ($\chi^2=25{\cdot}27$, $p=0{\cdot}089$; OR 0·54, 95% CI 0·48–0·62, $p<0{\cdot}0001$), suggesting this group of studies provided the most variability. We explored possible reasons for this finding via a series of sensitivity analyses. The association between the effect estimate for each study (i.e. the OR for incident dementia risk based on differential education) was tested against a number of pertinent study factors. The expected 'inverted funnel' relationship was found between dementia risk and sample size, indicative of no major systematic bias in our results (Egger & Smith, 1998; see Fig. 2). A significant negative association was also found between incident dementia risk (based on differential education) and the overall dementia rate for each cohort ($r=-0{\cdot}57$, $p=0{\cdot}04$, Fig. 3). Other cohort features such as median cohort age, education level, drop-out rate, or years of follow-up did not significantly correlate with the OR for incident dementia risk based on differential education. The overall dementia rate for each study was, however, as expected related to baseline cohort age ($\rho=0{\cdot}60$, $p=0{\cdot}018$) when examined using Spearman's procedure.

DISCUSSION

Our objective was to systematically integrate prospective dementia studies that have examined brain reserve. To do so, we combined studies in which brain-reserve indicators such as

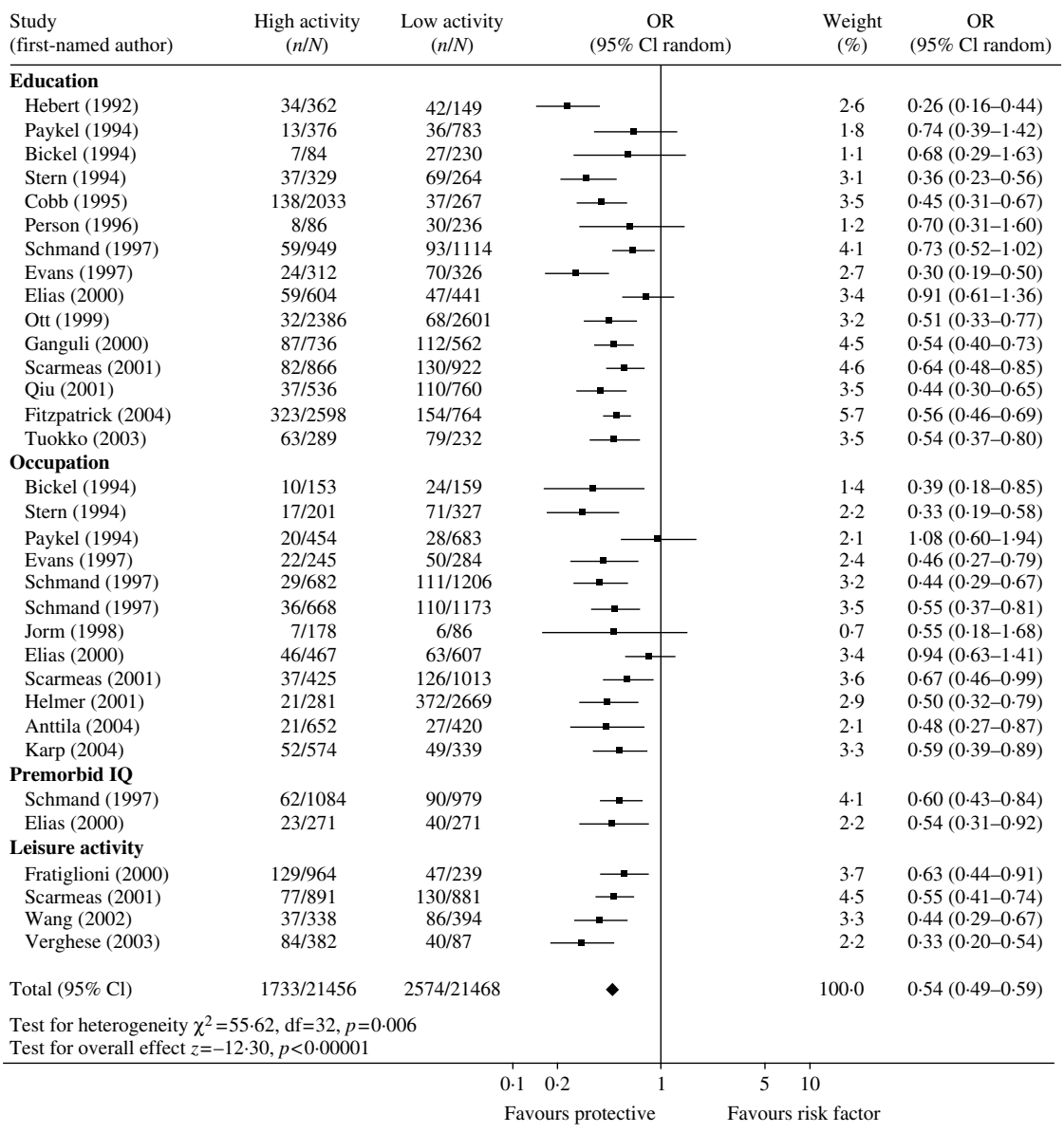

