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Differences in cognitive function at 18 y of age explain the association between low education and early dementia risk

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Major initiatives attempt to prevent dementia by targeting modifiable risk factors. Low education is frequently pointed to, due to its relationship with dementia. Impact of education is difficult to assess, however, because of associations with multiple other factors, requiring large population-representative samples to tease the relationships apart. We studied 207,814 Norwegian men born between 1950 and 1959 who underwent compulsory cognitive testing during military conscription as young adults, to systematically test associations of education, cognition, and other important factors. Participants were grouped into five education levels and seven cognitive levels. A total of 1,521 were diagnosed with dementia between ages 60 and 69 y. While having compulsory education only was associated with increased risk (Hazard ratio [HR] = 1.37, CI: 1.17 to 1.60), this association was markedly attenuated when controlling for cognitive test scores (HR = 1.08, CI: 0.91 to 1.28). In contrast, low cognitive score was associated with double risk of later diagnosis, even when controlling for education (HR = 2.00, CI: 1.65 to 2.42). This relationship survived controlling for early-life socioeconomic status and replicated within pairs of brothers. This suggests that genetic and environmental factors shared within families, e.g., common genetics, parental education, socioeconomic status, or other shared experiences, cannot account for the association. Rather, independent, nonfamilial factors are more important. In contrast, within-family factors accounted for the relationship between low education and diagnosis risk. In conclusion, implementing measures to increase cognitive function in childhood and adolescence appears to be a more promising strategy for reducing dementia burden.

education | cognition | dementia

Lower education is associated with increased dementia risk (1). Consistent with a view of education as a causal protective factor, dementia incidence has declined as educational attainment has increased (2), and the association does not appear to reflect differences in life-style factors, general somatic or psychiatric health, or known genetic risks (3–5). The Lancet commission for dementia prevention holds that 7% of cases could be avoided by targeting low education, placing it second on the list of modifiable risk factors (6). Research using schooling reforms as natural experiments has suggested causal effects of education on later-life cognition (7), but whether this translates to lower dementia risk has been questioned (8).

A popular hypothesis holds that education reduces dementia risk by increasing cognitive reserve, allowing highly educated persons to sustain more brain pathology without cognitive decline (9, 10). Consistent with this view, education does not protect against the development of neuropathology (11). An alternative hypothesis focuses on the relationship between education and cognitive function. If low education on average reflects lower earlier life functioning, baseline cognition is closer to the functional threshold of a dementia diagnosis. As a result, age-expected cognitive decline will lead to diagnosis at earlier ages for those with low education, without necessarily being associated with more or faster decline. Accordingly, low cognitive scores for males tested at military conscription were associated with higher dementia risk decades later (12–14), and the association was only partly accounted for by family factors (14). Similar relationships exist for women (15). Education could not explain the increased risk in these studies, but education has also been reported to account for the relationship between cognitive function and later dementia (16).

The question of whether the association between education and dementia exists independently of earlier cognitive function speaks directly to the potential causal impact of education. Here, we tested whether cognitive function from military conscription could account for increased early dementia risk with low education. 207,814 men in the age range 60 to 69 y born in Norway between 1950 and 1959, with cognitive test scores (17) from compulsory military conscription and dementia diagnoses from health registries, were studied, yielding 77.4% population coverage. To place dementia diagnosis risk in context, we also mapped the life-course trajectories of main life-events, such as employment and mortality, as functions of earlier-life cognitive scores. Patients

