Lifetime determinants of cognitive ageing, dementia and early death

Childhood school performance, education and occupational complexity: a life-course study of dementia in the Kungsholmen Project

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Abstract

Background: Cognitive reserve hypothesis predicts that intellectually demanding activities over the life course protect against dementia. We investigate if childhood school performance remains associated with dementia once education and occupational complexity are taken into account.

Methods: A cohort of 440 individuals aged 75+ from the Kungsholmen Project was followed up for 9 years to detect dementia. To measure early-life contributors to reserve, we used grades at age 9–10 extracted from the school archives. Data on formal education and occupational complexity were collected at baseline and first follow-up. Dementia was ascertained through comprehensive clinical examination. Cox models estimated the relationship between life-course cognitive reserve measures and dementia.

Results: Dementia risk was elevated [hazard ratio (HR): 1.54, 95% confidence interval (CI): 1.03 to 2.29] in individuals with low early-life school grades after adjustment for formal educational attainment and occupational complexity. Secondary education was associated with a lower risk of dementia (HR: 0.72, 95% CI: 0.50 to 1.03), although the effects of post-secondary and university degrees were indistinguishable from baseline. Occupational complexity with data and things was not related to dementia. However, an association was found between high occupational complexity with people and dementia, albeit only in women (HR: 0.39, 95% CI: 0.14 to 0.99). The pattern of results remained unchanged after adjustment for genetic susceptibility, comorbidities and depressive symptoms.

Conclusion: Low early-life school performance is associated with an elevated risk of dementia, independent of subsequent educational and occupational attainment.

Key words: Cognitive reserve, dementia, longitudinal studies

Key Messages

- Cognitive reserve has been used to explain the variation across individuals in the extent of pathology required for the clinical diagnosis of dementia.
- We demonstrate that early-life contributors to cognitive reserve, measured by school performance at age 10, are associated with the risk of dementia even after taking subsequent education and occupational complexity into account.
- Development of dementia risk is a life-course process that begins already in the early years of life. Childhood cognitive abilities contribute to successful ageing.

Introduction

Cognitive reserve hypothesis predicts that differences in brain network efficiency and flexibility underlie individual variations in the extent of brain damage required for the clinical diagnosis of dementia.^{1,2} Intellectual enrichment over the life course is being increasingly viewed as an important contributor to the cognitive reserve, allowing individuals to cope better with age-related changes.^{3–5} Lower risk of dementia has been reported among individuals with higher education or in complex occupational roles.^{6–8} Early-life cognitive ability is an intellectual prerequisite for both educational and occupational attainment in later life and may therefore contribute to cognitive reserve.^{9,10} Only few studies have managed to collect measures of early-life cognitive ability and contrast them against dementia risk in old age. Results from these studies indicate that there is an elevated risk of dementia in individuals with low early-life cognitive ability.^{11,12}

To date, it is still unclear whether early-life contributors to reserve continue to affect dementia risk in later life after conventional measurements of intellectual enrichment, such as education and occupational complexity, are taken into account. One study¹³ has found that low school grades at age 10 were associated with an elevated risk of dementia after adjustments for education and occupational complexity; however, the dementia diagnosis in that study was retrieved from inpatient and cause of death registers. Although the overall validity of the Swedish registers is high, the probability of detecting dementia is low in the registers.¹⁴ Misclassification of diagnosis due to low sensitivity could lead to underestimation of the relative risks, or bias the risk estimates if linked to the study exposures. A replication of analysis in a sample in which sensitivity and specificity of dementia diagnosis are high is therefore warranted.

In this study, we investigate the relationship between intellectual enrichment over the life course and dementia risk in the elderly who underwent an extensive clinical and neuropsychological assessment. To measure early-life cognitive ability, we extract grades on five representative

subjects from elementary school when individuals were 9–10 years old. Information on education and lifetime occupational attainment is collected at baseline (age 75) and the first follow-up. Our aim is to investigate how dementia risk is influenced by three contributors to cognitive reserve, measured at different stages over the life course: childhood cognitive ability, adult educational attainment and lifetime occupational complexity.

Methods**Study population**

The study population was derived from the Kungsholmen Project (KP), a longitudinal population-based cohort study on ageing and dementia in Swedish elderly persons. Study design of the KP has been described previously.¹⁵ Briefly, all 2368 individuals aged 75 or older, registered in the Stockholm district of Kungsholmen on 1 October 1987, were invited to participate and 1810 accepted. These individuals underwent nurse interviews as well as physician and psychologist evaluations at baseline, 3-, 6- and 9-year follow-up examinations. The regional ethics committee approved the project and informed consent was obtained from all participants.