FIG. 1. Summary of findings from cohort studies of brain-reserve and dementia incidence. Number of dementia cases (*n*) and total group numbers (*N*) for both the high and low brain-reserve groups are shown for each study, along with the odds ratio for dementia risk and 95% confidence interval. Definition of high and low brain reserve is as per source study (see Table 1 for more information). Predictor type for each study is shown in bold. Quantitative meta-analysis method was using random effects model. Result substantively unchanged using fixed effect model.

education, occupation, pre-morbid IQ and mentally stimulating leisure activity had been used for prediction of incident dementia. Overall, data based on over 29 000 individuals were integrated, and a high level of consistency was found. High brain reserve was associated with an approximate 50% reduction in the incidence of dementia.

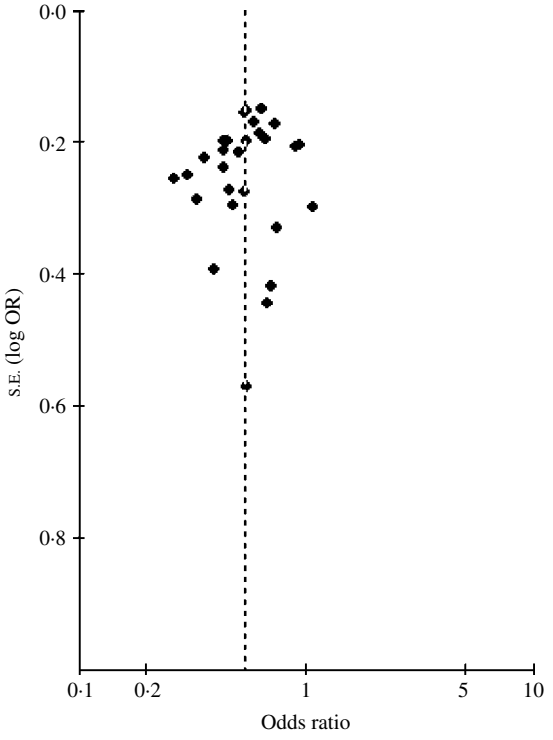

FIG. 2. Funnel plot of dementia incidence studies of brain reserve. The *x*-axis represents the odds ratio estimate for each study and the *y*-axis is a logarithmic function of sample size. No significant bias is apparent.

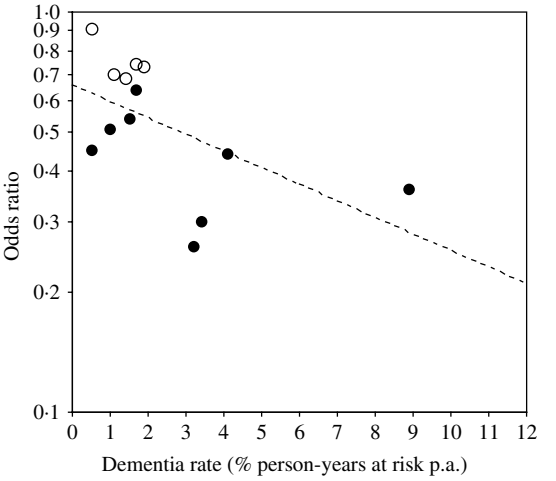

FIG. 3. Relationship between effect size for brain-reserve studies of education on dementia incidence (expressed as an odds ratio) and dementia rate for the cohort. Solid circles (●) represent studies with significant results, open circles (○) non-significant. Each data point represents a result from a unique study.

