A Life-Course Study of Cognitive Reserve in Dementia—From Childhood to Old Age

Serhiy Dekhtyar, Ph.D., Hui-Xin Wang, Ph.D., Kirk Scott, Ph.D., Anna Goodman, Ph.D., Ilona Koupil, M.D., Ph.D., Agneta Herlitz, Ph.D.

Objective: *To test a life-course model of cognitive reserve in dementia and examine if school grades around age 10 years, formal educational attainment, and lifetime occupational complexity affect the risk of dementia in old age.* **Methods:** *7,574 men and women from the Uppsala Birth Cohort Multigenerational Study were followed for 21 years. Information on school performance, formal education, and occupational attainment was collected prospectively from elementary school archives and population censuses. Dementia diagnosis was extracted from the two Swedish registers. Discrete-time Cox proportional hazard models were estimated.* **Results:** *Dementia was diagnosed in 950 individuals (12.5%). Dementia risk was lower among individuals with higher childhood school grades (hazard ratio [HR]: 0.79; 95% confidence interval [CI]: 0.68 to 0.93) and was lower among individuals in data-complex occupations (HR: 0.77; 95% CI: 0.64 to 0.92). Professional/university education predicted lower risk of dementia in minimally adjusted models (HR: 0.74; 95% CI: 0.60 to 0.91), although the effect faded with adjustment for occupational complexity. Lowest risk was found in the group with both higher childhood school performance and high occupational complexity with data (HR: 0.61; 95% CI: 0.50 to 0.75). Importantly, high occupational complexity could not compensate for the effect of low childhood grades. In contrast, dementia risk was reduced in those with higher school grades, irrespective of occupational complexity.* **Conclusion:** *Higher childhood school performance is protective of dementia risk, particularly when preserved through complex work environments in adulthood, although it will remain protective even in the absence of later-life educational or occupational stimulation.* (Am J Geriatr Psychiatry 2015; 23:885–896)

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Received September 9, 2014; revised January 19, 2015; accepted February 3, 2015. From the Department of Clinical Neuroscience, Section of Psychology (SD), the Aging Research Center, Department of Neurobiology, Care Sciences, and Society (H-XW), the Centre for Health and Equity Studies (IK), and the Department of Clinical Neuroscience, Section of Psychology (AH), Karolinska Institutet and Stockholm University, Stockholm, Sweden; the Centre for Economic Demography (KS) and Department of Economic History, Lund, Sweden; and the Faculty of Epidemiology and Population Health (AG), London School of Hygiene and Tropical Medicine, London, UK. Send correspondence and reprint requests to Serhiy Dekhtyar, Ph.D., Department of Clinical Neuroscience, Section of Psychology, Karolinska Institutet, Nobels Väg 9, 171 77 Stockholm, Sweden. e-mail: serhiy.dekhtyar@ki.se

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Dementia is one of the leading causes of disability, manifesting itself when the pathological processes in the brain reach the point of severe cognitive impairment.[1] Variations exist among individuals, however, in the degree of neuropathology required to cause the neuropsychological deterioration consistent with the clinical diagnosis of dementia.[2] To account for the discontinuity between the degree of brain damage and its clinical manifestation, the concept of *reserve* was proposed.[3] Biological attributes, such as brain size or synaptic connectivity, as well as aspects of life experiences, such as education or occupational characteristics, have been suggested as elements of reserve, protecting against the functional consequences of dementia neuropathology. Protection warranted by anatomical attributes has been referred to as *brain reserve*,[4] and compensatory mechanisms based on innate intelligence and life experience have been defined as *cognitive reserve*.[1,5]

Research on factors believed to influence cognitive reserve has consistently found an elevated risk of dementia in individuals with low education.[6,7] In addition to education, which is assumed to assist with brain network efficiency and flexibility,[8] it has been hypothesized that cognitive reserve may be influenced by occupational characteristics.[9] Demanding occupational roles that provide mental exercise and motivate individuals to continue to develop intellectual capacities have been found protective against dementia.[10,11] Education or occupational characteristics, however, can be affected by cognitive as well as social determinants.[12] Therefore, it can be argued that an early-life prerequisite for educational or occupational attainment, such as childhood cognitive ability, might be a more valid measure of reserve capacity,[13] although such measures are rarely available in dementia studies. The few that managed to obtain such information have reported elevated risk of dementia in individuals with low childhood cognitive ability.[14,15] It is, however, unclear to what extent education or occupational complexity continue to affect the risk of dementia when an early-life marker of reserve is taken into account, and a life-course model of cognitive reserve in dementia risk is yet to be tested.[16]

