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Original Contribution

Does Prolonged Education Causally Affect Dementia Risk When Adult Socioeconomic Status Is Not Altered? A Swedish Natural Experiment in 1.3 Million Individuals

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Intervening on modifiable risk factors to prevent dementia is of key importance, since progress-modifying treatments are not currently available. Education is inversely associated with dementia risk, but causality and mechanistic pathways remain unclear. We aimed to examine the causality of this relationship in Sweden using, as a natural experiment, data on a compulsory schooling reform that extended primary education by 1 year for 70% of the population between 1936 and 1949. The reform introduced substantial exogenous variation in education that was unrelated to pupils' characteristics. We followed 18 birth cohorts (n = 1,341,842) from 1985 to 2016 (up to ages 79–96 years) for a dementia diagnosis in the National Inpatient and Cause of Death registers and fitted Cox survival models with stratified baseline hazards at the school-district level, chronological age as the time scale, and cohort indicators. Analyses indicated very small or negligible causal effects of education on dementia risk (main hazard ratio = 1.01, 95% confidence interval: 0.98, 1.04). Multiple sensitivity checks considering only compliers, the pre-/post- design, differences in health-care-seeking behavior, and the impact of exposure misclassification left the results essentially unaltered. The reform had limited effects on further adult socioeconomic outcomes, such as income. Our findings suggest that without mediation through adult socioeconomic position, education cannot be uncritically considered a modifiable risk factor for dementia.

Alzheimer disease; causal estimation; compulsory schooling; dementia; education reform; natural experiments

Abbreviations: CI, confidence internal; HR, hazard ratio.

Prevention of dementia by taking action on modifiable risk factors is of key importance, since progress-modifying treatments are not currently available (1). Meta-analyses of observational studies have identified low educational level as a major risk factor for dementia (2, 3), with every additional year of education estimated to lower the risk of dementia by 7% (4). The magnitude of the association indicates that low education may be the second most important modifiable risk factor for dementia (1).

The clear correlation between education and dementia does not necessarily imply a causal relationship. Much of the evidence comes from observational studies, which can be confounded by (for example) early-life cognitive ability or socioeconomic background. Therefore, before concluding that low education is a modifiable risk factor for dementia, a causal effect of education on dementia risk must be explicitly determined. This was the primary aim of our study.

Natural experiments, such as reforms of compulsory schooling that affect educational attainment, can be used to estimate causal effects thanks to lower risk of confounding (5, 6). We adopted this approach and exploited spatial and temporal variation in education (Figure 1) introduced by a Swedish schooling reform that prolonged the duration of mandatory primary schooling (Folkskola) from 6 years to 7 years. To our knowledge, no previous studies using compulsory schooling reforms have investigated the causal effects of education on actual dementia diagnosis. The studied reform was implemented over a period of 13 years

Figure 1. Temporal and spatial distribution of a 1936 educational reform imposing an additional year of compulsory primary schooling in Sweden. The geographical units shown are parishes, which generally corresponded to the historical school districts. Gray shading indicates parishes that introduced the reform during the period 1936–1941 (A), 1942–1947 (B), or 1948–1953 (C). The date of introduction of the reform in a given parish was derived from historical standardized examination catalogs from 280 archives across Sweden. Rural and small school districts in the middle west and sparsely populated districts in the north, with the exception of the northernmost county (Norrbotten), implemented the compulsory schooling extension at the latest possible date (1949) or, in some rare exceptions (1.7% of school districts), even delayed its introduction. The southernmost region of Scania shows almost no reform implementation after 1936, since most southern school districts had already voluntarily introduced a mandatory seventh grade year before the national reform. Geographical data for mapping were obtained from the Swedish Mapping, Cadastral and Land Registration Authority (Lantmäteriet).

(1936–1949) across 2,463 school districts. With 70% of students attaining only a primary education at that time, the reform substantially increased education for a majority of the Swedish population (7). In detailed historical analyses conducted previously (7), we did not identify any threats to the assumption that the reform was exogenous to the individual.

Many plausible mechanisms behind causal effects of education on dementia have been proposed on the basis of associations from observational studies (8). For example, a longer duration of education may act through cognitive stimulation (i.e., a cognitive pathway). Prolonged education has been shown to causally affect intelligence (9–11) and thus raises the level of cognitive abilities. If such effects are maintained through adult life, the threshold for dementia diagnosis may be reached at a later age (12, 13). However, the possible timing and length of education needed to observe an effect on dementia (threshold effects) remain unknown. Some observational studies have indicated an association of only primary education with dementia (14),

while other researchers have reported benefits mainly for persons with postsecondary and university education (15). However, a dose-response meta-analysis (4) indicated that prolonging education at any stage is associated with decreased risk of dementia.

Effects of education on dementia could also act via life-course socioeconomic trajectories (i.e., socioeconomic pathways). For example, prolonged education often alters mid- and later-life socioeconomic conditions, such as income, wealth, or occupation. Observational studies examining education and other later-life socioeconomic factors provide mixed findings regarding the socioeconomic pathway. Dekhtyar et al. (15) reported that educational attainment no longer mattered when occupational complexity was taken into account, implying that leveraging educational attainment through socioeconomic pathways (i.e., occupational complexity) is needed to protect against dementia. However, other studies show an association even after adjustment for later-life socioeconomic factors, indicating that pathways other than the socioeconomic also matter. Overall, there are many other plausible midlife factors that may be mediators on the causal pathway, such as spare-time cognitive activity, health, lifestyle, or access to health care (8, 12), and they are correlated. In summary, evidence regarding both causality and mechanisms of the examined relationship is unclear.