Meta-analysis issues

There is continuing debate about the accuracy of quantitative meta-analysis of observational reports (MacMahon & Collins, 2001), with calls to enter the task in a 'spirit of sensitivity analysis' (Egger *et al.* 1998). Our results were highly consistent, with variability in incident dementia results restricted to those studies that examined the effect of education. Differences in dementia risk of entire cohorts seemed to be the main determinant of variance – those cohorts with higher overall dementia incidence rates produced stronger brain-reserve OR estimates. Other cohort factors such as age, overall educational level, follow-up duration and drop-out rate were not correlated to the education brain-reserve effect. This finding suggests that the most likely reason for conflicting reports in the epidemiological brain-reserve literature has been a lack of power, stemming from low event rates. This is not surprising given positive studies were detecting dementia rate differences between high and low education groups of approximately 2·5% *versus* 5% p.a.

A problematic higher order issue relates to the virtue of combining data of different types of *predictors* from the same sample. We integrated studies of the different brain-reserve measures separately and all pointed to a similar result (education OR 0·53, occupation OR 0·56, IQ OR 0·58, leisure activities OR 0·50), suggesting that the overall result (OR 0·54) was not inappropriately inflated. As shown in Table 1, some individual studies were able to control for other brain-reserve predictors simultaneously, with the most robust results coming from studies of mentally stimulating leisure activities than from studies of education or occupation. Covariate control was not possible in this meta-analysis as we were relying on summary data. Given this limitation, and to ensure there was no systematic bias present towards homogeneity, we repeated all analyses on a 'trimmed-down' information base using independent datasets. As there was no change in significance, the more expansive results are presented. Another alternative that could be investigated in the future would be to integrate *individual data* across the studies identified here, allowing for simultaneous control of confounds. This

strategy will require a high level of coordination and openness between research groups.

Prospective cohort studies were chosen for this meta-analysis so as to reduce the confounding influence of brain-reserve measures on test performance (Kittner *et al.* 1986; Fillenbaum *et al.* 1988; Jorm *et al.* 1988; Liu *et al.* 1994). Residual bias of this sort will, however, remain. For example, at baseline a subset of individuals close to diagnostic threshold are likely to have been those with low brain reserve. In this scenario follow-up diagnosis will be geared towards detecting incident dementia in low-reserve individuals rather than high (i.e. ascertainment bias, Tuokko *et al.* 2003). Another factor identified as a possible confound in the link between leisure activities and dementia risk, is that individuals in the preclinical dementia phase may actually be dropping off activities rather than mental activity working as a protective factor (Fabrigoule, 2002).

Two aspects of the studies reviewed here tend to minimize these issues. First, several source studies stipulated strong diagnostic guidelines such that an incident clinical dementia rating score of 0·5 was insufficient for diagnosis, and so exclude those who may have just 'slipped into' dementia criteria (Stern *et al.* 1994; Scarmeas *et al.* 2001; Verghese *et al.* 2003). Yet other studies showed little, if any, effect of simultaneously *controlling for baseline cognitive performance* on dementia risk (see Table 1). To argue this represents insufficient statistical adjustment implies that drop-off of leisure activities in preclinical AD occurs largely independent of individuals' cognitive status, a view, in our opinion, difficult to justify. Systematic bias was, therefore, not thought to be a major confound in this analysis, however, definitive exclusion is not possible given the limitations mentioned.

Public health perspective

We wished to put behavioural brain-reserve evidence in context with that of other possible neuroprotective strategies. Table 2 summarizes results from reviews of observational reports on interventions such as blood pressure control (Birkenhager *et al.* 2001), anti-inflammatory drugs (McGeer *et al.* 1996) and hormone replacement therapy (LeBlanc *et al.* 2001). High brain reserve compares remarkably well. This systematic review suggests evidence for a protective behavioural brain-reserve effect is as strong, and arguably more consistent, than that for other putative factors.

Table 2. *Risk estimates and 95% confidence intervals (CI) for different potential neuroprotective strategies, based on integration of observational reports*

	Risk	95% CI	*n*
High brain reserve	0·54	0·49–0·59	22
Hormone replacement therapy (LeBlanc *et al.* 2001)	0·66	0·53–0·82	10
Hypertension control (Birkenhager *et al.* 2001)	0·60	Not reported	2
Anti-inflammatory drugs (McGeer *et al.* 1996)	0·56	0·42–0·74	7

All risk estimates are adjusted odds ratios except for the study of hypertension control, which reported an adjusted relative risk. Estimate for brain reserve is derived from this review. *n* refers to the number of observational studies integrated in the report.