This is the first study to examine how dementia risk is affected by three factors influencing cognitive reserve, measured at different stages of the life-course: childhood, early adulthood, and mid-life. We can thereby analyze the relative importance of reserve components throughout the entire life-course in a large population-based study with prospectively collected exposure information, which has not been previously possible. We use school performance at age 10 years as a measure of early-life cognitive reserve, as previous research has indicated that the contribution of the cognitive component to teacher-assigned school grades is considerable.[17–19] Dementia diagnosis is extracted over a 21-year follow-up from two Swedish registers, which have previously been shown to be an appropriate source of dementia diagnoses.[20]

METHODS

Study Population

We conducted a cohort study of dementia risk using the Uppsala Birth Cohort Multigenerational Study.[21] This data set comprises 14,192 births registered at the Uppsala University Hospital between 1915 and 1929, and is broadly representative of the Swedish population during that historical period.[22] Of the 12,168 individuals alive and resident in Sweden in 1960 with register linkage, we excluded those who emigrated (N = 168), died (N = 1,792), or developed dementia before age 65 years (N = 26), leaving 10,182 eligible individuals. After exclusion of 2,608 participants with missing data, 7,574 individuals were followed for an average of 21 years (range of follow-up: 14–28 years).

Dementia Diagnosis

Dementia diagnosis was retrieved from the Swedish National Patient Register (NPR) as well as the Cause of Death Register (CDR).[23] During the period 1987–2000, the probability of detecting dementia in the NPR and the CDR combined has been 63% for prevalent cases and 39% for incident cases, and specificity was 98%.[20] Because of improved diagnostics, increased awareness of the disease, and growing register validity over time,[24] recording in the public records can be assumed to have changed between 1980 (start of the follow-up for the oldest individuals) and 2008 (end of the follow-up). To take this into account, we used discrete-time survival models adjusted for calendar-year indicators, allowing us to account for period-specific effects pertaining to all years during the follow-up period. Although it has been argued that the quality of dementia reporting in the NPR and the CDR combined is appropriate for a cohort study of dementia,[20] our ability to explicitly adjust for secular changes in reporting in the source material further justifies our usage of the registers for dementia diagnosis in this large population-based study.

Almost 30% of the cases had multiple dementia diagnoses listed over the course of disease in the registers. The most common sequence involved other dementia diagnoses later specified as either Alzheimer disease or vascular dementia. Identifying dementia subtypes with precision is known to be problematic,[25,26] especially over an extended follow-up period. We, therefore, opted for a global measure of dementia in order to avoid misclassification of dementia subtypes due to evolving diagnostic practices. It combines Alzheimer disease, vascular dementia, and other dementia. Date of onset was indicated by the first appearance of a dementia-related ICD code in the registers.

Early-Life School Performance

We used grades from the third year of elementary school (children were 9 or 10 years old) as a marker of early-life cognitive reserve. School grades have previously been shown to be associated with cognitive ability and IQ ($r \approx 0.5$) in Sweden and elsewhere,[17,19] although it should be noted that early-life school grades also may be affected by other factors, such as diligence or conscientiousness.

Grades from the following seven subjects were extracted: math, writing and grammar, speech and reading, religion studies, handwriting, local geography and history, and workbook exercises. School marks were entered as letter grades, ranging from the lowest (C) to the highest (A), with two-letter combinations (Ba) as well as additional qualifications with pluses and minuses (Ba+). We re-coded these values into a 19-point scale ranging from 0 to 18 in accordance with a scoring system suggested previously.[27] As some children were missing grades for certain subjects (mean of 0.9 subjects missing per child; range: 0−4), we calculated an overall mean score after standardizing grades in each subject individually. Within every school subject, each participant's school grade was converted into a subject-specific z-score. We then averaged z-scores across all school subjects to generate a mean school grade variable per individual. Factor analysis confirmed that a single latent factor explained much of the observed variation in the grades (first Eigenvalue: 4.26, second: 0.99),[12] justifying our decision to create a mean grades indicator. The resulting variable had a mean of 0.02 and a standard deviation of 0.74 (25th percentile: −0.50; median: −0.06; 75th percentile: 0.49; interquartile range: 0.99).