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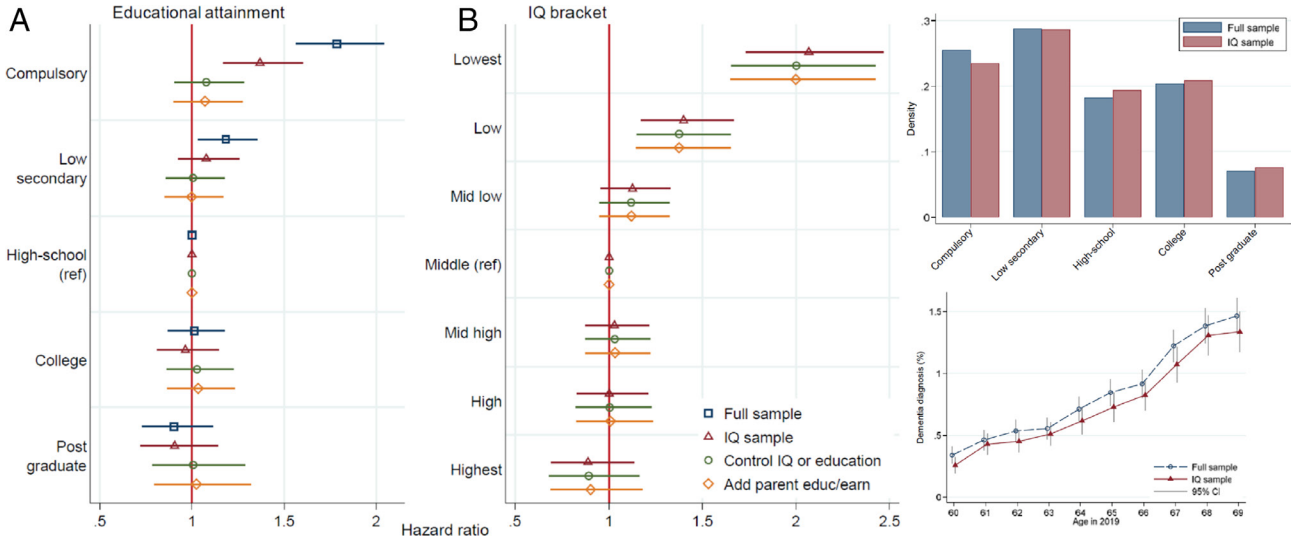

Fig. 1. (*A*) HR for dementia diagnosis with level of education, high school as reference. Blue squares: baseline model, complete sample; maroon triangles: baseline model, sample with IQ score; green circles: controlling for IQ; orange diamonds: additionally controlling for parental education/income. (*B*) HR for diagnosis with level of cognition: maroon triangles: baseline model; green circles: controlling for education; orange diamonds: additionally controlling for parental education/income. Error bars denote 95% CI. *Right top*: Distribution across educational categories. Blue: full sample (n = 268,614), maroon: sample with cognitive scores (n = 207,814). *Right bottom*: Percentage with dementia diagnosis. Blue circles: full sample, maroon triangles: sample with cognitive scores. Vertical bars denote 95% CI.

with relatively early dementia represent an important and understudied group with substantial reduction in years of healthy living. Although the genetic component is important, familial autosomal dominantly inherited Alzheimer's disease (AD) accounts for a small proportion of all early-onset cases (<0.1%) and other genetic and environmental factors need to be considered (5, 18).

Results

The correlation between education level and cognitive test scores was r = 0.60. Participants were categorized into five educational and seven cognitive levels, with the middle category of each as reference. A total of 1,521 participants (0.73%) with available cognitive scores were diagnosed with dementia between ages 60 and 69 y. Cox Proportional Hazards Model showed that low education was associated with higher risk of dementia diagnosis in the sample with cognitive scores (Hazard Ratio [HR] = 1.37, 95% CI: 1.17 to 1.60, $P < 0.001$), see Fig. 1. No other education group differed significantly in risk from the reference group. Results for the full population are included for comparison. Controlling for cognitive scores markedly attenuated the association so it was no longer significant (HR = 1.08, CI: 0.91 to 1.28, $P = 0.40$). The two lowest cognitive categories showed increased risk even when controlling for education (lowest: HR = 2.00, CI: 1.65 to 2.42, $P < 0.001$; second lowest: HR = 1.37, CI: 1.15 to 1.65, $P = 0.001$) and early-life socioeconomic status (parental education and income).