Six large longitudinal studies have now found that increased levels of leisure and mental activity in late life is associated with an approximate 50% lower incidence of dementia (Fabrigoule *et al.* 1995; Fratiglioni *et al.* 2000; Scarmeas *et al.* 2001; Wang *et al.* 2002; Wilson *et al.* 2002; Verghese *et al.* 2003). Strikingly, this finding persists even after controlling for other dementia predictors like age, general health, cerebrovascular disease, education, occupation and baseline cognition in each individual study. Some studies have even gone to the extent of excluding individuals with borderline cognitive impairment at initial evaluation (Scarmeas *et al.* 2001; Wilson *et al.* 2002; Verghese *et al.* 2003) and so further avoid the confound between cognitive decline and drop-off of leisure activities.

Evidence for dose dependency in the way mentally stimulating leisure activity affects dementia risk is also available. Fabrigoule *et al.* (1995) compared the risk for dementia in those that could complete no leisure activities to those that could complete 1, 2 or 3 different activities, finding relative risks (RR) for dementia of 0·77, 0·41 and 0·20 respectively. Wang and colleagues combined activity scores in the physical, emotional and intellectual domains and found that compared to those in the lowest level, risk decreased with each subsequent step (RR 0·56 for low, 0·34 for middle, and 0·29 for high activity levels) (Wang *et al.* 2002). Fratiglioni's

group noted a significant trend for increased dementia risk as an individual's social networks decreased (Fratiglioni *et al*. 2000). Verghese and colleagues found that the risk for dementia in a group with a moderate level of leisure activities was 50% compared to the low-activity group – those with the highest activity levels had their risk reduced to 33% (Verghese *et al*. 2003).

Together, accumulated evidence for behavioural brain reserve would seem to meet many of the AD 'risk factor tests' proposed by Hill in 1965: consistency, association, time-course, dose dependency and biological plausibility. Complex mental activity across the lifespan may, therefore, work as a neuroprotective factor in AD. Moreover, evidence of independent correlations between mentally stimulating activity in later life and dementia incidence suggests that brain reserve is not a static CNS property, nor that it is generally determined by early life experiences such as level of education, socio-economic deprivation or poor nutrition. Each of the six large epidemiological studies which have found late-life brain-reserve effects have, for example, controlled for covariates such as age and education. Sobering such an assessment are certainly those numerous examples of putative aetiological factors that have arisen from cohort studies but subsequently proven unsuccessful in clinical trial (Egger *et al*. 1998).

Testing brain-reserve implications

Randomized control trial is, therefore, the next logical and definitive way to address the brain-reserve question. The magnitude and reliability of the brain-reserve effect, sustained over a median follow-up time of 7 years, warrants serious attention towards design of such trials. Empirical test may in fact reveal that higher behavioural brain-reserve delays disease presentation rather than truly decreases dementia incidence. Yet from a public health perspective a delay of 5 years would halve the apparent prevalence of the disease (Katzman, 1993) and lead to significant personal, social and economic benefits. Brain-reserve interventions also benefit from a minimal potential for harm and are likely to increase general quality-of-life parameters such as self-confidence and social engagement.

The content of a brain-reserve-inspired intervention thus poses a challenge. Evidence reviewed here would suggest that cognitive–behavioural programmes based around mentally stimulating leisure activities and implemented post-retirement may be successful. The experience of smaller mental activity studies is instructive, since reversal of age-related cognitive decline has been shown, Schaie (1994), for example, found that a programme based on problem solving reversed 14-year decline in this ability in 40% of subjects. Another group (Kliegl *et al*. 1989) trained verbal memory to supra-normative levels in a group of healthy elderly and showed that the advantage persisted for at least a number of weeks. In the largest study of its kind, Ball *et al*. (2002) showed that 10 sessions of cognitive training in healthy elders could lead to cognitive *improvement* over 2 years follow-up as opposed to an expected cognitive decline.