In the initial analysis, we split the continuous mean grades variable into five 20%-segments to examine performance thresholds and found that all quintiles had similar dementia risk except for the lowest fifth of the individuals (Figure S1; available online). As a result, we created a binary indicator to identify individuals with the lowest 20% of grades versus the rest of the distribution. This categorization of the grades variable was used for all subsequent analyses.

Education

Information on completed education was extracted from the 1970 census. We recoded education into three dichotomous variables to identify elementary (up to 10 years of elementary school), senior high school (up to three years of senior high school after elementary schooling), and professional/university education (any education beyond senior high school diplomas). The age range of the participants at measurement was 41−55 years, indicating that we most likely captured their lifetime education.

Occupational Complexity

Principal occupation was determined by the occupation most frequently reported across the censuses of 1960, 1970, and 1980. If an individual held different positions across three censuses, we based their principal occupation on the 1970 poll (age 41−55 years), as research indicates that improvements in occupational prestige flatten after age 40.[28] To measure work complexity, we used the matrix derived for U.S. occupations using the 1970 U.S. census.[29] Each occupation was assigned a score reflecting the level of complexity at which a typical worker functions, with Swedish occupational codes matched to the

TABLE 1. Baseline Characteristics of the Study Population and of Incident Dementia Cases Detected During an Average of 21 Years Follow-up

Characteristic	Nondemented, % (N = 6,624)	Incident Dementia Cases, % (N = 950)	p
Birth cohort			
1915–1919	21	33	
1920–1924	33	36	
1925–1929	46	31	<0.001
Sex			
Male	54	52	
Female	46	48	0.18
Elementary school grades			
Lowest grades quintile	19	22	
Top four grades quintiles	81	78	<0.05
Education			
Elementary	64	64	
Senior high school	27	28	
Professional/university	9	8	0.56
Occupational complexity with data			
High complexity	32	27	
Low complexity	68	73	<0.05
Occupational complexity with people			
High complexity	11	10	
Low complexity	89	90	0.28
Occupational complexity with things			
High complexity	32	33	
Low complexity	68	67	0.53
Family social class at birth			
Advantageous social class	42	42	
Disadvantageous social class	58	58	0.88

Notes: High occupational complexity with data corresponds to "analyzing" tasks or higher.
High occupational complexity with people corresponds to "persuading" tasks or higher.
High occupational complexity with things corresponds to "operating/controlling" tasks or higher.
Advantageous social class: high/mediate non-manuals, entrepreneurs/farmers, and skilled manuals.
Disadvantaged class: lower non-manuals, unskilled manuals in production, unskilled manuals in service, housedaughter.

best-fitting category from the U.S. using a procedure described previously.[11] Complexity of 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). Work complexity scores were not normally distributed. In accordance with others,[9] we recoded them into three dichotomized variables to denote high complexity with data, people and things.