We subsequently excluded individuals who were older than 95 ($n = 7$), refused the clinical examination ($n = 110$), were diagnosed with dementia ($n = 225$) or had very low scores on a cognitive screening test at baseline (mini-mental state examination score < 20 , $n = 31$). Of these 1437 participants, 172 dropped out before the follow-up examination, 704 were removed due to missing information on school grades and 121 were dropped due to missing occupational histories or due to being homemakers, resulting in the population analysed in the study being 440 individuals who were followed for up to 9 years to detect incident dementia.

Dementia diagnosis

At each follow-up examination, participants underwent nurse interviews, clinical examinations and cognitive

testing. Dementia was diagnosed in accordance with *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III-R). A three-step procedure was employed in which preliminary diagnosis was set by the examining physician, to be confirmed by the second clinician who independently reviewed all subjects. Should the two disagree, a third opinion was sought from a specialist and a concordant diagnosis was accepted. For subjects who died during the follow-up, incident dementia was diagnosed according to clinical records, discharge diagnoses and death certificates. Time of dementia onset was set at the midpoint between follow-up examinations, or the midpoint between the clinical examination and the date of death due to dementia.

Elementary school grades

We used grades from archived report cards from the 3rd year of elementary school when individuals were 9 or 10 years of age, as a marker of early-life reserve. A correlation ($r \approx 0.50$) between school grades and cognitive ability has been reported previously,¹⁶ suggesting that school grades could reflect early-life intellectual capacities.

Although all participants resided in Kungsholmen, Stockholm, at baseline, many of them were born and attended elementary school elsewhere in Sweden. We first examined the *Swedish Mortality Database* (*Sverigesdödbok*) to locate each individual's residence at birth. Next, church books, containing detailed information on migration to and from the parish, were examined to map out each child's location around age 10. If a child moved between birth and age 10, several church books had to be searched. Having identified the parish of residence at age 10, each local office responsible for the enlistment rolls and examination catalogues of the respective schools was either visited or contacted, and the school grades dating back to 1901–22 were collected.

Grades on five representative school subjects (mathematics, reading, geography, history and writing) from the 3rd year of elementary school when children were aged 9 or 10 years old were extracted. School marks were entered as letter grades, ranging from the lowest (C) to the highest (A), with two-letter combinations (Ba), together with qualifications such as pluses and minuses (Ba+). As C- and A+ were rarely awarded, the result was a 19-level variable, coded from 0 (Grade C) to 18 (Grade A). This scale is identical to the system used in previous studies on school grades^{17,18} and is originally based on the system proposed by the Swedish educational authorities in 1942.¹⁹ In accordance with this scale, the following values were assigned to the letter-grades: A = 18, a = 15, AB+ = 13, AB = 12, AB— = 11, Ba+ = 10, Ba = 9, Ba— = 8, B+ = 7,

B = 6, B— = 5, BC = 3 and C = 0, ensuring equal spacing between C and A. Because some children had missing information on certain subjects (all five grades non-missing: 52%; one subject missing: 18%; two missing: 20%; three missing: 10%), we calculated an overall grades average by standardizing the grades in each subject first. Factor analysis indicated that a single latent factor explained most of the observed variation in all five subject grades (first Eigenvalue 3.27, second 0.71).

Education

Information on educational attainment was collected during the baseline investigation and refers to the highest-attained educational level. This variable was converted into a categorical indicator distinguishing between three levels of attainment: elementary schooling (less than 8 years of schooling), secondary education (8–10 years of schooling) and post-secondary and university education (>10 years of schooling).

Occupational complexity

Information on occupational attainment was collected during the nurse interview at the first follow-up examination,⁸ and lifetime occupation was assigned to the longest-held occupation. To assign work complexity rankings to the lifetime occupation, we used the matrix developed previously for the U.S. occupational positions based on the census of 1970.²⁰ Each occupation was assigned a score reflecting the level of complexity at which a typical worker functions, with Swedish occupational codes matched to the best-fitting category from the U.S., using a procedure described previously.²¹ Complexity of lifetime occupation was assessed along the dimensions of data, people and things with continuous scores ranging from simple (value 0) to complex tasks (values 6, 7 and 8, respectively). We converted continuous complexity scores into three dichotomized variables to denote high complexity with respect to data ('analysing' tasks or higher), people ('persuading' tasks or higher) and things ('driving-operating' tasks or higher).