Researchers are also beginning to discover possible neurobiological mechanisms behind the apparent advantage of mental stimulation. We have, for example, shown that 5 weeks of memory-based mental exercise increased resting phosphocreatine levels in the medial temporal lobe of healthy elders (Valenzuela *et al*. 2003), a finding notable given the reverse has been found in early AD (Valenzuela & Sachdev, 2001). Animal studies have revealed a diverse range of ultrastructural brain changes when environmental complexity is enriched, including neurogenetic, synaptic and dendritic responses (for a review see van Praag *et al*. 2000). Capacity for functional reorganization is also emerging as a powerful compensatory mechanism in late life, with atypical brain networks active in mediating mnemonic performance in successful ageing and early AD (Stern *et al*. 2000; Cabeza *et al*. 2002; Grady *et al*. 2003). Strikingly, capacity for such functional reorganization correlates with behavioural brain-reserve indicators such as education and leisure activities (Habeck *et al*. 2003; Scarmeas *et al*. 2003; Springer *et al*. 2005).

A number of experience-dependent neuroplastic mechanisms may, therefore, underlie the clinical brain-reserve effect, with different mechanisms salient at different temporo-spatial scales. It can be speculated that a raw threshold mechanism (Satz, 1993) may be at work at the microscopic scale, whereby generation of neurons, synapses and arborized dendrites secondary to mental stimulation is able to temporarily buffer the effects of degenerative disease. At the

higher-order scale, compensatory functional reorganization is likely to demonstrate a complex longitudinal association with lifespan mental activity and disease burden. Test of this brain-reserve heuristic may well provide fascinating data.

It is worth mentioning that brain-reserve measures may not be exclusively relevant to the elderly. In developed nations, steady increases in the amount and quality of secular education have occurred over the past century. Today about 83% of US citizens complete high-school, whereas in 1910 the figure was 13% (see Editorial in *Society*, 2001). Average school life expectancy in countries like Cambodia (6·9 years), Eritrea (4·6) and Papua New Guinea (6·1) remain, however, distressingly low (UNESCO Institute of Statistics, 2002). Life-expectancy increases in developing countries carry the potential for a precipitous increase in dementia rates if education levels do not rise in tandem. Vigilance in this regard will be required. As a general rule, our data support international efforts for increasing educational opportunities in poorer countries.

CONCLUSIONS

We have presented a systematic quantitative integration of the brain-reserve literature and focused on cohort studies in order to minimize bias. Dementia risk was 46% lower in high-reserve individuals, a finding replicated across more than 20 studies involving more than 29 000 individuals and over a median follow-up period of greater than 7 years. The consistency and magnitude of our findings strongly support testing interventions that increase behavioural brain reserve in randomized control trials. Research should also focus on increasing our neurobiological understanding of the brain-reserve effect in humans.

ACKNOWLEDGEMENTS

Thanks are due to Professor Carol Brayne for her useful comments on this manuscript. We appreciate the timely efforts of all those authors who provided additional information regarding their studies. M.V. conceptualized the study in addition to compiling the data, analysis and writing. P.S. provided conceptual input, checked data and contributed to writing. This work was supported by the National Health and Medical Research Council of Australia.

DECLARATION OF INTEREST

None.

REFERENCES

Albert, M. (1995). How does education affect cognitive function? *Annals of Epidemiology* **5**, 76–78.

Anttila, T., Helkala, E. L., Kivipelto, M., Hallikainen, M., Alhainen, K., Heinonen, H., Mannermaa, A., Tuomilehto, J., Soininen, H. & Nissinen, A. (2002). Midlife income, occupation, APOE status, and dementia: a population-based study. *Neurology* **24**, 887–893.

Ball, K., Bersch, D., Helmers, K., Jobe, J., Leveck, M., Marsiske, M., Morris, J., Rebok, G., Smith, D., Tennstedt, S., Unverzagt, F. & Willis, S. (2002). Effect of cognitive training interventions with older adults – a randomised control trial. *Journal of the American Medical Association* **288**, 2271–2281.

Bickel, H. & Cooper, B. (1994). Incidence and relative risk of dementia in an urban elderly population: findings of a prospective field study. *Psychological Medicine* **24**, 179–192.

Birkenhager, W., Forette, F., Seux, M., Wang, J. & Staessen, J. (2001). Blood pressure, cognitive functions, and prevention of dementias in older patients with hypertension. *Archives of Internal Medicine* **161**, 152–156.

