Education and Dementia Risk

Authors: Silvia H. Barcellos[1,2,3]* Leandro S. Carvalho[4,5], Kenneth M. Langa[6,7], Sneha Nimmagadda[5], and Patrick Turley[4,5]

Affiliations:

[1] La Follette School of Public Affairs, University of Wisconsin-Madison; Madison, WI, USA.

[2] Department of Population Health Sciences, University of Wisconsin-Madison, Madison, WI, USA.

[3] National Bureau of Economic Research; Cambridge, MA, USA.

[4] Center for Economic and Social Research, University of Southern California; Los Angeles, CA, USA.

[5] Department of Economics, University of Southern California; Los Angeles, CA, USA.

[6] Department of Internal Medicine, University of Michigan; Ann Arbor, MI, USA.

[7] Institute for Social Research, University of Michigan; Ann Arbor, MI, USA.

*Corresponding author.

Email: barcellos@wisc.edu

Address: 305 Observatory Hill Office Building, 1225 Observatory Drive, Madison, WI 53706.

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Abstract

There is little causal evidence on factors that can protect individuals against Alzheimer's Disease and Related Dementias (ADRD) risk. We study the causal effect of education on ADRD, exploiting a regression discontinuity generated by a compulsory schooling reform. ADRD was ascertained based on medical history, hospital records, and death registries, addressing concerns about selective sample attrition. We find that education reduces incidence of ADRD and may delay its onset. Using molecular genetic data, we show that the reform weakened the relationship between genetics and ADRD incidence, implying this genetic risk is not immutable and can be modified by social policy.

1. Introduction

Gains in life expectancy and population aging are driving a sharp rise in Alzheimer's Disease and Related Dementias (ADRD), with predicted global cases of 131.5 million people by 2050 (Prince et al. 2015; Livingston et al. 2017). In addition to imposing health and emotional costs on ADRD patients and their families, the severe cognitive and functional impairment that characterizes ADRD has a large economic cost. In the U.S. alone, ADRD's cost is estimated at $305 billion (Wong 2020). Without effective interventions to prevent or delay its onset, the economic burden of dementia could grow by as much as three-fold in the next 35 years (Livingston et al. 2017). For these reasons, it is crucial to understand what factors can decrease ADRD incidence and delay cognitive and functional decline in older ages.

Lower educational attainment has been identified as a major risk factor for ADRD, as education is strongly associated with better later-life cognition and lower ADRD risk (Sharp & Gatz 2011; Maccora et al. 2020; Seblova et al. 2023; Soh et al. 2023; Crimmins et al. 2010). However, little is known about whether and how much of this association reflects a causal effect from education to ADRD (Leslie 2021; Walters et al. 2024). Part of the challenge in distinguishing correlation from causation is that third factors, such as childhood circumstances, socioeconomic background, and genetics, may confound the relationship between education and ADRD. Also, there may be individual characteristics, such as self-control, that drive both behavioral risk factors and educational attainment.

Another obstacle to studying the education-ADRD relationship is that dementia is difficult to diagnose and measure. Cognitive decline often progresses slowly, and the threshold of disability that defines ADRD can be hard to identify reliably. Moreover, while brain pathology and cognition are correlated, there is not a one-to-one correspondence between them

(Aron et al. 2014; Buchman et al. 2014). Selective sample attrition is also a concern for most survey-based measures of ADRD (Weir et al. 2011). Survey participants who develop dementia are more likely to drop out, either because of survival bias or because they can no longer answer survey questions reliably.

We overcome these challenges by combining a natural experiment with dementia data constructed from administrative health records for a large cohort. In 1972, England, Scotland, and Wales increased the minimum age at which students could drop out of school from 15 to 16 years of age. The reform affected only students born after September 1, 1957, generating a discontinuity in the relationship between education and date of birth. We exploit this discontinuity using a regression discontinuity design to estimate the causal effect of education on dementia incidence.

We use data from the UK Biobank (UKB). The UKB's Outcome Adjudication Group identified dementia outcomes using hospital records, mortality data, and (self-reported) medical history. Date of first dementia diagnosis is also recorded, allowing us to study effects on age at onset. Crucially, these data are not biased by selective attrition; the study continues to follow its participants through linkages to administrative health and death registries. Our main outcome is an indicator for whether the individual had been diagnosed before December of 2022, when the first cohort affected by the reform was 65 years old—an age where the ADRD incidence is still low.