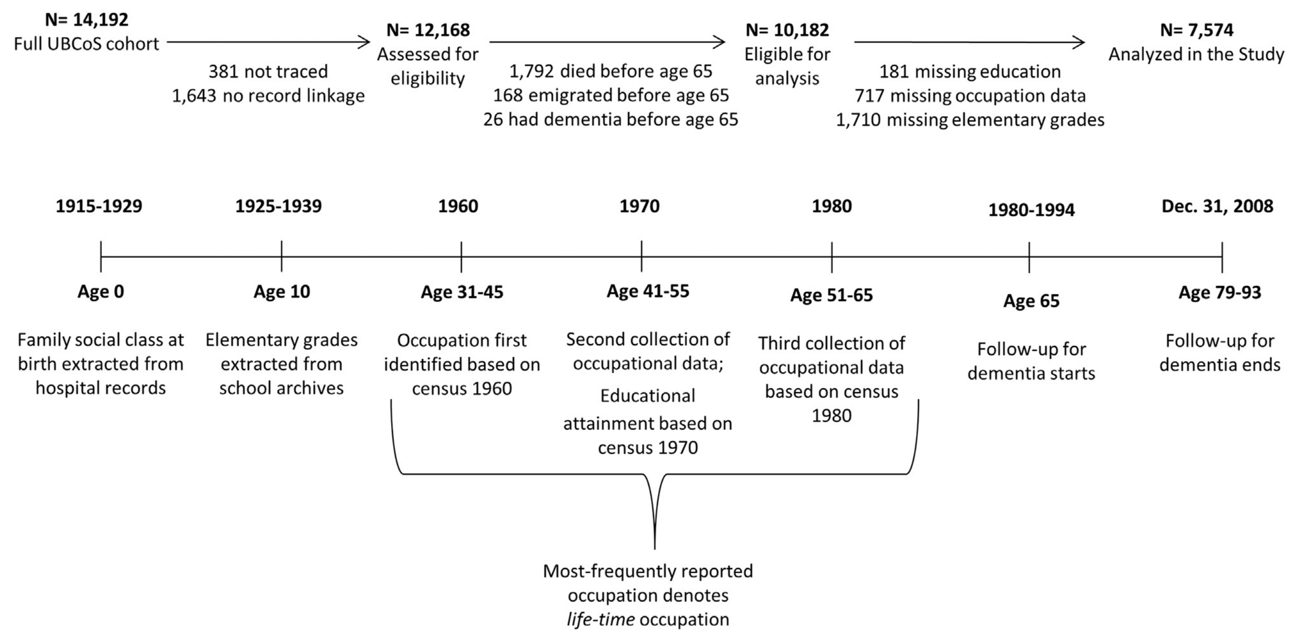
Confounders

We identified sex, birth cohort, and year of the follow-up as confounders. We also extracted information on parental social class at the time of birth to test effect modification by family status. This was based on father's occupation recorded in hospital's obstetric records and dichotomized to distinguish between advantageous and disadvantageous family social class at birth (Table 1).

Statistical Analysis

Discrete time proportional hazard models were used to estimate dementia risk associated with cognitive reserve indicators. Under discrete-time setup, each subject contributes one person-year of observation to the analysis for each age from 65 years until dementia onset, censoring, or the end of the follow-up. This arrangement allowed us to adjust for period effects associated with each year of the follow-up (1980–2008). We began by estimating bivariate associations between school grades, education, work complexity, and dementia. Then, we proceeded to mutually adjusted analyses, which progressively increased the number of reserve components estimated together. We concluded with a fully adjusted model that included childhood school grades, formal educational attainment, and occupational complexity as dementia predictors. To examine effect size of higher childhood school grades on dementia, we plotted the baseline survival curve

FIGURE 1. Study population flow. A total of 1,643 individuals with no record linkage are known to have died or emigrated before register linkage started. Dementia diagnosis extracted from the National Patient Register and the Cause of Death Register. If different occupations were reported across all three censuses, occupation during the 1970s poll is used to denote life-time occupation (applies to 20% of the analysis population).



estimated from the fully-adjusted model against the baseline survival raised to the relative risk of being in the higher school performance group. All models were adjusted for sex, year of the follow-up, and birth-cohort (5-year intervals). We then stratified the analysis by social class at birth to examine effect modification by social origin. We tested for interaction (likelihood-ratio test) between sex and early-life school grades, education, and each occupational complexity dimension. Finally, we examined the combined effect of school grades and occupational complexity on dementia. Four binary variables were generated to identify four groups depending on school grades and occupational complexity combinations over the life-course (low grades/low complexity, low grades/high complexity, high grades/low complexity, and high grades/high complexity). A proportional hazard model was estimated to obtain the effect of belonging to one of the three groups (reference category: low grades/low complexity).

RESULTS

Average follow-up time was 21 years, with the youngest individuals aged 79 years and the oldest aged 93 years at the end of follow-up (Fig. 1). During the follow-up, 950 participants developed dementia (12.5%).