Covariates

Age, sex and genetic susceptibility were considered as confounders. In additional analysis, we adjusted for known dementia comorbidities and depressive symptoms to investigate mediating effects of later-life health. Coronary heart disease, cerebrovascular disease, diabetes mellitus, malignancy and hip fracture were ascertained by reviewing the hospital discharge registers between 1969 and the baseline

(1987). Comorbidity was defined as the presence of any of these conditions. Depressive symptoms refer to self-reported persistent feelings of loneliness and low mood collected at baseline. Genomic DNA was prepared from peripheral blood samples at baseline, and Apolipoprotein E (APOE) genotyping was conducted following standard procedures by two technicians who were blind to all other data for the study population.

Statistical analysis

Logistic regression was used to evaluate the differences in baseline characteristics between participants and dropouts. Cox proportional hazard models were used to estimate dementia risk associated with childhood school grades, educational attainment and occupational complexity. All models were adjusted for sex and age at baseline.

We began with minimally adjusted models to assess direct effects between each component of intellectual enrichment and dementia risk after age 75. We then progressively increased the number of parameters estimated simultaneously, concluding with a fully-adjusted model that included childhood school grades, education and occupational complexity as correlates of dementia. The three dimensions of occupational complexity were correlated (data and people: 0.57; data and things: 0.12; people and things: -0.30; all $p < 0.001$). To avoid bias due to multicollinearity, we modelled each complexity measure separately.

We examined interactions between sex and each component of intellectual enrichment in minimally controlled models. We also examined interactions between components of intellectual enrichment over the life course by testing if an additional effect of combining low school grades with low educational or occupational attainment could be discerned. Additional analysis was conducted to examine whether the inclusion of comorbidities and depressive symptoms would attenuate the relationship. Finally, potential confounding effect of genetic risk (APOE $\epsilon 4$ allele) was evaluated. Proportionality assumption was tested in each model and no evidence of violation was found (Schoenfeld residuals test, lowest $p = 0.29$).

Results

Individuals analysed in the study and those excluded due to missing data on school grades and occupational complexity did not differ with respect to age, sex or occurrence of dementia. However, the excluded participants were more likely to have higher educational level [odds ratio (OR): 1.47; 95% CI: 1.16 to 1.85].

After following 440 individuals for up to 9 years (mean follow-up time: 5 years), 163 individuals were classified as

demented. Mean age at dementia onset was 86 years (range: 77 to 100 years). Baseline characteristics of the study participants are presented in Table 1. School grades, education and occupational complexity were related to each other. Mean school grades and continuous occupational complexity were correlated (strongest correlation with data complexity; $r = 0.12$; $p < 0.05$). Furthermore, higher educational degrees claimed a larger proportion of participants in complex occupational roles in terms of data and people (χ^2 test; both $p < 0.01$). Subjects with high occupational complexity with things, however, were most numerous in the group with only elementary education

Table 1. Baseline characteristics of non-demented participants and incident dementia cases detected over an average of 5 years of follow-up. Observations numbers and (%)

Characteristic	Non-demented N = 277	Incident dementia N = 163	p-Value
Age, years			
75–79	99 (36%)	43 (26%)	0.119
80–84	107 (39%)	76 (47%)	
85–89	44 (16%)	32 (20%)	
90+	27 (10%)	12 (7%)	
Sex			
Male	75 (27%)	32 (20%)	0.079
Elementary school grades			
Lowest performance quintile	36 (13%)	29 (18%)	0.171
Education			
Elementary	151 (54%)	96 (59%)	0.672
Secondary	83 (30%)	44 (27%)	
Post-secondary and university	43 (16%)	23 (14%)	
Work complexity with data			
High complexity	55 (20%)	28 (17%)	0.488
Work complexity with people			
High complexity	25 (9%)	9 (6%)	0.184
Work complexity with things			
High complexity	62 (22%)	23 (38%)	0.822
Comorbidities			
At least one disease	79 (29%)	48 (29%)	0.836
Depressive symptoms			
At least one symptom	77 (28%)	56 (34%)	0.150
APOE status			
$\epsilon 4$ allele	52 (25%)	47 (34%)	0.066

($p < 0.05$), which is expected since high things-complexity usually implies manual occupations. Finally, participants with the lowest school grades were most likely to have only elementary schooling ($p < 0.05$).