Despite the low incidence, our findings indicate that education has a negative causal effect on ADRD incidence. We find that individuals born right after September 1, 1957 stayed on average 0.14 years longer in school. They were also 0.2 percentage points less likely to have been diagnosed with ADRD. Our preferred 2SLS specification estimates that staying in school

one year longer reduced ADRD cumulative incidence by approximately 1 percentage point (p-value 0.01)—a surprisingly large effect. However, a variety of factors strengthen the evidence that education has a protective effect against ADRD. First, our natural experiment provides a compelling empirical strategy. Second, even the lower bound of our 95% confidence interval is substantial (a 0.23 percentage-point reduction). Third, this result is robust to a series of sensitivity analyses. Therefore, we attribute the large point estimate to estimation error rather than to flaws in our empirical design.

The UKB also genotyped its participants, allowing us to investigate whether education can mitigate the genetic risk for ADRD (Cook & Fletcher 2015). ADRD has a strong genetic basis, with an estimated twin-based heritability as high as 80% (Gatz et al. 2006; Bird 2005; Breteler 2000) and a SNP-heritability of 33% (Ridge et al. 2013). However, knowing that something is influenced by genes does not have clear implications for how society should respond (Jencks 1980) since it is an open question whether these genetic risks can be mitigated by behavioral changes, clinical interventions, or social policies.

Using molecular genetic data, we constructed a "polygenic index" (PGI) that measures one's genetic risk of developing ADRD. Importantly, the samples used to construct this measure exclude our working sample. The PGI is "fixed at conception" and therefore cannot be affected by the school reform.[1]

Our evidence indicates that the school reform mitigated the genetic risk of developing ADRD. For those individuals born right before September 1, 1957, a one standard deviation increase in the PGI increased the ADRD cumulative incidence by 0.24 percentage points. In contrast, for those born right after this cutoff birthdate, a one standard deviation increase in the

[1] Meaning that an individual's genetic makeup is drawn from their parents' gene pool at conception; therefore this makeup, or the PGI calculated based on it, is also fixed at conception and does not vary during one's lifetime.

PGI increased the ADRD cumulative incidence by 0.06 percentage points—a reduction of 0.18 percentage points (p-value 0.004). Our 95% confidence interval indicates that the school reform reduced the effect of the PGI on ADRD by at least 0.06 percentage points. These are encouraging results, suggesting that ADRD incidence from genetic factors can be mitigated, and that changes in environmental circumstances, such as education, can reduce ADRD incidence even in a population with high incidence due to their genes.

The main contribution of this paper is to provide rigorous evidence that education can reduce ADRD incidence and delay its onset. While previous studies found evidence that education causally improves cognition and slows cognitive decline (Banks & Mazzonna 2012; Nguyen et al. 2016; Brenowitz et al. 2020; Fletcher et al. 2021), we are aware of only one other study that has examined the causal relationship of education and ADRD (Seblova et al. 2021). It exploited temporal variation in when school districts in Sweden implemented a compulsory schooling age reform; early-adopters implemented the reform as early as 1936 while late-adopters implemented it as late as 1953. One concern is that, because of the reform's staggered rollout over 17 years, students in early-adopter and late-adopter school districts may have had different ADRD risks even in the absence of the reform. Seblova et al. (2021) finds no effect of education on ADRD risk; it also finds limited effects on socioeconomic outcomes such as income.

In contrast, we study a compulsory schooling age reform that lends itself to a credible regression discontinuity design. Multiple studies have used this reform before, speaking to the widely accepted credibility of this natural experiment (Clark & Royer 2013; Davies et al. 2018; Barcellos et al. 2018; Barcellos et al. 2023). Importantly, this reform did affect socioeconomic status, including income.

This study is not without limitations. Importantly, the cohort affected by the UK educational reform is still relatively young; those born on September 1, 1957 were 65 years old in 2022. While recent evidence shows that AD biomarker positivity occurs many years before symptom onset (Birdsill et al. 2022; Burnham et al. 2024), to date the vast majority of dementia diagnoses occurs after age 65 (Chen et al., 2023). Our estimates are based on diagnoses occurred up to age 65 and might not generalize to later onset dementia. Similarly, while our estimates are derived from a credible regression discontinuity design, they are specific to the UK educational reform under study and its effect on the complier population – i.e., individuals who would have dropped out at age 15 in the absence of the reform.