Individuals with non-missing information (N = 7,574) and those excluded due to missing data on covariates (N = 2,608) differed significantly ($p < 0.001$) with respect to social class at birth. The proportion born to parents of top social origin was higher among the excluded group (12%), than among the analysis population (7%). This is due to untraced grades being more common among children from higher socioeconomic status families, because of weaker data availability for private schools. Sex differences were also significant ($p < 0.001$), as the proportion of women was higher among the excluded because women are overrepresented among those with missing occupational information, likely due to being housewives.

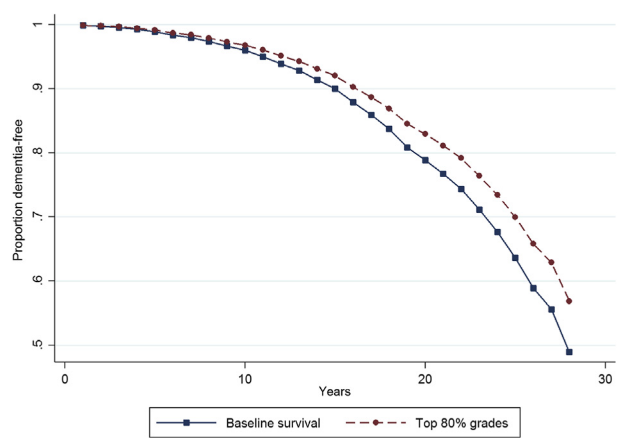
TABLE 2. **Effects of Grades, Education, and Occupational Complexity on Dementia. Discrete Time Cox Proportional Hazard Model**

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7
School grades							
Top 80% vs. bottom 20%	0.76*** (0.65 to 0.89)			0.78** (0.67 to 0.91)	0.78** (0.66 to 0.92)		0.79** (0.68 to 0.93)
Education							
Elementary		1 (Ref.)		1 (Ref.)		1 (Ref.)	1 (Ref.)
Senior high school		0.90 (0.78 to 1.04)		0.91 (0.79 to 1.06)		0.94 (0.81 to 1.09)	0.95 (0.82 to 1.10)
Professional and university		0.77* (0.60 to 0.97)		0.80† (0.63 to 1.02)		0.83 (0.63 to 1.10)	0.87 (0.66 to 1.15)
Occupational complexity							
High with data vs. low			0.72*** (0.61 to 0.86)		0.74*** (0.62 to 0.89)	0.74** (0.62 to 0.89)	0.75** (0.63 to 0.91)
High with people vs. low			1.12 (0.87 to 1.44)		1.12 (0.86 to 1.45)	1.19 (0.90 to 1.57)	1.17 (0.89 to 1.55)
High with things vs. low			1.08 (0.94 to 1.25)		1.08 (0.94 to 1.25)	1.08 (0.93 to 1.25)	1.08 (0.93 to 1.25)

Notes: 7,574 individuals and 950 dementia cases. Adjusted for calendar year during follow-up (1980–2008), birth cohort (5-year intervals), and sex.
*p <0.05.
**p <0.01.
***p <0.001.
†p <0.1.

Participants in the top 80% of childhood school performance were at a lower risk of dementia (hazard ratio [HR]: 0.76; 95% confidence interval [CI]: 0.65 to 0.89) than those in the worst-performing quintile (Table 2, model 1). Although senior high school was not protective against dementia relative to elementary education, subjects who continued to professional or university schooling experienced a significant reduction in dementia risk (HR: 0.77; 95% CI: 0.60 to 0.97, Table 2, model 2). Complexity with data was the only dimension of occupational complexity which significantly reduced dementia risk (HR: 0.72; 95% CI: 0.61 to 0.86, Table 2, model 3). This finding was unchanged when each dimension was tested individually. We found no interactive effect of sex with childhood school grades (p >0.05), education (p >0.05), or with any of occupational complexity domains (p >0.05). We found no evidence of effect modification by social class at birth, as the pattern of results was unchanged among children of advantageous and disadvantageous social backgrounds (not presented). We replicated the analysis after assigning women with missing occupational information, whom we suspected to be housewives, a complexity score for "other housekeeping work". Results remained unchanged (not presented).

