

Education, the brain and dementia: neuroprotection or compensation?

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The potential protective role of education for dementia is an area of major interest. Almost all older people have some pathology in their brain at death but have not necessarily died with dementia. We have explored these two observations in large population-based cohort studies (Epidemiological Clinicopathological Studies in Europe; EClipSE) in an investigation of the relationships of brain pathology at death, clinical dementia and time in education, testing the hypothesis that greater exposure to education reduces the risk of dementia. EClipSE has harmonized longitudinal clinical data and neuropathology from three longstanding population-based studies that included post-mortem brain donation. These three studies started between 1985 and 1991. Number of years of education during earlier life was recorded at baseline. Incident dementia was detected through follow-up interviews, complemented by retrospective informant interviews, death certificate data and linked health/social records (dependent on study) after death. Dementia-related neuropathologies were assessed in each study in a comparable manner based on the Consortium to Establish a Registry for Alzheimer's Disease protocol. Eight hundred and seventy-two brain donors were included, of whom 56% were demented at death. Longer years in education were associated with decreased dementia risk and greater brain weight but had no relationship to neurodegenerative or vascular pathologies. The associations between neuropathological variables and clinical dementia differed according to the 'dose' of education such that more education reduced dementia risk largely independently of severity of pathology. More education did not protect individuals from developing neurodegenerative and vascular neuropathology by the time they died but it did appear to mitigate the impact of pathology on the clinical expression of dementia before death. The findings suggest that an understanding of the mechanisms leading to functional protection in the presence of pathology may be of considerable value to society.

Keywords: dementia; education; brain; ageing

Abbreviations: CAA = cerebral amyloid angiopathy; CC75C = Cambridge City Over-75s Cohort; CI = confidence interval; EClipSE = Epidemiological Clinicopathological Studies in Europe; MRC CFAS = Medical Research Council Cognitive Function and Ageing Study; OR = odds ratio

Introduction

Longitudinal studies have shown that individuals who experienced higher levels of education in earlier life are at lower risk of clinical dementia during ageing (Stern *et al.*, 1994; Ott *et al.*, 1995;

Letenneur *et al.*, 1999). Education is therefore thought to either protect, or provide resilience, against dementia-related pathology. Education is related to higher socioeconomic status, a more advantaged and healthy lifestyle and potentially less exposure to environmental toxins, all of which may protect against the

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development of brain disease and consequent dementia, particularly vascular brain disease (Del Ser *et al.*, 1999).

An alternative hypothesis is that more educated people may functionally compensate for neuropathological burden, commonly referred to as the brain or cognitive 'reserve' hypothesis (Katzman, 1993; Stern, 2002, 2006; Valenzuela and Sachdev, 2006; Valenzuela *et al.*, 2007, 2008), according to which more pathology is necessary to bring about clinical dementia compared to less educated people. Results are not consistent across measures of pathology and structure (Bennett *et al.*, 2003; Dufouil *et al.*, 2003; Mortimer *et al.*, 2003; Christensen *et al.*, 2007; Koepsell *et al.*, 2008; Roe *et al.*, 2008). For example, while education has been reported to reduce dementia risk associated with amyloid load (Bennett *et al.*, 2005), head circumference (Mortimer *et al.*, 2003), neuritic plaques (Koepsell *et al.*, 2008; Roe *et al.*, 2008) and Braak stage (Koepsell *et al.*, 2008), there are conflicting reports of no educational effect on atrophy (Christensen *et al.*, 2007), diffuse plaques (Roe *et al.*, 2008) and tangles (Bennett *et al.*, 2005; Roe *et al.*, 2008). Education has been reported to diminish the cognitive consequences of severe but not of mild white matter pathology (Dufouil *et al.*, 2003), but the opposite pattern has been reported for tangles and neuritic plaques (Koepsell *et al.*, 2008; Roe *et al.*, 2008).

There is also a possibility that apparent effects of education arise from ascertainment bias (Tuokko *et al.*, 2003). A careful meta-analysis of existing studies, however, did not support this interpretation (Valenzuela and Sachdev, 2006).

Relationships between education, neuropathology and dementia remain unclear despite the important implications for the understanding of successful ageing. The present study combines data from three prospective population-based autopsy studies of older individuals, providing a sample of sufficient power to investigate three questions, namely (i) does education protect against the accumulation of pathologies in the brain? (ii) does education appear to compensate for cognitive impairment associated with pathology? and (iii) does such compensation vary with pathological severity?