The rest of the paper is structured as follow. Section 2 presents the data. Section 3 describes the school reform. The main results are presented in Section 4. Section 5 investigates whether the school reform mitigated the genetic risk for ADRD. Section 6 examines some potential mechanisms for the main results. Section 7 concludes.

2. Data

We use data from the UK Biobank (UKB), a large, population-based study initiated by the UK National Health Service (NHS) (Sudlow et al. 2015). Between 2006 and 2010, invitations were mailed to 9.2 million people between the ages of 40 and 69 who were registered with the NHS and lived up to about 25 miles from one of 22 study assessment centers distributed throughout the UK (Allen et al. 2012). The UKB sample is formed by 502,363 individuals who agreed to participate.

The UKB's Outcome Adjudication Group identified dementia outcomes using hospital records, mortality data, and (self-reported) medical history. A validation study has shown that at least 84.5% of the diagnoses coded based on this algorithm are true positives (Wilkinson et al. 2019). These diagnoses are also associated with plasma proteins that have been implicated in ADRD (Guo et al. 2024) – see Appendix Figure 2. Our main dementia outcome is equal to 1 if a participant had been diagnosed by December 2022 (and 0 otherwise)[2]; at the cohort level this measure translates into cumulative incidence in December 2022. Date of first dementia diagnosis was also recorded, allowing us to study effects on age at onset.

Our working sample consists of between 45,715 to 107,200 of UKB participants, depending on our sample restrictions. We will first discuss the natural experiment before detailing the criteria used to define this sample. A better understanding of the natural experiment is necessary to comprehend the sample restrictions. The Online Appendix provides details about the construction of the working samples (Appendix Figure 1) and of the variables used in the analysis (Appendix Table 1, Appendix Table 2, and Appendix Table 3).

3. The Natural Experiment

In 1972, England, Scotland, and Wales increased the minimum age at which students could drop out of school from 15 to 16 years of age. The reform (The 1972 Raising of School-Leaving Age Act or ROSLA) affected only students born on or after September 1, 1957, who

[2] If the individual had died before December 2022 from non-ADRD related causes, we coded this observation as a 0. We show in Appendix Table 4 that this coding choice does not drive our results. First, we estimate a multinomial logit model that distinguishes between developing ADRD; dying from a non-ADRD related cause; or being alive without ADRD. We then estimate a logit model that does not distinguish between the last two. The two specifications yield identical estimates, which lead us to conclude that our main findings are not driven by effects of the school reform on mortality.

had to stay in school until at least age 16 ("treated"). Students born on August 31, 1957 or before were still allowed to drop out at age 15 ("control").

Figure 1A shows that the ROSLA introduced a sharp discontinuity in the relationship between education and date of birth. The markers show the fraction who stayed in school until (at least) age 16 (y-axis), separately by year of birth (x-axis). Year of birth runs from September 1 of a given year to August 31 of the following year. The lines correspond to linear trends (in exact date of birth), with different trends for those born before and after September 1, 1957, the birthdate cutoff. The graph includes individuals born within 4 years of this cutoff. The sample is further restricted to UKB participants born in England, Scotland, or Wales or who immigrated to the UK when they were 14 years of age or younger (N = 107,200).[3]

There is a large jump for the cohort born between September 1957 and August 1958, which was the first cohort required to stay in school until age 16. They were 14 percentage points more likely to stay in school until age 16 than those born right before the birthdate cutoff.

This setting provided a unique opportunity to study the causal effects of education on ADRD incidence. If, as hypothesized, there is a causal relationship between education and ADRD, then one would expect to observe a corresponding discontinuity in the relationship between ADRD and date of birth at September 1, 1957. Because individuals born right before and right after this date would have had similar ADRD incidence in the absence of the policy, any observed discontinuity could be attributed to the difference in schooling engendered by the policy.

[3] We excluded from the sample participants for whom data on the age at which they left full-time education were missing.