FIGURE 2. Proportion of participants who remain dementia-free according to baseline survival and exposure to childhood school grades. The *baseline-survival curve* (straight line) is based on the baseline survival estimates obtained from the fully adjusted Cox proportional hazard model (Table 2; model 7). The *top 80% grades* survival curve is based on the baseline survival estimates raised to the relative risk of the higher school grades variable from the fully-adjusted model (Table 2; model 7). Grades from the seven school subjects are standardized and averaged into an overall third-grade mean.



Reserve Over the Life-Course

In the mutually adjusted models, we examined whether childhood school performance, formal education, and lifetime occupational complexity independently predicted dementia risk. Three findings emerged (Table 2). First, the protective effect of childhood school performance remained statistically significant upon gradual adjustment for education (model 4), occupational complexity (model 5), and in a fully adjusted model (model 7: HR: 0.79; 95% CI: 0.68 to 0.93). Second, high data complexity remained the only dimension of occupational complexity associated with a reduced risk of dementia in a fully adjusted model (HR: 0.75; 95% CI: 0.63 to 0.91, model 7). Finally, although the protective effect of highest educational attainment remained marginally significant upon adjustment for childhood school grades, it vanished once occupational complexity was taken into account (model 6). In a fully controlled model (model 7), we found no statistically significant differences in dementia risk across educational groups, whereas complexity with data and childhood school grades preserved statistically significant protective effects.

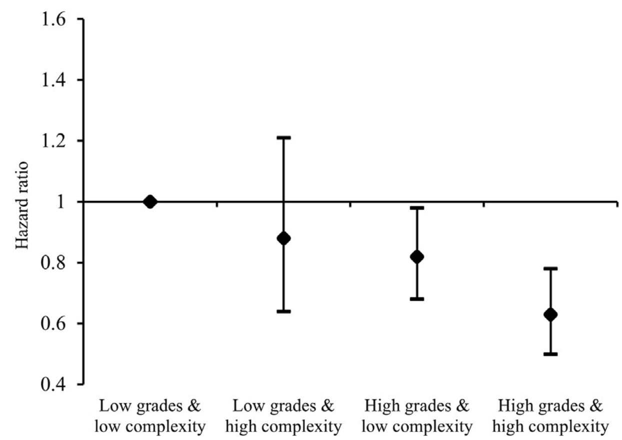
To assess the effect size of higher childhood school grades estimated from the fully adjusted model (Table 2, model 7), we examined the difference between the proportion of participants who remain dementia-free over the follow-up according to baseline survival estimates, and the proportion of disease-free individuals with higher school grades (Fig. 2). To do that, we re-estimated the fully adjusted model to obtain the estimates of baseline survival. Next, we raised the baseline survival estimates to the relative risk of having higher childhood school. By plotting the two survival curves (one for baseline survival, and one for the exposed group), we can visually examine the differences in the proportion of participants who remain dementia-free over the follow-up period.

As seen in Figure 2, the effects of childhood school performance emerge by approximately 10 years of the follow-up and expand afterwards. By 19 years of follow-up, the proportion of dementia-free participants is 4% greater in the exposed group relative to the estimates of baseline survival based from the fully adjusted model. By the end of the follow-up period, the proportion of dementia-free individuals in the top 80% of school performers is close to 60%, whereas based on the baseline survival estimates, this proportion should be just under 50% in the entire population.

Grades−Work Complexity Combinations

We examined how dementia risk was influenced by childhood school grades and occupational complexity with data, as previous analysis indicated that these were the only reserve components associated with dementia risk in the fully adjusted model. Four combinations of school grades and data complexity were constructed and examined in a single model (Fig. 3). Relative to the low−low combination, dementia risk was not significantly different for the combination of low childhood school performance and high data complexity (HR: 0.88; 95% CI: 0.64 to 1.21). It was, however, significantly lower for the combination of higher school performance and low data complexity (HR: 0.82; 95% CI: 0.68 to 0.98). The greatest protection was enjoyed by those with both higher childhood school performance and high occupational complexity with data (HR: 0.63; 95% CI: 0.50 to 0.78). The parameter estimate for the combination of higher childhood school performance and low work complexity was statistically different from that of higher childhood school performance and high work complexity ($p < 0.01$).