Minimally-adjusted models

Having transformed the mean school grades variable into five groups based on the quintile distribution, we found that the top four quintiles were all associated with a lower risk of dementia relative to the lowest 20% (Supplementary Table S1, available as Supplementary data at *IJE* online). In other words, we found no evidence of a dose-response relationship between childhood school grades and dementia. Consequently, we converted the mean school grade variable into a binary indicator distinguishing the worst performers (lowest 20%) from the remaining 80% of the school grades distribution. This variable was used in all subsequent analyses. Individuals with the lowest school grades around age 10 were at an elevated risk of dementia (Figure 1).

Both secondary and post-secondary levels were associated with a reduced risk of dementia compared with elementary education, although the protective effects of post-secondary/university education were indistinguishable from baseline. High occupational complexity with data and people was associated with a reduced risk of dementia, although in both cases confidence intervals contained 1. High complexity with things was associated with an elevated risk of dementia, although the confidence interval for the effect size was very wide.

We found no evidence of interaction between sex and childhood school grades, educational attainment or complexity with data or things. We did, however, find an interaction between sex and high complexity with people, suggesting that women in people-intensive occupational role have a reduced risk of dementia (Figure 2).

Mutually-adjusted models

Low childhood school grades remained associated with an elevated risk of dementia after adjustments for education, all three occupational complexity dimensions, and in a

Figure 2. Effects of occupational complexity with people on risk of dementia, stratified by sex. Age-adjusted hazard ratios and 95% confidence intervals from Cox proportional hazard model, 107 men and 333 women.

Figure 1. Effects of childhood school grades, education, and work complexity on risk of dementia. Age- and gender-adjusted hazard ratios and 95% confidence intervals from Cox proportional hazard regressions including 440 observations and 163 dementia events. Low childhood grades modelled as worst 20% grades vs the rest of the distribution. Reference category for education: elementary education.

fully adjusted model (Table 2). The effect of secondary education remained upon adjustments for childhood school grades and occupational complexity with data and things, although it vanished once occupational complexity with people was adjusted for. Complexity with people exhibited the clearest protective effect of the three complexity dimensions, although the confidence interval was quite wide.

There was no evidence of interaction between childhood school grades and educational attainment, or any dimension of occupational complexity, for the risk of dementia. Interaction term between education and any of the occupational complexity dimensions contained 1.

In additional analysis, all models were re-estimated with additional adjustment for comorbidities and depressive symptoms, and no meaningful attenuation of the reported effects was observed [HRs of childhood school grades from fully adjusted models: 1.57 (data-adjusted); 1.52 (people-adjusted); 1.53 (things-adjusted), all $p < 0.05$; education controlled for in all models]. The effects of early-life school performance also persisted after adjustment for APOE $\epsilon 4$ allele genotypes in the analysis.

Discussion

We examined whether three measures of intellectual enrichment over the life course are associated with dementia risk in elderly individuals who underwent detailed clinical examination over 9 years of follow-up. We found that

subjects with low school grades at age 9–10 were at an elevated risk of dementia in late life. Higher education decreased the risk of dementia, whereas occupational complexity was not associated with dementia. However, women in occupations characterized by high complexity with people had a reduced risk of disease.

Low childhood school grades are likely an indication of low baseline cognitive abilities. Even after moderation by subsequent life experiences, these low initial capabilities are found to contribute to an elevated the risk of dementia in late life. Growing evidence supports the link between early-life cognitive ability and dementia in late life.^{11,12,22} Furthermore, early-life intelligence quotient (IQ) has been implicated in predicting the level²³ as well as the rate²⁴ of decline in cognitive functioning. Our finding is in accordance with an earlier study, where individuals with lower school grades had a 20% higher risk of dementia in late life.¹³ In the present study, the effect was stronger (hazard ratio of about 1.5), possibly because dementia diagnosis in the previous study relied on inpatient and cause-of-death registers which likely underestimated the risk effect.