Linear probability models yielded similar results. There was no attenuation of effects when using within-family variation in cognitive score to predict risk. In the baseline model, the point estimate of dementia prevalence in the lowest score category is 0.70 percentage point (95% CI: 0.55 to 0.86) higher than that in the reference category, compared to 0.90 percentage point (CI: 0.50 to 1.30) in the model with family fixed effects. For education, the point estimate for the lowest educational category relative to high school level (reference category) is 0.22 percentage points (CI: 0.11 to 0.33) in the baseline model compared to 0.05 (CI: −0.23 to 0.33) in the model with family fixed effects, suggesting that within-family factors can account for the relationship.

Life-events were mapped as a function of cognitive scores (Fig. 2). The lowest cognitive category was associated with a steep reduction in employment, from ~90% at age 30 y to ~50% at 60 y. Disability increased from <20% to ~50%, and they had fewer children, were less often married, and had a sharper increase in mortality. The second lowest category showed the same tendencies to a lesser extent.

Discussion

Increased early dementia risk associated with low education was markedly attenuated in this sample when controlling for earlier cognitive function. In contrast, low cognitive function was a risk factor even when correcting for education. Although education prior to the age at testing could affect scores (19) and hence reduce risk, the risk for cognition was not weakened when education was accounted for. Within-family variation in cognitive ability showed the same association to early dementia diagnoses. This means that factors shared within families, such as sibling-shared genes, socioeconomic status, parental education, or other shared family experiences, could not account for the findings. In contrast, shared family genetic or nongenetic factors could explain the risk associated with low education. The results underscore the importance of taking factors associated with cognitive function in early adulthood into account for later-life diagnoses (20).

These patterns are consistent with different interpretations. Individuals with low cognitive ability may already be closer to a functional threshold and thus likely to meet dementia criteria earlier following normal age-related decline. This is in accordance with findings that education is associated with level of cognitive function but not different decline (21). The lowest cognitive category, similar to IQ < 79, had double risk of early dementia diagnosis. Here, age-normative loss of function can be detrimental for daily life function. This is mirrored in the employment rate for this group, declining from ~90% in young adulthood to ~50% at age 60 y, compared to ~75% for the second lowest category at this age. Accordingly, while low function was a risk, high function was not protective compared to the reference group.

An alternative explanation is that people with various levels of intelligence engage in different activities and get exposed to events and environments which influence dementia risk via various

Fig. 2. Life-events as a function of cognitive scores.

pathways, such as occupation, income, health, and family. Low cognitive level was indeed associated with deviating trajectories of important life events. However, controlling for several such factors do not remove the risk (12, 22). A third theory is that cognitive level is an indicator of "system integrity", reflecting how well the system is "put together" (23). Lower abilities may signify a vulnerable system, in line with the increased mortality rates. This may partly reflect earlier and even prenatal events (24, 25), affecting cognitive function and risk for later disease.

Important considerations include that associations with education will vary across time and societies (26). Further, only men were studied, and results may differ for women. A high share of all cases of dementia is never diagnosed, possibly affecting the associations. The sample was relatively young, and other associations could be observed in samples with higher dementia prevalence or for late-onset dementia. Relatedly, we could not distinguish between dementia types. Nevertheless, the results align with recent findings that brain atrophy is not related to education (27) but to cognitive function independently of education (28). Relationships between cognition and brain structure are established early (29) and are unlikely to be heavily influenced by education. Furthermore, genetic evidence converged on cognitive function having an independent effect on dementia risk, while the association with education is driven by cognition (30, 31). Hence, the present results are in accordance with recent neuroscientific and genetic evidence, indicating that suggestions of education per se being a modifiable risk factor may be overly optimistic (6).

Materials and Methods

Ethical approval by the Regional Committees for Medical and Health Research Ethics (Approval No. 2018/434). Cognitive scores are aggregated across three speeded tests of arithmetic, word similarities, and "Raven-like" figures. Cox proportional hazard models were used for the main analyses, and linear probability models for family fixed effects, using Stata 17.0.

Data, Materials, and Software Availability. Some study data available [Data used are Norwegian registry data. Health and conscription registry data can be requested from https://helsedata.no/, while data on education, earnings, disability pension, and family can be requested from Statistics Norway (https://www.ssb.no/en/data-til-forskning/utlan-av-data-til-forskere)].

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