We aimed to provide evidence regarding 1 specific causal pathway behind the effects of education on dementia. When studying compulsory schooling reforms, it is typically difficult to disentangle the pathways of effects, since the reforms often come with several changes (5, 8, 16). However, the Folkskola reform resulted in very small effects on adult socioeconomic outcomes, such as continued education, income, and pensions, in our previous analyses (7, 17). Thus, in the current study, we primarily examined effects of education not mediated through socioeconomic outcomes (henceforth referred to as direct effects). Specifically, we examined the effect of prolonging education by 1 year at age 13 years on risk of dementia at age ≥65 years. We believe that our estimate most closely captures the early-life cognitive stimulation mechanism. We also used 2 educational measures (years of education and highest level of education achieved) for a complementary examination of the observational association.

METHODS

Study design and setting

We conducted a register-based cohort study exploiting linkage of pseudonymized data between several health registers and previously identified (7, 17) exposure to reform of an old type of Swedish primary schooling, Folkskola. The study was approved by the Regional Ethical Review Board in Stockholm. The study-specific analysis was preregistered (18).

Participants

The study's target population was 18 full birth cohorts (1920–1937) of Swedish-born individuals. We excluded persons who died, emigrated, or received a dementia diagnosis prior to reaching their 65th birthday. People from geographical areas where reform exposure could not be determined were also excluded (see Web Figure 1, available at https://doi.org/10.1093/aje/kwaa255).

Exposures

The Folkskola reform. We have described the Folkskola reform in detail elsewhere (7, 17). In short, in the late 19th century, all Swedish children started 6-year primary schooling (Folkskola) during the year in which they reached 7 years of age. Education was free of charge and attendance high. Prior to 1936, most Swedish children (70%) completed only primary schooling, which was compulsory. In 1936, the Swedish parliament passed a bill enforcing the introduction of a seventh year of compulsory schooling by 1949. Lack of time to cover the full primary-school curriculum was the main motive for the reform. Implementation of the reform affected children at the age of 13 years and took place at the local level; thus, an extra school year was gradually introduced across 2,463 school districts. Our previous analyses showed that compliance was high, resulting in substantial shifts in educational attainment. The reform resulted in an average increase of 0.7 years of education but had very small effects on later-life socioeconomic factors, such as continued education, income, and pensions (7, 17).

Reform changes and exogeneity. The reform did not come with any other changes to the school system, such as introduction of new subjects or changes in tracking to secondary education, and thus did not affect classroom composition. Salaries for teachers were covered by the central government and not individual school districts, and there was an oversupply of teachers at the time. Sweden was neutral during the Second World War, which subsequently did not cause any major disruptions, particularly not in ways related to the timing and geographical spread of the reform. Therefore, we did not identify any threats to the assumption that the reform was exogenous to the individual.

Reform exposure assignment. Information on the timing of the reform implementation at the local level was derived manually from historical standardized examination catalogs from 280 archives across Sweden. High data coverage was reached, with 98% of the 2,463 school districts included. We used these data and parish of residence at birth (which typically overlapped with school district) from Swedish registers to assign reform exposure.

There are some possible reasons for misclassification of reform assignment. First, children may change residences between birth and school age. Using external data on the 1930–1934 birth cohorts, we estimated such residential mobility to be approximately 13% (17). Second, some children born in hospitals may have the hospital parish recorded as the place of birth rather than the actual place of residence. The subsequent misclassification was estimated to be 12%. Therefore, the overall misclassification could have amounted to 25% (12% + 13%). According to an empirical examination, only one-third (approximately 8.3%) of the misclassifications resulted in an actual change of

exposure status, because children could move to a school district that had the same length of schooling as the one they were born in. To further demonstrate the robustness of our results, we excluded birth cohorts born in parishes where a hospital opened in a sensitivity analysis.

Complementary measures of educational achievement. We used 2 educational measures for a complementary examination of the observational association between education and dementia. First, highest level of achieved education was derived from 1970 census data and was converted to Swedish educational classification codes (SUN2000), which resemble codes used in the International Standard Classification of Education (ISCED 1997). The empirical analysis used 3 categories: primary education, at least some secondary education, and at least some university education. Second, duration of education (in years) was derived by combining information from census data regarding length of primary and secondary schooling and length of postsecondary education (7).

Outcome

Dementia diagnoses were identified in the National Inpatient Register and the Cause of Death Register using *International Classification of Diseases* codes (*International Classification of Diseases, Tenth Revision*, codes F00.0, F00.1, F00.2, F00.9, F01.0, F01.1, F01.2, F01.3, F01.8, F01.9, F02.0, F02.3, F03.9, G30.1, G30.8, G30.9, G31.1, and G31.8A; *International Classification of Diseases, Ninth Revision*, codes 290, 249B, and 331A). The study individuals were followed from 1985 to the end of 2016. A person was classified as having dementia if any available diagnosis for hospitalization or death, main or supporting, contained a relevant code (19). The onset of dementia diagnosis was approximated by the earliest date of hospitalization or the date of death. Such operationalization of timing does not capture the true onset of the condition, which probably occurs years prior to hospitalization or death.