Materials and methods

Sample characteristics

The Epidemiological Clinicopathological Studies in Europe collaboration (EClipSE; <http://www.eclipsestudy.eu>) is based on the harmonization of neuropathological and longitudinal clinical data of brain donors from three population-based prospective longitudinal studies of ageing, which include a brain donation program in Europe [Medical Research Council Cognitive Function and Ageing Study (MRC CFAS; England and Wales; <http://www.cfas.ac.uk>); Cambridge City Over-75s Cohort study (CC75C; England; <http://www.cc75c.group.cam.ac.uk>) and Vantaa 85+ (Finland) (EClipSE, 2009). These three studies constitute half of all such studies worldwide (Zaccai *et al.*, 2006). All studies were approved by research ethics committees.

Participants were interviewed at intervals (range 1–7 years) in each study to establish the presence of dementia and other health-related conditions, and to systematically collect longitudinal sociodemographic and cognitive information. The baseline surveys for the three studies

were conducted in 1985–87 (CC75C), 1989–93 (MRC CFAS) and 1991 (Vantaa 85+). The major difference between the studies was participant age at baseline: MRC CFAS: >65 years; CC75C: >75 years and Vantaa 85+: >85 years. Total initial cohort size and brain donation rates also varied: MRC CFAS: 18226, 3%; CC75C: 2165, 10% and Vantaa 85+: 553, 52%. Donation rate differences were due to approaches used to recruit into the brain donation programmes. Brain donation was offered to individuals in sub-samples selected by stratified random sampling, weighted to those who were older and cognitively impaired. The full range of cognitive function and abilities in the population are robustly represented within the brain donation programme of each study. There are currently 970 participants in Version 1.0 of the EClipSE database.

In each of the studies the participants, or for a small number, an informant, reported the number of years of formal education they had completed. Data on education, dementia, age and sex were available for 90% ($n=872$). Participants were not included in analyses because of missing data, including education (6%), those who could not be classified as either demented or not demented at death (4%), both education and dementia (<1%) and one with missing age (<1%).

Classification of clinical dementia

Clinical dementia status at death was determined differently in the three studies. In MRC CFAS (Savva *et al.*, 2009) and CC75C (Brayne *et al.*, 2009), classification was based on all information available for each participant including any interview during the last years of life, a retrospective informant interview after death and the death certificate. MRC CFAS employed the Geriatric Mental State Automated Geriatric Examination for Computer Assisted Taxonomy (AGECAT) (Copeland, 2002) and CC75C employed the Cambridge Mental Disorders of the Elderly Examination (O'Connor *et al.*, 1989) (CAMDEX) to assess the presence of dementia. Clinical review of all available data for each brain donor was also conducted in CC75C as the CAMDEX was not conducted in later stages of the study.

Vantaa 85+ participants were assessed by neurologists at each interview (Polvikoski *et al.*, 1995). They were considered demented if they fulfilled Diagnostic and Statistical Manual of Mental Disorders third edition revised (DSM-III-R) criteria (APA, 1987). Health and social work records were used to identify incident dementia between interview and death.

The interval between last clinical examination and death varies between participants, with the majority <2 years. Retrospective interviews and death certificates (MRC CFAS and CC75C) and linked health and social work records (Vantaa 85+) were employed to detect incident dementia between last interview and death. Information on the severity of dementia at death was not available.

Classification of neuropathological markers

In all studies, paraffin-embedded brain tissue samples were assessed for neuropathology blind to clinical status. MRC CFAS and CC75C employed the full Consortium to Establish a Registry for Alzheimer's Disease (Mirra *et al.*, 1991) protocol for anatomical sampling and lesion profile, together with Braak staging of tau pathology (tangles). Vantaa 85+ has more limited measures including the Consortium to Establish a Registry for Alzheimer's Disease neocortical neuritic plaque score, neocortical cerebral amyloid angiopathy (only for those aged

95 years and older), lacunes, haemorrhages, infarcts and Braak stage for tau. For neuropathological factors not represented in Vantaa 85+, only MRC CFAS and CC75C individuals are represented in the analyses. Neuropathological markers assessed in the current analysis include neocortical and hippocampal neuritic plaques, diffuse plaques, tangles, cerebral amyloid angiopathy and atrophy, together with atherosclerosis (major vessels supplying the brain and the circle of Willis), lacunes, infarcts, white matter pallor, Braak stage and brain weight.