We exploit this natural experiment using a regression discontinuity design (RDD). The RDD identifying assumption is that, in the absence of the reform, our outcome of interest would have been smooth across the September 1, 1957 threshold. Figure 1B provides evidence that supports this assumption. It shows the fraction of UKB participants *whose parents* had been diagnosed with ADRD, separately by date of birth. *Parents* of those born right after September 1, 1957 were as likely to suffer from ADRD as *the parents* of those born right before September 1, 1957. Appendix Figure 4 shows that other pre-reform characteristics are smooth across the birthdate cutoff, including individuals' genetic risks for ADRD.[4] These results strengthen our confidence that the RDD results provide unbiased estimates of the causal effects of education on the ADRD of UKB participants.

4. Main Results

Our findings indicate that education has a negative causal effect on ADRD incidence. Figure 2A shows the relationship between ADRD and date of birth. There is a sharp decline in ADRD cumulative incidence among those born after September 1, 1957. Appendix Figure 5 shows that there were similar declines for men and women.

Table 1 presents regressions estimates. Column (1) in the top panel estimates the first-stage:

$$SLA_i = \alpha_0 + \alpha_1 Post_i + \alpha_2 DoB_i + \alpha_3 (Post_i \times DoB_i) + u_i. \quad (1)$$

where SLA_i is individual i's school-leaving age; $Post_i$ is an indicator for whether individual i was born on or after September 1, 1957; and DoB_i is individual i's date of birth. Date of birth is

[4] Appendix Figure 3 shows the results from a McCrary Test.

measured in days relative to the cutoff, such that $DoB = 0$ for someone born on September 1, 1957. The term DoB_i captures linear birth cohort trends in education. The term $(Post_i \times DoB_i)$ allows these trends to be different for those born before and after September 1, 1957. Column (1) of Table 1 confirms the graphic results shown in Figure 1: The ROSLA led students to stay approximately 0.14 years longer in school.

The reduced-form is estimated in column (2) of the top panel:

$$ADRD_i = \beta_0 + \beta_1 Post_i + \beta_2 DoB_i + \beta_3 (Post_i \times DoB_i) + v_i. \quad (2)$$

where $ADRD_i$ is an indicator for whether individual i had been diagnosed with dementia by December of 2022. Column (3) in the top panel estimates a two-stage least squares model:

$$ADRD_i = \gamma_0 + \gamma_1 SLA_i + \gamma_2 DoB_i + \gamma_3 (Post_i \times DoB_i) + \varepsilon_i. \quad (3)$$

where $Post_i$ is used to instrument for SLA_i.

The sample is restricted to those born within 1,217 days of September 1, 1957 (or approximately 3⅓ years), which is the optimal bandwidth determined by Calonico et al. (2014)'s optimal bandwidth selection procedure. Appendix Figure 6 shows that our results are robust to alternative bandwidth choices. We estimate robust standard errors. While common to cluster standard errors on the running variable, recent research advises against it (Kolesár & Rothe 2018). Nevertheless, because the running variable is measured very finely (exact date of birth), clustering on the running variable produces nearly identical standard errors. Moreover, controlling for seasonality in birth date (e.g. month of year) does not affect our results (Appendix Table).

Column (2) of Table 1 estimates that those born after September 1, 1957 were 0.2 percentage points less likely to have been diagnosed with ADRD. This is a large decline considering that the cumulative incidence among those born before this date was approximately

0.46% – prevalence is relatively low because of the age of the sample (the cumulative incidence for the first cohort affected by the reform was measured when they were 65 years old). Column (3) estimates that staying in school one year longer reduced ADRD cumulative incidence by 1.4 percentage points (p-value 0.036).

Columns (4) to (6) re-estimate these same equations using a different sample, namely those who left school at age 18 or younger. This sample restriction yields tighter confidence intervals because of the stronger first-stage. It yields unbiased estimates under the assumption that the school reform did not affect the fraction who stayed in school until at least age 19 – Appendix Figure 7 shows that this was the case.

Column (6) shows our preferred 2SLS specification. For those who left school at age 18 or younger, staying in school one year longer reduced ADRD cumulative incidence by approximately 1 percentage point (p-value 0.01))—a notably large effect. However, this estimate is imprecise, as reflected in our 95% confidence interval, which ranges from a 0.23 to a 1.69 percentage-point reduction. Given the wide confidence interval, we caution against placing too much weight on the point estimate. Importantly, despite the large standard errors, our findings provide strong causal evidence that education has a substantial negative effect on dementia incidence. Appendix Table 4 shows that our results are not driven by any potential effects of the school reform on mortality.