Statistical analysis

We used Cox proportional hazards models for estimating the causal effect of education on the risk of dementia diagnosis. We fitted 2 sex-stratified models and 1 sex-adjusted model for the entire sample. Chronological age was used as the underlying time scale. Individuals' follow-up started on their 65th birthday. The specification had a dummy variable for every cohort. The Cox model included stratified baseline hazards for the school district (d). This corresponds to the equation

$$\lambda_d(t|X) = \lambda_{0,d}(t)\exp(\beta_1 R_{d,c} + \beta_2 F_i + \beta_3' \boldsymbol{C_i}), \quad (1)$$

where $\lambda_{0,d}$ captures the baseline hazard, which is allowed to vary for each school district. $R_{d,c}$ indicates whether an individual was assigned to the reform based on their birth cohort c and school district d. F_i is a dummy variable for females (only in the sex-adjusted model), and $\boldsymbol{C_i}$ is a vector of birth cohort dummy variables. The β_1 coefficient measures the effect of reform on the risk of dementia and is the main estimate of interest. The overall β regression coefficients are estimated by maximizing a partial likelihood function L, which is obtained by multiplying the likelihood function for each school district. Robust standard errors were clustered at the school-district level. We had sufficient statistical power to detect a 2% change in the log hazard ratio, or a hazard ratio of 0.98 (Web Appendix 1). The proportionality of hazards assumption was examined using plots of the log cumulative hazard function, as well as statistically in the main models. There were no violations of proportionality. SAS 9.4 software (SAS Institute, Inc., Cary, North Carolina) was used for data management and Stata 15 (StataCorp LLC, College Station, Texas) for all statistical analyses.

Sensitivity analyses. Several sensitivity analyses were conducted. First, we employed the strongest possible design by creating a pre-/post- sample (Web Appendix 2) that included only school districts with both exposed and unexposed cohorts. Second, we stratified our analyses by educational tier to assess the effect of the reform with the sample limited to compliers (those attending Folkskola). There was a plurality of pathways through the educational system at the time of implementation of the reform, but about 70% of all pupils completed only compulsory education in the Folkskola, which was the reform's target (7). Consequently, the reform did not affect the entire population but only those who received this form of schooling. We hypothesized that any effect on dementia risk should have been apparent only among compliers, while those with an education higher than Folkskola (noncompliers) should not have displayed any effect, since they completed a type of schooling not targeted by the reform. Third, the probability of hospitalization might have biased our findings because we used the National Inpatient Register to identify dementia cases. Therefore, we also fitted a model adjusting for the number of all-cause hospitalizations. Fourth, exposure to the reform was assigned using parish of birth as a proxy for place of residence at the time of schooling, but in some cases the parish of the hospital rather than the parish of residence may have been registered. Thus, we excluded cohorts of people born after a hospital had been opened in their parish. Fifth, since death could be a competing risk masking the reform's effect on dementia (20), we also fitted a model with death after age 65 years as the main outcome. We hypothesized that such masking would be unlikely if the reform did not affect mortality. Finally, to investigate the possibility that the effect would set in with a delay or be driven by spurious cohort trends, we fitted a model including lag times and lead times for the effect of the reform indicator on dementia risk. Additional sensitivity analyses included post-hoc specifications of the model to include an interaction between an indicator of urban location and birth cohort (urban × birth cohort), since urban regions were more likely to implement the reform early.

Observational analysis. Additional Cox proportional hazards survival models were used to estimate the observational association between duration of education (in years)

Table 1. Characteristics of Study Participants Followed Up for Dementia in the National Inpatient Register and the Cause of Death Register From 1985 to 2016, by Sex, Sweden

Variable	Men (n = 652,623)			Women (n = 689,219)		
	No.	%	Mean (SD)	No.	%	Mean (SD)
Dementia diagnosis						
Either source	80,538	12.34		112,100	16.26	
NIR	64,999	9.96		87,120	12.64	
CDR	48,335	7.41		69,390	10.07	
Exposed to Folkskola reform	361,547	55.40		379,224	55.02	
Highest level of education attained						
Compulsory schooling	405,793	62.18		497,975	72.25	
High school	177,213	27.15		131,134	19.03	
University degree	69,617	10.67		60,110	8.72	
Pre-/post- sample	467,259	71.60		494,705	71.78	
Hospital birth	247,400	37.91		259,107	37.59	
Duration of education, years			8.72 (2.55)			8.43 (2.11)
Age at censoring, years			80.42 (6.94)			82.57 (6.68)
Age of dementia cases, years			81.52 (6.05)			82.99 (6.00)
Age of noncases, years			80.27 (7.04)			82.49 (6.80)

Abbreviations: CDR, Cause of Death Register; NIR, National Inpatient Register; SD, standard deviation.

and dementia and between the highest level of education achieved (categorically) and dementia. We also examined the assumption of linearity in the observational association by fitting an unrestricted model using a binary indicator for each year of education. All of the models had stratified baseline hazards at the school-district level, included a dummy variable for every cohort, and had robust standard errors clustered at the school-district level.