Cabeza, R., Anderson, N., Locantore, J. & McIntosh, A. (2002). Aging gracefully: compensatory brain activity in high-performing older adults. *Neuroimage* **17**, 1394–1402.

Cobb, J., Wolf, P., Au, R., White, R. & D'Agostino, R. B. (1995). The effect of education in the incidence of dementia and Alzheimer's disease in the Framingham study. *Neurology* **45**, 1707–1712.

Egger, M. & Smith, G. (1998). Meta-analysis – bias in location and selection of studies. *British Medical Journal* **316**, 61–66.

Egger, M., Schneider, M. & Smith, G. (1998). Spurious precision? Meta-analysis of observational studies. *British Medical Journal* **316**, 140–144.

Elias, M. F., Beiser, A., Wolf, P. A., Au, R., White, R. F. & D'Agostino, R. B. (2000). The preclinical phase of alzheimer disease: a 22-year prospective study of the Framingham Cohort. *Archives of Neurology* **57**, 808–813.

Evans, D., Hebert, L., Beckett, L., Scherr, P., Albert, M., Chown, M., Pilgrim, D. & Taylor O. (1997). Education and other measures of socioeconomic status and risk of incidence Alzheimer's disease in a defined population of older persons. *Archives of Neurology* **54**, 1399–1405.

Fabrigoule, C. (2002). Do leisure activities protect against Alzheimer's disease? *Lancet Neurology* **1**, 11.

Fabrigoule, C., Letenneur, L., Dartigues, J. F., Zarrouk, M., Commenges, D. & Barberger-Gateau P. (1995). Social and leisure activities and risk of dementia: a prospective longitudinal study. *Journal of the American Geriatric Society* **43**, 485–490.

Fillenbaum, G., Hughes, D., Heyman, A., George, L. & Blazer, D. (1988). Relationship of health and demographic characteristics to Mini-Mental State examination score among community residents. *Psychological Medicine* **18**, 719–726.

Fitzpatrick, A., Kuller, L., Ives, D., Lopez, O., Jagust, W., Breitner, J., Jones, B., Lyketsos, C. G. & Dulberg, C. (2004). Incidence and prevalence of dementia in the Cardiovascular Health Study. *Journal of the American Geriatrics Society* **52**, 195–204.

Fratiglioni, L., Wang, H. X., Ericsson, K., Maytan, M. & Winblad, B. (2000). Influence of social network on occurrence of dementia: a community-based longitudinal study. *Lancet* **355**, 1315–1319.

Ganguli, M., Dodge, H., Chen, P., Belle, S. & DeKosky, S. (2000). Ten-year incidence of dementia in a rural elderly US

community population – the MoVIES project. *Neurology* **54**, 1109–1116.

Gilleard, C. (1997). Education and Alzheimer's disease: a review of recent international epidemiological studies. *Aging and Mental Health* **1**, 33–46.

Grady, C., McIntosh, A., Beig, S., Keightley, M., Burian, H. & Black, S. (2003). Evidence from functional neuroimaging of a compensatory prefrontal network in Alzheimer's disease. *Journal of Neuroscience* **23**, 986–993.

Habeck, C., Hilton, J., Zarahn, E., Flynn, J., Moeller, J. & Stern, Y. (2003). Relation of cognitive reserve and task performance to expression of regional covariance networks in an event-related fMRI study of nonverbal memory. *Neuroimage* **20**, 1723–1733.

Hebert, L. E., Scherr, P. A., Beckett, L. A., Funkenstein, H. H., Albert, M. S., Chown, M. J. & Evans, D. A. (1992). Relation of smoking and alcohol consumption to incident Alzheimer's disease. *American Journal of Epidemiology* **135**, 347–355.

Helmer, C., Letenneur, L., Rouch, I., Richard-Harston, S., Barberger-Gateau, P., Fabrigoule, C., Orgogozo, J., Dartigues, J. (2001). Occupation during life and risk of dementia in French elderly community residents. *Journal of Neurology, Neurosurgery & Psychiatry* **71**, 303–309.

Hill, A. (1965). The environment and Alzheimer's disease: association or causation? *Proceedings of the Royal Society of Medicine* **58**, 295–300.