Survival Analysis

Figure 2A and Table 1 showed the effect on ADRD cumulative incidence as of December of 2022, when individuals born on September 1, 1957 were 65 years old. Figure 2B shows a

survival analysis that examines the dynamics of these effects over time as study participants aged. In particular, we ran a series of regressions of the following form:

$$ADRD_i^{age} = \theta_0^{age} + \theta_1^{age} Post_i + \theta_2^{age} DoB_i + \theta_3^{age} (Post_i \times DoB_i) + \xi_i^{age} \quad (4)$$

where $ADRD_i^{age}$ is an indicator for whether individual i had been diagnosed with ADRD by September 1st of year $1957 + age$. For example, $ADRD_i^{50}$ is an indicator for whether individual i had been diagnosed with ADRD by September 1, 2007. Notice that equation (4) is similar to equation (2). One difference is that we estimate equation (4) multiple times, one for each age between 50 and 65. Appendix Figure 8 shows regression discontinuity scatterplots at these different ages.

Figure 2B plots the hazard rates, separately for those born right before September 1, 1957 (solid black line) and for those born right after (red dashed line). More specifically, the solid black line plots the estimates of θ_0^{age} against age while the red dashed line plots the estimates of $\theta_0^{age} + \theta_1^{age}$ against age. Intuitively, the vertical distance between the red and black lines at a given age corresponds to the effect of the policy on ADRD cumulative incidence at the given age. The shaded area shows 95% confidence intervals for the difference between the two hazards—the difference is statistically significant at the 5% level for a given age when the solid black line is outside the shaded area.

The figure suggests that the additional schooling induced by the school reform delayed ADRD onset. We formally test this hypothesis using a Cox proportional hazard model (Appendix Figure 9), and we can reject the hypothesis that the two groups share the same hazard rate (p-value 0.025). Given these results, we anticipate that the gap between the two groups will widen over time as they age further.

5. Genetics and Heterogenous Effects

A common misperception is that the influence of genetics on a disease such as ADRD cannot be altered by environmental interventions – presumably because it is assumed that this influence reflects a biological, immutable relationship. However, because genetic effects can operate through environmental channels, intervening on those channels could in principle influence genetic effects (Goldberger 1979; Benjamin et al. 2024). In this section, we investigate whether education can mitigate the genetic risk for ADRD (Cook & Fletcher 2015). We begin by discussing how we measure this risk.

Measuring Genetic Risk of Developing ADRD

As a measure of one's genetic risk factor for developing ADRD, we constructed an ADRD polygenic index (PGI). Our PGI was constructed using two different types of genetic variation. The first type are Single Nucleotide Polymorphisms (SNPs). SNPs are locations in the human genome where individuals differ by a single genetic marker. At most SNPs, people can have one of two possible genetic variants. In genetic data, one of these two possible genetic variants is arbitrarily chosen as the "reference allele". Because a person has two copies of each chromosome, they will either have 0, 1, or 2 copies of the reference allele. The number of reference alleles an individual has at a SNP is called *their genotype for that SNP*.

The second type of variation are the APOE variants. APOE is a gene on chromosome 19 that can be classified into four different variants, numbered APOE1 to APOE4. Each person has two copies of the APOE gene, one for each of their copies of chromosome 19. Individuals with some APOE variants are at much greater risk of developing ADRD—e.g., having two copies of

APOE4 is associated with a 10-fold higher risk. We quantify a person's APOE genotype with a set of indicator variables corresponding to each possible pair of APOE variants a person may have (e.g., an indicator for having one copy of APOE3 and one copy of APOE4).

Our PGI is a weighted sum of millions of an individual's genotypes:

$$\sum_j g_{ij} w_j + \sum_k APOE_{ik} \lambda_k$$

where i indexes the individual, j indexes a SNP, and k indexes the different possible pairs of APOE variants a person may have. The variable g_{ij} is individual i's genotype at SNP j while $APOE_{ik}$ is an indicator for whether individual i has the k-th pair of APOE variants. The weights assigned to the different SNPs, w_j, are constructed to maximize the power of the variation across SNPs to predict the outcome of interest – in our case, ADRD. The weights for the SNP genotypes are based on the largest Genome Wide Association Study (GWAS)[5] for Alzheimer's disease that omits the UK Biobank (Kunkle et al. 2019).[6] We use a simple model to estimate the weights for the pair of APOE variants, λ_k (see Appendix Table 5 for more details).[7,8] Because APOE has such a large

[5] A GWAS scans the entire genome and estimates associations between individual genotypes and an outcome of interest. Specifically, a GWAS is a series of regressions of some outcome onto the genotype of each SNP, one at a time, and a set of covariates which normally include sex, age, and the first several principal components of the genetic data.