RESULTS

Of the study's target population (n = 1,972,038) of 18 birth cohorts, we included 1,341,842 subjects in the study after excluding persons who died (n = 254,614), immigrated (n = 191,556), received a dementia diagnosis prior to age 65 years (n = 2,855), or had an unknown reform exposure status (n = 170,694), or for other reasons (n = 10,477). Details of the sample derivation are shown in Web Figure 1. Table 1 presents sex-stratified descriptive statistics. More than half of the sample (55.4% of men and 55.1% of women) had been exposed to a prolonged education due to the primary schooling reform, and 12.3% of the men and 16.3% of the women received dementia diagnoses during hospitalization or on their death certificate.

Analyses of the reform indicated very small or negligible causal effects of education on the risk of dementia diagnosis (women: hazard ratio (HR) = 1.01 (95% confidence interval (CI): 0.97, 1.04); men: HR = 1.02 (95% CI: 0.99, 1.06); overall: HR = 1.01 (95% CI: 0.98, 1.04); see Figure 2 and Table 2). Sensitivity analyses targeting pre-/post- changes, differences in health-care-seeking behavior, and impact of exposure misclassification left the results essentially unaltered (Figure 2 and Table 2). The lag- and lead-time analyses did not indicate any effect—neither a delayed one nor a spurious one—due to cohort trends (Web Figure 2). Post-hoc analyses including interactions between urban location and birth cohort also did not indicate any effect (Web Figure 3).

The reform had limited effects on mortality, making competing risk of death an unlikely explanation for the results (Web Tables 1 and 2). Further, we found that the reform had very small effects on the number of all-cause hospitalizations (Web Table 3). Together with the sensitivity analyses adjusting for all-cause hospitalization, we think it is unlikely that the general probability of hospitalization confounded our main findings.

In contrast to the negligible reform effects, education was clearly inversely associated with dementia risk in observational analyses (Figures 2 and 3, Table 3). One extra year of education was associated with a 3% lower risk of hospitalization or death with a dementia diagnosis (HR = 0.97, 95% CI: 0.96, 0.97; Table 3). The unrestricted specification showed no strong deviation from linearity in the association between duration of education and risk of dementia (Figure 3), especially prior to 14 years of education, suggesting that the magnitudes of association were similar for every 1-year increase in education. The categorical variable of highest level of attained education displayed an educational gradient, with university-educated persons having the lowest risk of dementia compared with those with only a compulsory education (HR = 0.82, 95% CI: 0.81, 0.84; Table 3).

Table 2. Hazard Ratios[a] (From the Main Analysis and Sensitivity Analyses) for the Effect of the Folkskola Compulsory Schooling Reform (1936–1949) on Risk of Receiving a Dementia Diagnosis in the National Inpatient Register or Cause of Death Register (1985–2016), Sweden, 1936–2016

Analysis and Sample	Men				Women				Overall[b]	
	No. of Persons	No. With Dementia	HR	95% CI	No. of Persons	No. With Dementia	HR	95% CI	HR	95% CI
Main Analysis										
Total	652,574[c]	80,538	1.02	0.99, 1.06	689,198[d]	112,100	1.01	0.97, 1.04	1.01	0.98, 1.04
Sensitivity Analyses										
Pre-/post- analysis[e]										
Total	467,230	59,335	1.01	0.98, 1.04	494,695	82,882	0.99	0.96, 1.02	1.00	0.98, 1.02
Folkskola education	344,146	44,622	1.02	0.98, 1.06	348,631	60,854	1.00	0.97, 1.03	1.01	0.98, 1.03
More than Folkskola education	123,084	14,713	1.00	0.94, 1.05	146,064	22,028	0.97	0.93, 1.02	0.98	0.95, 1.02
Sample limited to educational tiers[f]										
Folkskola education	430,777	54,842	1.03	0.99, 1.07	430,511	73,814	1.01	0.98, 1.05	1.02	0.99, 1.04
More than Folkskola education	221,797	25,696	0.99	0.95, 1.05	258,687	38,286	0.97	0.93, 1.03	0.99	0.95, 1.02
Adjustment for no. of all-cause hospitalizations[g]										
Total	652,574	80,538	1.02	0.99, 1.05	689,198	112,100	1.00	0.97, 1.04	1.01	0.99, 1.04
Folkskola education	430,777	54,842	1.03	0.99, 1.07	430,511	73,814	1.02	0.98, 1.05	1.02	0.99, 1.05
More than Folkskola education	221,797	25,696	0.99	0.95, 1.04	258,687	38,286	0.98	0.93, 1.04	0.99	0.95, 1.03
Examination of exposure misclassification[h]										
Total	405,200	53,824	1.03	0.99, 1.06	430,106	76,727	1.02	0.99, 1.05	1.02	0.99, 1.05
Folkskola education	312,410	41,843	1.02	0.99, 1.07	320,130	58,322	1.02	0.99, 1.07	1.03	0.99, 1.06
More than Folkskola education	92,790	11,981	1.04	0.97, 1.12	109,976	18,405	1.00	0.94, 1.06	1.02	0.98, 1.07

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] HRs were derived from a Cox proportional hazards survival model, with stratified baseline hazards at the school-district level. All models included a dummy variable for every cohort and robust standard errors clustered at the school-district level.

[b] Results were adjusted for sex.