Neuropathological variables were scored by neuropathologists as ‘none’, ‘mild’, ‘moderate’ or ‘severe’ (semi-quantitative). Exceptions were lacunes, infarct, haemorrhage and white matter pallor (absent or present), Braak stage (0–6) and brain weight (g). For the analysis, some scores were simplified. Where a pathological severity category occurred with a frequency of <10%, it was merged with the closest category (i.e. none with mild, or moderate with severe). Brain weight was categorized into sex-specific tertiles and Braak stage into three groups (0–2, 3–4 and 5–6).

Statistics

Data are from Version 1.0 of the EClipSE database. STATA 10 Intercooled (Texas, Stata Corporation, 2001) was used for statistical analysis. All analyses were adjusted for age at death, sex and study (MRC CFAS, CC75C or Vantaa 85+).

Logistic regression analysis was used to investigate the association between education and dementia. There were two types of neuropathological analyses. First, the effects of education on the risk of neuropathological variables, regardless of dementia status, were assessed with ordered/binary logistic regressions (proportional odds assumption examined using the Brandt test). Second, we assessed how associations between neuropathological markers and clinical dementia (outcome) changed following the addition of an education main effect (i.e. does education enable compensation?) and then an interaction between education and pathology (i.e. is this putative compensation for all or limited severity levels?) via a series of binary logistic regressions. Likelihood ratio tests were conducted between models.

Each non-binary neuropathological variable was fitted as a series of indicator variables when used as a predictor. Years of education was fitted as a linear trend with increasing group. To ensure that the effects of education were not driven by the Vantaa 85+ participants (who were older and less educated), sensitivity analyses were undertaken in those <85 years old and in those ≥85 years old. The results did not change and are not shown.

Results

Participant characteristics

The number of participants from each study, their age, sex, years of education and dementia status are presented in Table 1. The major variable that differs between the studies is the distribution of years of education. The majority of Vantaa 85+ donors received 4–7 years of education, while the majority of CC75C and MRC CFAS donors received 8–11 years. The potential contribution of this cohort effect was explored in additional sensitivity analyses and by replicating analyses using an alternative measure of education (educational opportunity where education was defined as below the median, median and above, with median within study). These analyses were consistent with those presented here (data not shown).

Table 1 Characteristics of study participants including dementia status, years of education, sex and age relative to original study

	MRC CFAS	CC75C	Vantaa 85+	EClipSE total
Total number	414	213	245	872
Demented	232	113	141	486
Non-demented	182	100	104	386
Median years of education	9	9	4	9
Range of years of education	5–24	7–21	0–16	0–24
0–3 years	0	0	59	59
4–7 years	13	2	171	186
8–11 years	362	181	3	546
>12 years	39	30	12	81
Female (%)	58	70	82	68
Median age	87	91	92	90
Age range	68–103	79–107	86–106	68–107

Does education affect clinical dementia risk and the accumulation of neuropathological markers?

More exposure to formal education (per year) was associated with a lower risk of clinical dementia at death [odds ratio (OR) = 0.89; 95% confidence interval (CI) 0.83–0.94].

No neurodegenerative or vascular pathology varied as a function of education. Greater educational exposure was however associated with greater brain weight (controlling for age, sex and study) (OR=1.14, 95% CI 1.06–1.24). For example, 8% of those with 4–7 years of education were in the highest brain weight tertile compared to those with 8–11 years (32%) and ≥12 years (36%) of education. Of those with 4–7 years of education, 46% were in the lowest brain weight tertile compared to those with 8–11 years (38%) and ≥12 years (22%) of education.

Does education mitigate the cognitive effects of neuropathological markers and does any effect of education alter with neuropathological severity?

Each neuropathological factor was associated with clinical dementia (significance varied between $P<0.01$ and $P=0.03$) after adjustment for age, sex and study, except for haemorrhage ($P=0.55$). When education (in years) was introduced into the models (between pathologies and clinical dementia), dementia risks conferred by each pathological severity did not change, reinforcing the finding that the effect of education on dementia risk is not through the accumulation of neurodegenerative or vascular markers.

The prevalence of clinical dementia was attenuated by an increasing ‘dose’ of education for all pathological variables except brain weight (OR=0.93; 95% CI 0.84–1.01, likelihood ratio test $P=0.09$). Figure 1 and Supplementary Fig. 1 show

decreasing prevalences of dementia for each pathology variable across stratified groups for educational exposure for most severities of pathology. This suggests that education is an independent factor associated with dementia (i.e. education mitigates the dementia effects of pathologies) and is not mediated through the pathological measures investigated.