Low early-life cognitive ability might also affect health-related behaviours and lifestyle choices, which could subsequently put individuals at an elevated risk of dementia. Stroke and heart disease are implicated in the risk of dementia,²⁵ and both have been previously linked with intelligence.²⁶ In fact, it has been shown that lower childhood cognitive ability is associated with an elevated risk of

Table 2. Effects of childhood school grades, education, and work complexity on dementia. Mutually-adjusted models

VARIABLES	(1) Grades & EDU	(2) Grades & Data	(3) Grades & People	(4) Grades & Things	(5) EDU & Data	(6) EDU & People	(7) EDU & Things	(8) Grades & EDU & Data	(9) Grades & EDU & People	(10) Grades & EDU & Things
Low grades	1.52 (1.02–2.26)	1.60 (1.07–2.34)	1.55 (1.05–2.31)	1.58 (1.06–2.34)				1.54 (1.03–2.29)	1.50 (1.01–2.23)	1.51 (1.02–2.25)
Elementary education	1 (Ref)				1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
Secondary education	0.73 (0.51–1.04)				0.69 (0.48–0.99)	0.72 (0.51–1.03)	0.71 (0.50–1.01)	0.72 (0.50–1.03)	0.75 (0.53–1.07)	0.73 (0.51–1.05)
Post-secondary+	0.94 (0.55–1.61)				0.90 (0.53–1.54)	0.94 (0.55–1.59)	0.90 (0.53–1.54)	0.93 (0.54–1.59)	0.97 (0.56–1.65)	0.94 (0.55–1.61)
High data complexity		0.99 (0.63–1.58)			1.04 (0.65–1.65)			1.09 (0.68–1.75)		
High people complexity			0.68 (0.33–1.40)			0.70 (0.34–1.44)			0.73 (0.36–1.51)	
High things complexity				1.11 (0.76–1.64)			1.09 (0.74–1.61)			1.06 (0.72–1.56)

Age- and gender-adjusted hazard ratios and 95% CIs, Cox proportional hazard regression, 440 observations and 163 dementia events. Robust confidence intervals in parentheses. Low grades coded as lowest fifth vs. the rest.

vascular dementia, but not Alzheimer's disease, suggesting that mediation by mid-life vascular factors is important.²⁷ We explicitly tested the possibility of early-life school grades' effects being mediated by subsequent health status, and adjusted for comorbidities and depressive symptoms. As the effects of early-life school grades remained virtually unchanged after adult health status was accounted for, we concluded that the link between early-life school grades and dementia is mainly due to genuine reserve pathways of neural efficiency and compensation. This is in line with the recent neuroimaging literature, which is increasingly pointing to the existence of a neural basis of cognitive reserve.¹ Finally, in additional analysis, we excluded the possibility of confounding by genetic susceptibility.

Dementia risk was reduced in individuals with an educational level beyond elementary, although protective effects of the highest levels were not apparent. Protective effects of non-basic educational attainment have been found before.⁶ Lack of additional advantage from post-secondary and university education may be due to loss of power, as a result of sample size reduction, and low rates of transitioning into higher education. It should also be noted that in another study,¹³ superior education protected against dementia, whereas intermediary attainment did not. Consequently, we believe the cut-off point at which educational attainment is protective against dementia may vary depending on the age composition of the cohort in question and the structure of the educational system, as well as the labour market characteristics at the time. In line with this, others have argued that the association between education and cognitive ageing might in fact be a misspecified model for the relationship between age/time/period and cognitive impairment.²⁸

Finally, among occupational complexity dimensions, only complexity with people, and only in women, was implicated in dementia risk. Protective effects of work complexity with people have been reported previously.^{8,21,29} Continuous exposure to intellectually demanding tasks at work might be a source of exercise, leading to greater sophistication in cerebral networks in old age and allowing for dementia neuropathology to be tolerated for longer during the disease progression.³⁰ With respect to complexity with people in particular, it has been suggested that in addition to intellectual stimulation, this construct partly reflects the effects of interpersonal demands and social networks that might provide an additional line of defence against dementia.²⁹ A rich social network has been associated with a lower risk of dementia in the same source study population where the majority (75%) of the participants were women.³¹ Furthermore, protective effects of social engagement with friends against cognitive decline appear to be more pronounced among

women,³² which might explain why we were able to detect the effect of work complexity with people only when an interaction term with sex was introduced.