[c] Forty-nine men were censored on the same date as they became at risk and hence excluded from the analyses, reducing the sample size from 652,623 (Table 1) to 652,574.

[d] Twenty-one women were censored on the same date as they became at risk and hence excluded from the analyses, reducing the sample size from 689,219 (Table 1) to 689,198.

[e] The pre-/post- design harmonized the study sample by including only school districts that had both exposed and unexposed cohorts. Overall, the pre-/post- design limited the role regional trends could play.

[f] "Compliers" (approximately 70% of the population) were persons who received an education in the form of schooling that was affected by the reform (Folkskola education). Persons receiving other types of schooling (more than Folkskola education) should not have displayed any effect.

[g] Sensitivity analyses considering all-cause hospitalization included a number of all-cause hospitalizations during follow-up for every individual.

[h] Exposure misclassification sensitivity analyses excluded cohorts for which hospital location rather than place of residence at birth may have been registered, which could have led to misclassification.

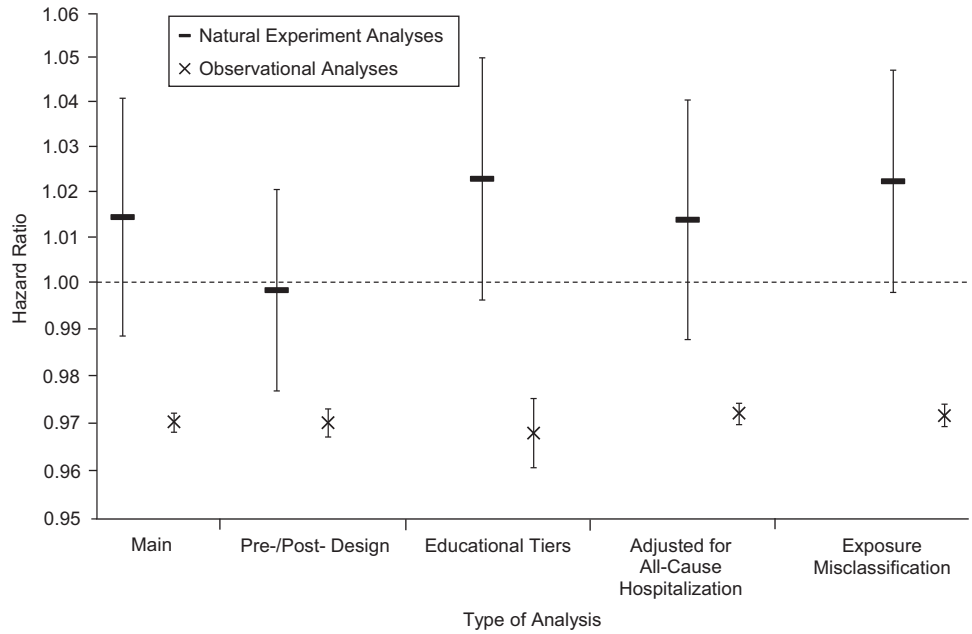

Figure 2. Results of main and sensitivity analyses examining A) the effect of exposure to the primary schooling reform on hospitalization or death with a dementia diagnosis (i.e., natural experiment analyses) and B) the association between duration of education (years) and hospitalization or death with a dementia diagnosis (i.e., observational analyses) in Sweden, 1936–2016. Dementia diagnoses were obtained from the Swedish National Inpatient Register or Cause of Death Register between 1985 and 2016. All hazard ratios were derived from Cox proportional hazards survival models, with stratified baseline hazards at the school-district level. All models adjusted for sex and included a dummy variable for every cohort and robust standard errors clustered at the school-district level. The first sensitivity analysis (pre-/post- design) limited analyses to school districts with both exposed and unexposed cohorts. The second sensitivity analysis (educational tiers) limited the analyses to persons who attended the type of primary school in which education was prolonged by the reform (i.e., compliers). The third sensitivity analysis adjusted for the number of all-cause hospitalizations during follow-up for every individual in order to limit the possibility that the findings were driven by health-care-seeking due to use of health-care registers for the outcome. The final sensitivity analysis addressed reform exposure misclassification and excluded cohorts of people born in parishes where a hospital was open; in those locations, hospital rather than place of residence at birth may have been registered, which could have led to exposure misclassification. Bars, 95% confidence intervals.

DISCUSSION

In this long-term follow-up of a Swedish natural experiment that exposed 13-year-old children to an extra year of primary school, we found no evidence of a causal effect of education on risk of dementia diagnosis in inpatient records or on death certificates. Sensitivity analyses addressing the impacts of possible exposure misclassification and possible differences in health-care-seeking behavior and limiting analyses to compliers did not substantially alter these results. The point estimate of the reform effect and its confidence interval (HR = 1.01, 95% CI: 0.98, 1.04) indicated that any real protective effect of the reform was probably very small and of limited practical importance. The reform did not substantially affect later socioeconomic outcomes. Thus, the pathway of the studied effect was mainly restricted to potential improvements in cognitive performance from prolonged cognitive stimulation or knowledge acquisition (11). Therefore, the effect of education on dementia risk mediated via a cognitive pathway, if any, is with a very high probability lower than the 7% decreased risk of dementia per year of education reported in a meta-analysis of observational studies (4) and also lower than the 3% decreased risk (HR = 0.97, 95% CI: 0.96, 0.97) present in our observational analyses.