The protective effect of education varied by pathological severity for brain weight and Braak stage (Fig. 1). Brain donors with more years of education had a decreased risk of dementia for low/medium brain weight but not for high brain weight, compared to those with less education. Within the high brain weight tertile there was actually an increase in the risk of dementia with increasing education, but this was driven by the only individual with both low education and high brain weight being non-demented. For Braak stage, those with more years of education were at reduced dementia risk when Braak stage was ≤ 4 (i.e. none/mild/moderate) but not when Braak stage was 5–6 (i.e. severe) as compared to those with less education.

Discussion

The analysis undertaken in this large population-based cohort did not demonstrate any protective effect of years in education on the accumulation of neurodegenerative or vascular pathologies in the brain at death. Education did, however, mitigate the association between pathology burden and cognitive decline so that, for a specific pathological burden, those who had experienced more education early in life were at reduced dementia risk in old age. The average time elapsed between completion of education and death was >70 years in the EClipSE cohort, such that these associations between education, neuropathological burden and clinical dementia are remarkable. The evidence appears strong based on these three population-based cohorts of old European individuals who have been followed for up to 20 years.

The results support the 'brain reserve hypothesis' (Stern, 2006; Valenzuela and Sachdev, 2006; Valenzuela *et al.*, 2007; Valenzuela, 2008) where those who remain in education for longer are able to compensate for pathological burden in later life, rather than a hypothesis based on a protective effect of education against the accumulation of pathology arising from life-long environmental factors (Del Ser *et al.*, 1999). The finding that low education is associated with an increased incidence of dementia (Stern *et al.*, 1994; Cobb *et al.*, 1995; Ott *et al.*, 1995) therefore appears to be due not to an increased burden of neuropathology, but rather to an increased vulnerability to cognitive deterioration.

Previous data related to this problem are scarce and subject to deficiencies. These include but are not limited to: samples which do not represent the population, small sample sizes, limited pathological/structural measures and limited distribution of education across the group. We have tried to address these factors. Any attempt to correlate a complex risk factor robustly, where exposure occurs in early life, against outcomes up to 70 years later, including brain pathology, needs access to large cohorts in which the demographic, clinical and pathological data are coherent and reliable. The EClipSE data were derived from three studies that, while subtly different, share key methodological approaches

across data collection and study design that have enabled us to combine them without difficulty. The resulting cohort is large enough to support the statistical approach used to demonstrate the associations observed in this analysis. However the study has significant limitations. Some heterogeneity may have been introduced by the varying dementia classification systems used. The Vantaa 85+ participants completed fewer years of education than those in MRC CFAS and CC75C, which could have interfered with the analysis of the effect of education. To address this we also ran analyses relating to educational 'opportunity' across the studies (results not shown). The results were not changed although the effects were stronger for years of education, suggesting the effect is mediated through the 'dose' of education rather than opportunity for education.

Not all participants in each of the original studies donated their brains but each of the individual studies have analysed their data to assess biases. The Vantaa 85+ brain donors, comprising more than half of all respondents in that study, are highly representative with no systematic biases. MRC CFAS and CC75C donor cohorts over-represent people who were older and cognitively impaired, compared to the study populations as a whole, because that was the way in which those studies were designed. Consent for brain donation was targeted to a subsample of the total cohort with representation from the whole spectrum. However the characteristics of this sample were defined and known. All deaths, both in the targeted samples and the entire cohort, have been ascertained. The analytical methods are robust and adequately powered (though interactions are difficult to detect) but we did not adjust for multiple comparisons, which might introduce some false positive results. Results were run within the individual studies and associations seen in the results did not change.

More years in education did not protect individuals against the accumulation of neurodegenerative or vascular pathologies in the brain. This has previously been reported by Del Ser *et al.* (1999) for neurodegenerative pathologies, but they found that low education was associated with increased vascular neuropathology. Low educational achievement would be expected to result, on average, in lower socioeconomic achievement and status over a lifetime at the level of the population as a whole (although clearly there will be many examples of individual early school leavers going on to high levels of achievement in social, intellectual and financial terms), and it would also be expected that lower socioeconomic groups within society would include a greater proportion of individuals who experienced a low number of years in education. It is known that low socioeconomic status is a risk factor for cardiovascular disease and early death (Clark *et al.*, 2009). This implies that low education might be expected to correlate with increased risk of cardiovascular and cerebrovascular disease in the population. Therefore, it is possible that groups in society with the least education were more likely to die due to severe vascular pathology before being eligible for entry into these population-based studies. Despite these survival effects, we are able to demonstrate that cognitive outcomes associated with both cerebrovascular atherosclerosis and cerebral infarction are attenuated by education for the group with the highest exposure level.