Jorm, A. E., Scott, R., Henderson, A. & Kay, D. (1988). Educational level differences on the Mini-Mental State: the role of test bias. *Psychological Medicine* **18**, 727–731.

Jorm, A. F., Rodgers, B., Henderson, A., Korten, A., Jacomb, P. A., Christensen, H. & Mackinnon, A. (1998). Occupation type as a predictor of cogntive decline and dementia in old age. *Age and Ageing* **27**, 477–483.

Karp, A., Kareholt, I., Qui, C., Bellander, T., Winblad, B. & Fratiglioni, L. (2004). Relation of education and occupation-based socioeconomic status to incident Alzheimer's disease. *American Journal of Epidemiology* **159**, 175–183.

Katzman, R. (1993). Education and the prevalence of dementia and Alzheimer's disease. *Neurology* **43**, 13–20.

Katzman, R., Terry, R., DeTeresa, R., Brown, T., Davies, P., Fuld, P., Reinbing, X. & Peck, A. (1988). Clinical, pathological and neurochemical changes in dementia: a subgroup with preserved mental status and numerous neocortical plaques. *Annals of Neurology* **23**, 138–144.

Kittner, S., White, L., Farmer, M., Wolz, M., Kaplan, E., Moes, E., Brody, J. & Feinleib, M. (1986). Methodological issues in screening for dementia: the problem of education adjustment. *Journal of Chronic Disease* **39**, 163–170.

Kliegl, R., Smith, J. & Baltes, P. (1989). Testing the limits and the study of age differences in cognitive plasticity of a mnemonic skill. *Developmental Psychology* **26**, 247–256.

LeBlanc, E., Janowsky, J., Chan, B. & Nelson, H. (2001). Hormone replacement therapy and cognition: systematic review and meta-analysis. *Journal of the American Medical Association* **285**, 1489–1499.

Levine, M., Walter, S., Lee, H., Haines, T., Holbrook, A. & Moyer, V. (1994). Users guides to the medical literature IV. How to use an article about harm. *Journal of the American Medical Association* **271**, 1615–1619.

Liu, C., Teng, E., Lin, K., Hsu, T., Guo, N., Chou, P., Hu, H., Cheng, W. & Chiang, B. (1994). Performance on a dementia screening test in relation to demographic variables. *Archives of Neurology* **51**, 910–915.

MacMahon, S. & Collins, R. (2001). Reliable assessment of the effects of treatment on mortality and major morbidity. II: Observational studies. *Lancet* **357**, 455–462.

Mayeux, R. (2000). Evil forces and vulnerable brains. *Neurology,* **55**, 1428–1429.

McGeer, P., Schulzer, M. & McGeer, E. (1996). Arthritis and anti-inflammatory agents as possible protective factors for Alzheimer's disease: A review of 17 epidemiologic studies. *Neurology* **47**, 425–432.

Mortimer, J. A. (1997). Brain reserve and the clinical expression of Alzheimer's disease. *Geriatrics* **52** (Suppl. 2), S50–S53.

Neuropathology Group MRC CFAS (2001). Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS). *Lancet* **375**, 169–175.

Ott, A., van Roossum, C., van Harskamp, F., van de Mheen, H., Hofman, A. & Breteler, M. (1999). Education and the incidence of dementia in a large population-based study: The Rotterdam study. *Neurology* **52**, 663.

Paykel, E. S., Brayne, C., Huppert, F. A., Gill, C., Barkley, C., Gehlhaar, E., Beardsall, L., Girling, D. M., Pollitt, P. & O'Connor, D. (1994). Incidence of dementia in a population older than 75 years in the United Kingdom. *Archives of General Psychiatry* **51**, 325–332.

Persson, G. & Skoog, I. (1996). A prospective population study of psychosocial risk factors for late onset dementia. *International Journal of Geriatric Psychiatry* **11**, 15–22.

Qiu, C., Backman, L., Winblad, B., Aguero-Torres, H. & Fratiglioni, L. (2001). The influence of education on clinically diagnosed dementia incidence and mortality data from the Kungsholmen Project. *Archives of Neurology* **58**, 2034–2039.

Satz, P. (1993). Brain reserve capacity on symptom onset after brain injury: a formulation and review of evidence for threshold theory. *Neuropsychology* **7**, 273–295.