Mendelian randomization studies, which use education-related genetic variants as an instrument for education, have also been carried out to examine a causal effect of education on dementia (21, 22). These studies produced imprecise estimates and probably suffered from potential violations of the randomization assumptions due to confounding by early-life intelligence (23). Our study complements the results from Mendelian randomization studies by having comparable power. Moreover, we did not identify any exogeneity violations for the studied reform (7, 17). In line with our findings, in one Mendelian randomization study, Anderson et al. (24) found little evidence for a causal effect of educational attainment on Alzheimer disease risk independent of intelligence.

Nguyen et al. (23) reported effects of multiple compulsory schooling reforms on dementia probability, which was a continuous score (not a case prediction) derived from a predictive model from assessment of cognitive performance. This result is consistent with a recent meta-analysis showing

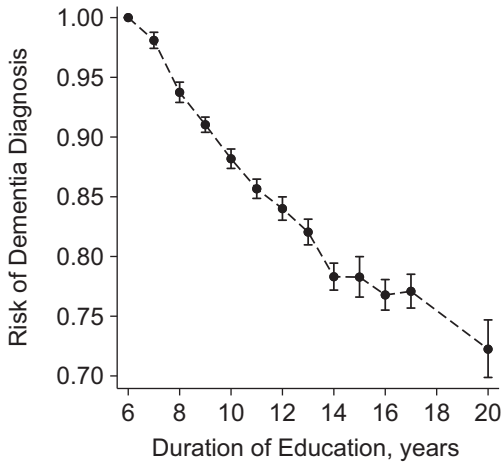

Figure 3. Observational association between duration of education and risk of a dementia diagnosis in data from the National Inpatient Register or Cause of Death Register (1985–2016), not assuming a linear relationship, Sweden, 1936–2016. Risk was captured by means of hazard ratios derived from Cox proportional hazards survival models, with stratified baseline hazards at the school-district level. The model used binary indicators for each year of education and adjusted for sex, and it included a dummy variable for every cohort and robust standard errors clustered at the school-district level. Bars, 95% confidence intervals.

robust effects of policy changes on cognitive performance in older age (25). To the best of our knowledge, the present study is the first to have assessed the causal effects of education on risk of an actual dementia diagnosis using a compulsory schooling reform and is certainly the first to have done this in a large general population study. Furthermore, our study allowed for unique examination of 1 specific causal pathway because of the known design of the reform and limited spillover effects.

We primarily assessed the impact of staying in primary school for an additional year, which was unrelated to adult socioeconomic factors, since the reform had limited effects on adult incomes and pensions (7, 17). Small returns of compulsory schooling extentions, especially in Europe, are consistent with the recent economics literature (26–28). There are several potential reasons for such findings. For example, the studied reform did not result in increased opportunities for secondary or tertiary education. Obtaining higher degrees (credentials) is probably a key mechanism for changes in socioeconomic trajectories, since it allows access to more valued jobs, yet this mechanism was not in play here. Further, in our sample the reform was mainly a rural phenomenon, which can influence the external validity of our findings as well as the returns of the reform. Rural schools were of lower quality, and access to economic opportunities was more limited in these areas.

The pathways of the studied variation in education are probably restricted to potential improvements in cognitive performance from prolonged cognitive stimulation or knowledge acquisition (11), which, if maintained through adult life, may result in surpassing the threshold for dementia diagnosis at a later age (12, 13). Most children affected by the studied reform achieved only the lowest possible educational level of the time. Perhaps the reform did not provide sufficient cognitive stimulation, as its focus was on in-depth learning of an unaltered curriculum. We cannot exclude the possibility that the cognitive pathway may be at play when education is more demanding or when quality of education is substantially increased. It may also be that changes in midlife conditions are needed for maintaining education-related cognitive benefits throughout the life span (15, 29).

Table 3. Estimated Hazard Ratios (From 2 Cox Proportional Hazards Survival Models[a]) for the Observational Associations of Length of Education and Highest Level of Attained Education With Risk of Receiving a Dementia Diagnosis in the National Inpatient Register or Cause of Death Register (1985–2016), Sweden, 1936–2016

Variable	Men (n = 652,574[b])		Women (n = 689,198[c])		Overall[d] (n = 1,341,772)	
	HR	95% CI	HR	95% CI	HR	95% CI
Duration of education, years	0.97	0.97, 0.98	0.96	0.96, 0.97	0.97	0.96, 0.97
Highest level of education attained						
Compulsory schooling	1.00	Referent	1.00	Referent	1.00	Referent
High school	0.91	0.90, 0.92	0.93	0.92, 0.95	0.92	0.91, 0.93
University degree	0.83	0.81, 0.85	0.82	0.80, 0.84	0.82	0.81, 0.84

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Models had stratified baseline hazards at the school-district level, included a dummy variable for every cohort, and had robust standard errors clustered at the school-district level.

[b] Forty-nine men were censored on the same date as they became at risk and hence excluded from the analyses, reducing the sample size from 652,623 (Table 1) to 652,574.

[c] Twenty-one women were censored on the same date as they became at risk and hence excluded from the analyses, reducing the sample size from 689,219 (Table 1) to 689,198.

[d] Results were adjusted for sex.