More education was associated with greater brain weight. For every one year increase in education, there was a 10% increase in

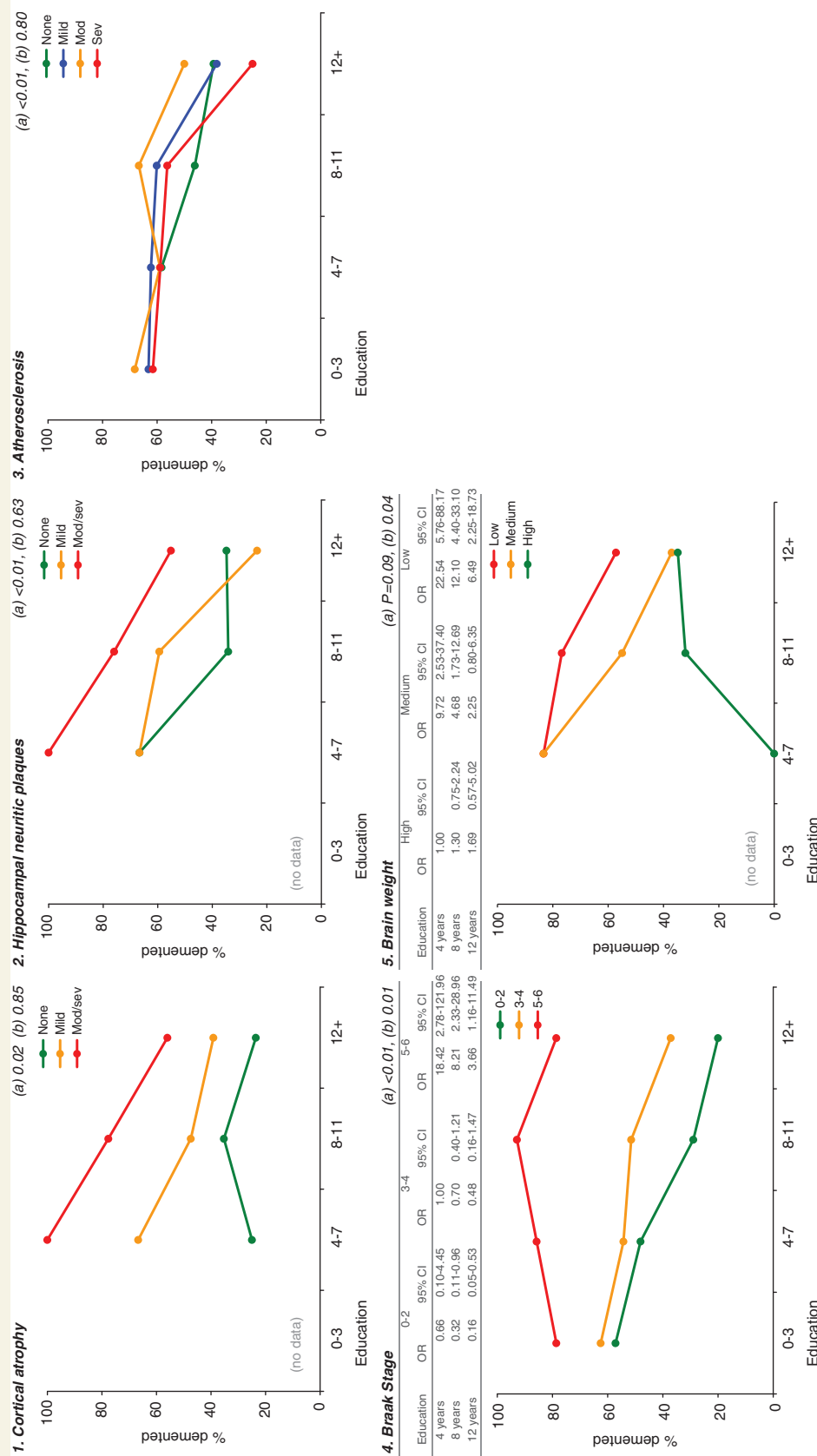


Figure 1 Percentage of demented participants (y-axis) relative to years of education (x-axis) and pathological severity for (1) cortical atrophy, (2) hippocampal neuritic plaques, (3) atherosclerosis, (4) Braak stage and (5) brain weight. Each graph illustrates how education attenuates association between pathology and dementia. Graphs 1–3 have been selected as examples of this education main effect (see Supplementary material for all markers). For Graphs 4–5, this education effect interacted with pathological severity and for these ORs (and 95% CIs) for dementia by education and pathological severity (adjusted for age, sex and study) have been provided to illustrate interactions. Significance values (P) provided are likelihood ratio tests results assessing the significance of the (a) introduction of education main effect (does education mitigate the effect of pathology on dementia?) and (b) interaction term between pathological severity and education (is this education effect dependent on pathological severity?). For those graphs without data 0–3 years, Vantaa 85+ data were not available.

the probability of being in a higher brain weight tertile at death. Despite this finding, we did not show an association with atrophy (neocortical or hippocampal), similar to Christensen *et al.* (2007), but unlike Coffey *et al.* (1999). Atrophy is a subjective assessment of gyral, sulcal and ventricular volumes. Whilst it must influence the ultimate brain weight, the two measures may be dissociated because there is wide variation in the initial size of the brain. We do not have a source of data that enables us to predict the maximum brain weight achieved during the lifetime of each donor. Those with more education may have had heavier brains to begin with (such that a larger brain may predispose to more education being undertaken) or may have heavier brains at death because educational experiences lead to greater brain weight through enhanced synaptodendritic development, more complex axonal projections and enhanced myelination and neurogenesis (Stern, 2006; Valenzuela *et al.*, 2008). These theoretical mechanisms are not mutually exclusive.

Supporting the brain reserve hypothesis, education enabled individuals to compensate for all types of neurodegenerative and vascular burden, and there was evidence of an association for brain weight (i.e. effect did not reach conventional significance levels but was in the correct direction). For brain weight and Braak stage, this protective effect of education varied across severity. These patterns were not consistent between markers. Education protected against dementia for low/medium brain weight (i.e. the most deleterious categories) but for Braak stage, education protected against dementia to the greatest extent when none, mild or moderate (i.e. not the most deleterious). The effect for brain weight was similar to a study in which head circumference was assessed (Mortimer *et al.*, 2003). The effect for Braak stage most likely reflects stages 5/6 being a dementia threshold, where it is highly unlikely that an individual will not be demented and education cannot exert any detectable protective effect. This threshold effect has been proposed previously for neuritic plaques (Roe *et al.*, 2008).