Scarmeas, N., Levy, G., Tang, M., Manly, J. & Stern, Y. (2001). Influence of leisure activity on the incidence of Alzheimer's disease. *Neurology* **57**, 2236–2242.

Scarmeas, N., Zarahn, E., Anderson, K., Hilton, J., Flynn, J., Van Heertum, R., Sackeim, H. & Stern, Y. (2003). Cognitive reserve modulates functional brain responses during memory tasks: a PET study in healthy young and elderly subjects. *Neuroimage* **19**, 1215–1227.

Schaie, K. (1994). The course of adult intellectual development. *American Psychologist* **49**, 304–313.

Schmand, B., Smit, J., Geerlings, M. & Lindeboom, J. (1997). The effects of intelligence and education on the development of dementia. A test of the brain reserve hypothesis. *Psychological Medicine* **27**, 1337–1344.

Schofield, P. (1999). Alzheimer's disease and brain reserve. *Australasian Journal on Ageing* **18**, 10–14.

Society (2001). Social science and the citizen [Editorial]. *Society* (July/August), pp. 2–18.

Springer, M., McIntosh, A., Winocur, G. & Grady, C. (2005). The relation between brain activity during memory tasks and years of education in young and older adults. *Neuropsychology* **19**, 181–192.

Stern, Y. (2002). What is cognitive reserve? Theory and research application of the reserve concept. *Journal of the International Neuropsychological Society* **8**, 448–460.

Stern, Y., Gurland, B., Tatemichi, T., Tang, M., Wilder, D. & Mayeux, R. (1994). Influence of education and occupation on the incidence of Alzheimer's disease. *Journal of the American Medical Association* **271**, 1004–1010.

Stern, Y., Moeller, J., Anderson, K., Luber, B., Zubin, N., DiMauro, A., Park, A., Campbell, C., Marder, K., Bell, K., Van Heertum, R. & Sackheim, H. (2000). Different brain networks mediate task performance in normal aging and AD – defining compensation. *Neurology* **55**, 1291–1297.

Tuokko, H., Garrett, D., McDowell, I., Silverberg, N. & Kristjansson, B. (2003). Cognitive decline in high-functioning older adults: reserve or ascertainment bias? *Aging & Mental Health* **7**, 259–270.

UNESCO Institute of Statistics (2002). Transition rate (primary to secondary) and school life expectancy by country and by gender for the school years 1998/1999 and 1999/2000. (www.unesco.org). Accessed 1 Sept. 2002.

Valenzuela, M. & Sachdev, P. (2001). Magnetic resonance spectroscopy in AD. *Neurology* **56**, 592–598.

Valenzuela, M. J., Jones, M., Wen, W., Rae, C., Graham, S., Shnier, R. & Sachdev, P. (2003). Memory training alters

hippocampal neurochemistry in healthy elderly. *Neuroreport* **14**, 1333–1337.

van Praag, H., Kempermann, G. & Gage, F. H. (2000). Neural consequences of environmental enrichment. *Nature Reviews Neuroscience* **1**, 191–198.

Verghese, J., Lipton, R., Katz, M., Hall, C., Derby, C., Kuslansky, G., Ambrose, A., Sliwinski, M. & Buschke, H. (2003). Leisure activities and the risk of dementia in the elderly. *New England Journal of Medicine* **348**, 2508–2516.

Wang, H., Paillard-Borg, S., Karp, A., Winblad, B. & Fratiglioni, L. (2002). Physical activity, emotional support, and intellectual stimulation in relation to dementia risk in the elderly: results from the Kungsholmen Project. *Eighth International Conference on Alzheimer's Disease and Related Disorders* [Abstract].

Wilson, R. S., Mendes De Leon, C. F., Barnes, L. L., Schneider, J. A., Bienias, J. L., Evans, D. A. & Bennett, D. A. (2002). Participation in cognitively stimulating activities and risk of incident Alzheimer disease. *Journal of the American Medical Association* **287**, 742–748.

Yoshitake, T., Kiyohara, Y., Kato, I., Ohmura, T., Iwamoto, H., Nakayama, K., Ohmori, S., Nomiyama, K., Kawano, H. & Ueda, K. (1995). Incidence and risk factors of vascular dementia and Alzheimer's disease in a defined elderly Japanese population: the Hisayama Study. *Neurology* **45**, 1161–1168.