Limitations

First, in the absence of explicitly measured childhood cognitive ability, we used elementary school grades from age 9–10 as a proxy because they are known to be correlated to a considerable extent.¹⁶ At the same time, school grades might be affected by characteristics unrelated to cognitive ability, for instance diligence or conscientiousness. Second, information on school grades was extracted only for a subsample of study participants who attended elementary school in and around Stockholm. Those with missing data on early-life school grades did not differ from the analysed sample in terms of sex or age, although they were more likely to have higher educational attainment. Importantly, rates of dementia occurrence did not differ between the excluded individuals and the analysis sample. Third, a series of models were fitted as part of the analysis, potentially increasing the risk of a multiple comparison bias. Importantly, the direction of the associations and the point estimates were consistent across the range of comparisons, and the main effect of school grades was largely preserved following a Bonferroni correction. Fourth, we found that individuals who avoided the lowest quintile of grades experienced a lower risk of dementia ([Supplementary table S1](#), available as [Supplementary data](#) at *IJE* online). The pattern of risk reduction varied by quintile: it was the largest in the second, followed by the fourth and the third, and the lowest in the top performance group. Although there might be concerns about the power to detect reliable associations in this study, we argue that the effects of performance quintiles rather indicate a lack of a dose-response relationship between improved grades and dementia: as long as the worst performance is avoided, no additional benefits are reaped by the high attainment. Reliability of these conclusions is further strengthened by being in line with a previous finding of an elevated risk of dementia in individuals with the lowest school grades.¹³

Conclusion

Individuals with low school grades in early life were at an elevated risk of dementia in late life, even after later-life measures of intellectual enrichment were taken into account, thereby strengthening previous findings. We also found that dementia risk is further reduced in individuals with higher education and in women in people-intense occupational roles. Dementia risk develops over the entire

life course and early-life cognitive abilities appear to contribute to successful ageing.

Supplementary Data

Supplementary data are available at *IJE* online.

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Author contributions

AH came up with the idea for the study and obtained funding. All authors were involved in the design of the study and data interpretation. SD analysed the data and drafted the article. All authors participated equally in revising the manuscript and approved the final version. SD acts as the guarantor for this study

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References

1. Steffener J, Stern Y. Exploring the neural basis of cognitive reserve in aging. *Biochim Biophys Acta* 2012;**1822**:467–73.
2. Stern Y. Cognitive reserve. *Neuropsychologia* 2009;**47**: 2015–28.
3. Vemuri P, Lesnick TG, Przybelski SA *et al.* Association of lifetime intellectual enrichment with cognitive decline in the older population. *JAMA Neurol* 2014;**71**:1017–24.
4. Valenzuela MJ, Sachdev P, Wen W, Chen X, Brodaty H. Lifespan Mental Activity Predicts Diminished Rate of Hippocampal Atrophy. *PLoS One* 2008;**3**:e2598.
5. Fratiglioni L, Paillard-Borg S, Winblad B. An active and socially integrated lifestyle in late life might protect against dementia. *Lancet Neurol* 2004;**3**:343–53.
6. Meng X, D'Arcy C. Education and dementia in the context of the cognitive reserve hypothesis: a systematic review with meta-analyses and qualitative analyses. *PLoS One* 2012;**7**:e38268.
7. Stern Y, Gurland B, Tatemichi TK, Tang MX, Wilder D, Mayeux R. Influence of education and occupation on the incidence of Alzheimer's disease. *JAMA* 1994;**271**:1004–10.
8. Karp A, Andel R, Parker MG, Wang HX, Winblad B, Fratiglioni L. Mentally stimulating activities at work during midlife and dementia risk after age 75: follow-up study from the Kungsholmen Project. *Am J Geriatr Psychiatry* 2009;**17**:227–36.
9. Schmand B, Smit JH, Geerlings MI, Lindeboom J. The effects of intelligence and education on the development of dementia. A test of the brain reserve hypothesis. *Psychol Med* 1997;**27**:1337–44.
10. Satz P. Brain reserve capacity on symptom onset after brain injury: A formulation and review of evidence for threshold theory. *Neuropsychology* 1993;**7**:273–95.
11. Whalley L, Starr J, Athawes R, Hunter D, Pattie A, Deary I. Childhood mental ability and dementia. *Neurology* 2000;**55**:1455–59.
12. Snowdon DA, Kemper SJ, Mortimer JA, Greiner LH, Wekstein DR, Markesbery WR. Linguistic ability in early life and cognitive function and Alzheimer's disease in late life: findings from the Nun Study. *JAMA* 1996;**275**:528–32.
13. Dekhtyar S, Wang H-X, Scott K, Goodman A, Koupil I, Herlitz A. A life-course study of cognitive reserve in dementia. From childhood to old age. *Am J Geriatr Psychiatry* 2015;**23**: 885–96.
14. Jin YP, Gatz M, Johansson B, Pedersen NL. Sensitivity and specificity of dementia coding in two Swedish disease registries. *Neurology* 2004;**63**:739–41.
15. Fratiglioni L, Viitanen M, Bäckman L, Sandman P-O, Winblad B. Occurrence of dementia in advanced age: the study design of the Kungsholmen Project. *Neuroepidemiology* 1992;**11**(Suppl 1): 29–36.
16. Rosander P, Bäckström M, Stenberg G. Personality traits and general intelligence as predictors of academic performance: A structural equation modelling approach. *Learning and Individual Differences* 2011;**21**:590–96.
17. Dekhtyar S, Wang H-X, Scott K, Goodman A, Koupil I, Herlitz A. Associations of head circumference at birth with early life school performance and later-life occupational prestige. *Longitudinal and Life Course Studies* 2015;**6**:26–42.
18. Husén T *Talent, Opportunity and Career: A Twenty-Six Year Follow-Up of 1500 Individuals*. Stockholm: Almqvist and Wiksell, 1969.
19. SOU. *Betänkande med utredning och förslag angående betygssättningen* [Official report and proposal for elementary school grading]. Stockholm: SOU, 1942.
20. Roos P, Treiman D. DOT scales for the 1970 census classification. In: Miller A, Treiman D, Cain P (eds). *Works, Jobs, and Occupations: A Critical Review*. Washington, DC: National Academy Press, 1980.
21. Andel R, Crowe M, Pedersen NL *et al.* Complexity of work and risk of Alzheimer's disease: a population-based study of Swedish twins. *J Gerontol B Psychol Sci Soc Sci* 2005;**60**: P251–58.
22. Bezerra AB, Coutinho ES, Barca ML, Engedal K, Engelhardt E, Laks J. School attainment in childhood is an independent risk factor of dementia in late life: results from a Brazilian sample. *Int Psychogeriatr* 2012;**24**:55–61.