FIGURE 3. **Combined effect of childhood school performance and work complexity with data on dementia risk. Adjusted for calendar year during follow-up (1980−2008), sex, birth cohort (5 years), and education. Occupational complexity dichotomized as "analyzing"/higher versus rest. Childhood school performance dichotomized as lowest grades quintile versus rest. Reference group: low grades and low occupational complexity with data. Low grades + high complexity HR: 0.88 (95% CI: 0.64 to 1.21). High grades + low complexity HR: 0.82 (95% CI: 0.68 to 0.98). High grades + high complexity HR: 0.63 (95% CI: 0.50 to 0.78). Wald test H_0: high grades + high complexity = high grades + low complexity: χ^2 [1 df] = 7.71; $p < 0.01$.**



DISCUSSION

After an average of 21 years of follow-up of 7,574 participants, we found that dementia risk was lower among individuals with higher childhood school grades. We also found that high occupational complexity with data, but not with people or things, reduced the risk of dementia. Although the effects of higher education were protective after adjustment for childhood school performance, they disappeared after controlling for work complexity. Finally, the lowest risk of dementia was found in individuals who leveraged higher childhood school grades into complex occupational roles in adulthood.

The link between childhood school grades and dementia is consistent with literature linking early-life cognitive ability with late-life cognitive decline and dementia.[14,15,30−33] In accordance with the cognitive reserve theory, children with low early-life grades may have lower brain network efficiency or flexibility, making them more vulnerable to dementia pathology. Childhood school performance likely reflects properties of the central nervous system, such as processing speed and capacity, which could affect the rate of decline associated with age and mitigate the impact of pathology on the clinical development of dementia.[31,34] There is also evidence of functional reorganization, among the elderly, of those neural networks used by the younger persons to complete the same cognitive task.[35] This suggests that a compensatory network is used to maintain function in the face of age-related physiological changes—and early-life school performance might be an early indicator of the extent to which this functional reorganization will be successful.

An alternative explanation could be that low childhood school performance affects adult health behaviors and outcomes, which are then implicated in dementia risk.[36] Individuals with poor school grades may have difficulties in accessing health services, exposing themselves to otherwise preventable conditions, such as heart disease and stroke—established correlates of dementia.[37,38] Thus, one study has shown that lower childhood cognitive ability predicted higher risk of vascular dementia, but not Alzheimer disease, pointing to potential mediation by mid-life vascular risks.[39] On the other hand, it has been reported in three longitudinal studies that greater reserve did not protect against developing neurodegenerative and vascular neuropathology, although it did diminish the impact of pathology on the clinical expression of dementia before death,[34] highlighting neural efficiency and compensation pathways.

Protective effects of educational attainment on dementia have been reported in several previous studies.[40] We replicated these findings in a minimally adjusted model with education as a single predictor of dementia, as well as upon adjustment for early-life school grades. Hence, childhood school performance and formal educational attainment each exert protective effects on dementia risk. We also found, however, that protective effects of education disappeared once occupational complexity was adjusted for, suggesting that more advanced education has to be leveraged into complex occupational roles in order to protect against dementia. Comparable findings were reported previously when supervisory roles were found to outweigh the effects of education on dementia,[13] or when protective effects of education on the odds of cognitive impairment were found to be diluted upon adjustment for occupational complexity with data.[41]

Therefore, education and occupational complexity might be connected by the mechanisms of a "use it or lose it" model,[42] in which protection warranted by education is realized only when supplemented by continuing mental activity that draws on these reserves. It has been suggested that cognitive demands of complex occupations may be more important for the long-term development of dementia than education alone.[43] A neuroimaging study has echoed this conclusion by demonstrating that mid-life occupational complexity had a stronger impact on gray matter integrity than education.[44]

Consistent with previous literature on occupational complexity and dementia,[45,46] we found that participants in data-intense occupations were at a lower risk of dementia. This is in line with a model of cognitive reserve whereby continuous intellectually demanding activities lead to a preservation of cognitive abilities.[45] We did not, however, find reliable effects of high complexity with people or things. With respect to things complexity, both protective and damaging effects have been reported previously.[9–11] This dimension could reflect heightened exposure to adverse labor conditions, occupational hazards, or toxins—and some studies reported an elevated risk of dementia in individuals working in predominantly manual occupations.[47,48] Lack of protective effects of occupational complexity for people in our study is in contrast with some,[9,11] but not all,[49] previous studies. The mechanisms through which people-intense occupations might protect against dementia are still largely unknown,[43] and further research is needed to clarify the link between dementia and occupational complexity with people.