There may be sensitive periods of life in which an exposure is especially important (12). We examined the effect of an extra year of schooling at age 13 years. While previous studies have indicated the malleability of intelligence in adolescence (10), the literature indicates that returns are larger for earlier interventions (7). Further, effects of education are always estimated relative to alternative activities. Therefore, generalizing findings across historical periods and societies that vary with regard to such alternatives to education is difficult. Finally, the absence of an effect in our study does not exclude the possibility that other types of variation in education may causally affect dementia risk. For example, it remains to be investigated whether variations in education that result in larger positive effects on adult life conditions (e.g., better occupational conditions) affect the risk of dementia. Researchers must become better at describing the variations in education, including mechanisms, mediators, and timing, that they examine (5, 8, 30).

We used the National Inpatient and Cause of Death registers to identify dementia cases. The use of administrative data increases power and allows for comprehensive coverage of the entire population but also comes with some limitations. Validation studies report high specificity (>91%) of the dementia outcome in Swedish registers (31, 32). However, sensitivity is lower, indicating that nearly half of dementia cases may be missed. To assess sensitivity and the presence of differential misclassification, we obtained education-stratified estimates for the cohorts included in this study from Rizzuto et al. (32). Combining both registers, the sensitivity for our cohorts was 73.9% (95% CI: 64.7, 81.8%) for persons with fewer than 8 years of education and 68.2% (95% CI: 55.6, 79.1%) for those with 8 years or more. Thus, there was no substantial evidence of education-related dementia misclassification, and sensitivity was improved for our cohorts when both registers were combined. Previous analyses suggest that more cases might be missed at older ages, when dementia is more common and people are more likely to reside in nursing homes with on-site care (33). This may underestimate lifetime risk, yet the prevalence of dementia in our sample was 12.3% for men and 16.8% for women, which is in line with the prevalence from national cohort studies of 13.3% (95% CI: 10.5, 16.1) for men and 16.1% (95% CI: 13.9, 18.4) for women (34).

Another limitation is that the date of hospitalization or death does not correspond to the onset of dementia (32). Thus, an alternative explanation for our findings is that we were unable to capture the effect of the reform on dementia due to our operationalization of onset. The reform may have had an effect on dementia in a way that did not postpone hospitalization with a dementia diagnosis or its presence on death certificates. Use of registers has implications regarding dementia severity. We hypothesized that hospital records and death certificates would capture moderate-to-severe cases of dementia. A limitation stemming from this is a likely underestimation of milder cases, which may be the reason behind the attenuated observational association estimate in this study as compared with the meta-analytical estimate. An advantage is that the sensitivity for moderate-to-severe dementia was probably high: We followed people to high ages (79–96 years), and the vast majority (93.6%) were hospitalized at least once during follow-up, with the mode being 3 hospitalizations. Further, we believe that moderate or severe dementia is likely to be noted by hospital staff.

In conclusion, our investigation of a compulsory schooling reform that prolonged primary schooling by 1 year at age 13 years suggested very small or negligible effects of education, if any, on the risk of dementia diagnosis. Researchers have identified low educational level as a major risk factor for dementia (1–4) and often treat education as a modifiable factor, implicitly assuming that prolonging education may substantially reduce dementia incidence. We conclude that this is unlikely to be a generally valid assumption and caution against an overly optimistic view on the proportion of dementia risk that is modifiable. It is possible, however, especially considering reports of robust effects of education on old-age cognitive performance (25), that other variations in education, such as those that affect life-span conditions, may reduce dementia risk. And, of course, a possible lack of effects on dementia does not undermine the importance of education for other health outcomes (5) and for economic and social development.