23. Gow AJ, Johnson W, Pattie A, Whiteman MC, Starr J, Deary IJ. Mental ability in childhood and cognitive aging. *Gerontology* 2008;**54**:177–86.
24. Richards M, Shipley B, Fuhrer R, Wadsworth M. Cognitive ability in childhood and cognitive decline in mid-life: longitudinal birth cohort study. *BMJ* 2004;**328**:552.
25. Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K. Midlife cardiovascular risk factors and risk of dementia in late life. *Neurology* 2005;**64**:277–81.
26. Lawlor D, David Batty G, Clark H, McIntyre S, Leon D. Association of childhood intelligence with risk of coronary heart disease and stroke: findings from the Aberdeen Children of the 1950s cohort study. *Eur J Epidemiol* 2008;**23**: 695–706.
27. McGurn B, Deary IJ, Starr JM. Childhood cognitive ability and risk of late-onset Alzheimer and vascular dementia. *Neurology* 2008;**71**:1051–56.
28. Jones RN, Manly J, Glymour MM, Rentz DM, Jefferson AL, Stern Y. Conceptual and measurement challenges in research on cognitive reserve. *J Int Neuropsychol Soc* 2011;**17**:593–601.
29. Kröger E, Andel R, Lindsay J, Benounissa Z, Verreault R, Laurin D. Is Complexity of Work Associated with Risk of Dementia?: The Canadian Study of Health and Aging. *Am J Epidemiol* 2008;**167**:820–30.
30. Churchill JD, Galvez R, Colcombe S, Swain RA, Kramer AF, Greenough WT. Exercise, experience and the aging brain. *Neurobiol Aging* 2002;**23**:941–55.
31. Fratiglioni L, Wang H-X, Ericsson K, Maytan M, Winblad B. Influence of social network on occurrence of dementia: a community-based longitudinal study. *Lancet* 2000;**355**:1315–19.
32. Zunzunegui M-V, Alvarado BE, Del Ser T, Otero A. Social Networks, Social Integration, and Social Engagement Determine Cognitive Decline in Community-Dwelling Spanish Older Adults. *J Gerontol B Psychol Sci Soc Sci* 2003;**58**:S93–S100.