As information technology has reshaped the landscape of modern occupational roles, making data-intense workplaces much more prevalent, the beneficial effect of work complexity with data on dementia is enjoyed by a much wider proportion of population today than 30–50 years ago. As data-intense occupations become even more common in the future, occupational complexity in the context of dementia should become even less of a dividing factor across individuals. This does not mean that protection due to data complexity will wane—it is just that nearly everyone will be able to extract these benefits.

Our key finding is that the establishment of reserve which mitigates the impact of pathology on the clinical expression of dementia is a life-long process that begins early in life. We demonstrated that the greatest protection against dementia is extended to those who leverage better school performance in childhood into demanding occupations in adulthood, confirming synergetic properties of reserve over the life course.[50] Crucially, those with higher early-life school grades, but who lack later-life stimulation in the form of high occupational complexity, are nevertheless able to extract protection from higher reserve. It appears that cognitive development in the very early stages of the life course (possibly together with innate prerequisites for cognitive reserve) is of greater significance for the risk of dementia than later-acquired or enhanced reserve capacity in the form of education or occupational complexity in our cohort. Later-life engagement in stimulating activities does, however, have a protective effect on dementia, and from an interventions standpoint, it might be unwise to refrain from efforts aimed at expanding educational opportunities or promoting continuous engagement in intellectual activities, especially if interventions for this older cohort are considered. At the general population level, however, interventions at modifiable factors, such as poverty, nutritional deficiency, or psychosocial disadvantage, which prevent infants and children from attaining their developmental potential, should also be promoted, as they could help postpone the incidence of neurodegenerative disorders in late life.

Limitations

This study may have missed dementia cases due to low sensitivity in the registers—although we are confident about high specificity (i.e., 98%) of diagnoses.[20] Systematic under-reporting of dementia that could be linked to exposures analyzed in this study is unlikely, considering that access to health care is universal and highly subsidized in Sweden.[51,52] If under-reporting of dementia diagnoses in the registers is nonsystematic, the resulting risk estimate should only be diluted. Furthermore, if low sensitivity is coupled with high specificity, then no bias of the risk estimate is introduced.[53] Consequently, it has been argued that the quality of dementia recording in the Swedish National Patient Register is acceptable when used in combination with the Cause of Death Register.[20] In order to adjust our estimates for the change in diagnostic techniques and dementia awareness between 1980 and 2008 we used discrete-time survival models, controlling for the period effects associated with each year of the follow-up.

Lacking an explicit measure of cognitive ability, we analyzed school grades at age 10 years. These constructs are correlated ($r \approx 0.5$)[17,19] and we have previously shown that grades are associated with other indicators of low cognitive ability such as being kept back in school or having a recognized learning difficulty.[54] Moreover, our factor analysis of the raw school grade variables indicated that a single latent factor explained most of the variation in school performance.[12] Nevertheless, we recognize that teacher-assigned grades might be influenced by factors other than students' intelligence and, therefore, refrain from equating childhood school grades with cognitive ability. Brain development between conception and age 10 years could also affect childhood school grades,[55,56] although this would fit our conclusion that the development of reserve in dementia risk is a life-long process that begins early in life.

We could not determine occupation for 717 participants, 98% of whom were women. In a sensitivity analysis, we assigned these suspected housewives a complexity score for paid housework. Because our main results remained unchanged, these participants were excluded from final analysis to avoid misclassification.

CONCLUSION

In the first study in which the simultaneous effect of childhood, early adulthood, and mid-life indicators of cognitive reserve were examined, we found that low childhood school performance increased dementia risk, and that the increased risk could not be mitigated by high education or complex work environments in adulthood. This study highlights the importance of early-life school performance, particularly when preserved through intellectually demanding work environments in later life, although this early-life reserve is protective even in the absence of later-life occupational stimulation. The formation of cognitive reserve that helps mitigate the impact of pathology on the clinical expression of dementia appears to be a life-course process that already begins early in life.

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The authors declare no conflicts of interest.

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