The cognitive mechanisms underlying this compensatory ability are unknown. It may be that brain reserve is related to better executive function and declarative memory (Buckner, 2004). It is beyond the scope of this article to investigate these putative cognitive mechanisms and we hope that these results stimulate further research into brain reserve, both in terms of its neurobiological and cognitive correlates. The effects of a more advanced education are also potentially associated with differences in the intensity or nature of sustained neuropsychological activity across the whole lifespan and we cannot exclude the possibility that the effects of education on dementia risk are mediated, or moderated, by life-style factors far more proximate to the end of life than the initial formal period of schooling. A recent article has suggested that computerized 'brain training' in adulthood (18–60 years) confers no benefits to general cognitive function (Owen *et al.*, 2010).

In summary, there appears no evidence to suggest that those with less education have a greater burden of vascular or neurodegenerative pathologies at death in old age, compared to those who undertook more education. Those with more education do appear to have heavier brains and maintain cognition in the face of a burden of neuropathology compared to those with less education. Education attenuates dementia risk but does not mitigate

it altogether. This finding may help to explain why individuals differ in their ability to withstand a burden of neurodegenerative or vascular brain disease before expressing clinical dementia (MRC-CFAS, 2001; Polvikoski *et al.*, 2001; Matthews *et al.*, 2009; Brayne *et al.*, 2009). Socioeconomic developments that lead to a reduction in factors potentially associated with smaller brains, and that increase total early life exposure to education, may have progressive benefits in terms of dementia prevalence in the population over time. The converse effect may be of public health significance in lower and middle income countries, where deprivation is common and access to education limited. Changes in the age-structure within populations over time are most apparent in such countries, which comprise the largest potential source of growth in proportion to the global population who live into later life. Further studies of education, mid-life risk and more detailed biological markers will help us to understand these findings better. Interest in education is known to be good for population health and equity. This study provides strong support for this investment, which is of relevance for policy decisions about the importance of resource allocation including between health and education sectors.

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Supplementary material

Supplementary material is available at *Brain* online.

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