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REFERENCES

1. Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. *Lancet*. 2017;390(10113): 2673–2734.
2. Sharp ES, Gatz M. Relationship between education and dementia: an updated systematic review. *Alzheimer Dis Assoc Disord*. 2011;25(4):289–304.
3. Caamaño-Isorna F, Corral M, Montes-Martínez A, et al. Education and dementia: a meta-analytic study. *Neuroepidemiology*. 2006;26(4):226–232.
4. Xu W, Tan L, Wang HF, et al. Education and risk of dementia: dose-response meta-analysis of prospective cohort studies. *Mol Neurobiol*. 2016;53(5):3113–3123.
5. Hamad R, Elser HC, Tran DC, et al. How and why studies disagree about the effects of education on health: a systematic review and meta-analysis of studies of compulsory schooling laws. *Soc Sci Med*. 2018;212:168–178.
6. Lleras-Muney A. The relationship between education and adult mortality in the United States. *Rev Econ Stud*. 2005; 72(1):189–221.
7. Fischer M, Karlsson M, Nilsson T, et al. The long-term effects of long terms—compulsory schooling reforms in Sweden. *J Eur Econ Assoc*. 2020;18(6):2776–2823.
8. Glymour MM, Manly JJ. Compulsory schooling laws as quasi-experiments for the health effects of education: reconsidering mechanisms to understand inconsistent results. *Soc Sci Med*. 2018;214:67–69.
9. Brinch CN, Galloway TA. Schooling in adolescence raises IQ scores. *Proc Natl Acad Sci*. 2012;109(2):425–430.
10. Lager A, Seblova D, Falkstedt D, et al. Cognitive and emotional outcomes after prolonged education: a quasi-experiment on 320 182 Swedish boys. *Int J Epidemiol*. 2017; 46(1):303–311.
11. Ceci SJ. How much does schooling influence general intelligence and its cognitive components? A reassessment of the evidence. *Dev Psychol*. 1991;27(5):703–722.
12. Liu S, Jones RN, Glymour MM. Implications of lifecourse epidemiology for research on determinants of adult disease. *Public Health Rev*. 2010;32(2):489–511.
13. Satz P. Brain reserve capacity on symptom onset after brain injury: a formulation and review of evidence for threshold theory. *Neuropsychology*. 1993;7(3):273–295.
14. Dekhtyar S, Wang HX, Fratiglioni L, et al. Childhood school performance, education and occupational complexity: a life-course study of dementia in the Kungsholmen Project. *Int J Epidemiol*. 2016;45(4):1207–1215.
15. Dekhtyar S, Wang H-X, Scott K, et al. A life-course study of cognitive reserve in dementia—from childhood to old age. *Am J Geriatr Psychiatry*. 2015;23(9):885–896.
16. Prince M, Wimo A, Guerchet M, et al. *World Alzheimer Report 2015. An Analysis of Prevalence, Incidence, Cost and Trends*. London, United Kingdom: Alzheimer's Disease International; 2015. https://www.alz.co.uk/research/WorldAlzheimerReport2015.pdf. Accessed September 4, 2019.
17. Fischer M, Karlsson M, Nilsson T. Effects of compulsory schooling on mortality: evidence from Sweden. *Int J Environ Res Public Health*. 2013;10(8):3596–3618.
18. Lövdén M, Seblova D. Analysis plan: study on education and dementia using the Swedish educational reform (Folkskola). https://osf.io/kjptf/. Published December 13, 2018. Accessed November 10, 2020.
19. Garcia-Ptacek S, Kåreholt I, Cermakova P, et al. Causes of death according to death certificates in individuals with dementia: a cohort from the Swedish Dementia Registry. *J Am Geriatr Soc*. 2016;64(11):e137–e142.
20. Berry SD, Ngo L, Samelson EJ, et al. Competing risk of death: an important consideration in studies of older adults. *J Am Geriatr Soc*. 2010;58(4):783–787.
21. Larsson SC, Traylor M, Malik R, et al. Modifiable pathways in Alzheimer's disease: Mendelian randomisation analysis. *BMJ*. 2017;359:j5375.
22. Østergaard SD, Mukherjee S, Sharp SJ, et al. Associations between potentially modifiable risk factors and Alzheimer disease: a Mendelian randomization study. *PLoS Med*. 2015; 12(6):e1001841.
23. Nguyen TT, Tchetgen Tchetgen EJ, Kawachi I, et al. Instrumental variable approaches to identifying the causal effect of educational attainment on dementia risk. *Ann Epidemiol*. 2016;26(1):71–76.e3.
24. Anderson EL, Wade KH, Hemani G, et al. The causal effect of educational attainment on Alzheimer's disease: a two-sample Mendelian randomization study [preprint]. *bioRxiv*. 2017. (doi: 10.1101/127993). Accessed July 26, 2019.
25. Ritchie SJ, Tucker-Drob EM. How much does education improve intelligence? A meta-analysis. *Psychol Sci*. 2018; 29(8):1358–1369.
26. Grenet J. Is extending compulsory schooling alone enough to raise earnings? Evidence from French and British compulsory schooling laws. *Scand J Econ*. 2013;115(1):176–210.
27. Devereux PJ, Hart RA. Forced to be rich? Returns to compulsory schooling in Britain. *Econ J*. 2010;120(549): 1345–1364.
28. Pischke J. The impact of length of the school year on student performance and earnings: evidence from the German short school years. *Econ J*. 2007;117(523):1216–1242.
29. Lövdén M, Bäckman L, Lindenberger U, et al. A theoretical framework for the study of adult cognitive plasticity. *Psychol Bull*. 2010;136(4):659–676.
30. Rehkopf DH, Glymour MM, Osypuk TL. The consistency assumption for causal inference in social epidemiology: when a rose is not a rose. *Curr Epidemiol Rep*. 2016;3(1): 63–71.
31. Nilsson ED, Melander O, Elmståhl S, et al. Copeptin, a marker of vasopressin, predicts vascular dementia but not Alzheimer's disease. *J Alzheimers Dis*. 2016;52(3): 1047–1053.
32. Rizzuto D, Feldman AL, Karlsson IK, et al. Detection of dementia cases in two Swedish health registers: a validation study. *J Alzheimers Dis*. 2018;61(4):1301–1310.
33. Seblova D, Quiroga ML, Fors S, et al. Thirty-year trends in dementia: a nationwide population study of Swedish inpatient records. *Clin Epidemiol*. 2018;10:1679–1693.
34. Fratiglioni L, Ding M, Santoni G, et al. *Demensförekomst i Sverige: Geografiska och Tidsmässiga Trender 2001–2013. Resultat Från den Svenska Nationella Studien om Åldrande, Vård och Omsorg—SNAC*. Stockholm, Sweden: Stockholm Gerontology Research Center; 2017. https://www.snac-k.se/wp-content/uploads/2019/05/PrevDemSwe-20171212.pdf. Accessed July 26, 2019.