[6] There are several methods for producing PGI weights from GWAS coefficients, but each of them transforms the GWAS coefficients in a way that is meant to account for the correlation structure that exists in the genome. The GWAS associations corresponding to the HapMap3 SNPs were transformed to account for linkage disequilbrium (LD) using the SBayesR method (Lloyd-Jones et al. 2019), and the EUR subsample of the 1000 Genomes Project data as a reference panel (Clarke et al. 2012). Due to the outsized effect of the APOE region of ADRD risk, we omitted the region on chromosome 19 from basepair position 44.4-46.5Mb (Baker & Escott-Price 2020).

[7] To avoid overfitting, these weights were estimated using a set of UK Biobank participants outside our optimal bandwidth.

[8] Following the standard practice, we restrict the sample to individuals whose genetic principal components cluster with the EUR subsample of a genomics reference panel, the 1000 Genomes Project. Due to Euro-centric bias in data collection, most currently published GWASs, including Kunkle et al. (2019), are based on samples with "European" ancestries. As a result, PGIs based on currently available GWAS coefficients are substantially more predictive in European-ancestry samples (Martin et al. 2019) and may not generalize to groups with African, Asian, Hispanic, or other non-European ancestries. This sample restriction reduces the correlation between a person's genotypes and their environment—such a correlation could produce omitted variable bias in estimates of the effect of genetic variables, such as PGIs, on various outcomes.

effect on ADRD incidence, much of the variation in our PGI was driven by APOE (58% of those in the top half had at least one E4 allele, while only 0.02% of those in the bottom half did). Importantly, our PGI is fixed at conception and therefore cannot be affected by the school reform.

Graphical Results

Figure 3 investigates how two groups – those in the bottom and top halves of the distribution of this PGI – were affected by the school reform. The black markers and black line show effects on those in the bottom half, who have a lower genetic risk of developing ADRD. The red markers and red line show effects on those in the top half, who have a higher genetic risk of developing ADRD.

Figure 3A shows that the policy affected the education of the two groups similarly. In both cases, those born right after September 1, 1957 were 14 percentage points more likely to stay in school until age 16 than those born right before. Thus, any differences in the effect of the policy on ADRD across the two groups cannot be explained by differences in how much the policy impacted the education of these two groups.[9]

Figure 3B shows the ADRD cumulative incidence for the two groups, separately by year of birth. For the cohorts born before September 1, 1957, there is a gap between the red and black lines, reflecting the larger ADRD incidence among those in the top half of the distribution of the PGI. If risk due to genetic factors were immutable, the gap between the red and black lines would remain for those born after September 1, 1957.

The reform caused, however, a greater reduction in the cumulative incidence of ADRD of those in the top half, virtually closing the gap between the two groups. It reduced the difference

[9] Note that the two groups – those with low and high genetic risks – are allowed to have different trends in Figure 3.

in the cumulative incidence between the two groups from 0.18 percentage points to 0.02 percentage points.

Regression Estimates

We further investigate these results in the bottom panel of Table 1. We re-estimate the same specifications as in the table's top panel, allowing the effects now to vary with one's continuous genetic risk factor. Columns (1) and (2) estimate:

$$Y_i = \delta_0 + \delta_1(Post_i \times G_i) + \delta_2 Post_i + \delta_3 G_i + \delta_4 DoB_i + \delta_5(Post_i \times DoB_i) + \epsilon_i \quad (5)$$

where Y_i is SLA_i in column (1) and $ADRD_i$ in column (2); and G_i is individual i's PGI. Column (3) in the bottom panel estimates a two-stage least squares model:

$$Y_i = \eta_0 + \eta_1(SLA_i \times G_i) + \eta_2 SLA_i + \eta_3 G_i + \eta_4 DoB_i + \eta_5(Post_i \times DoB_i) + \zeta_i \quad (6)$$

where again $Post_i$ is used to instrument for SLA_i and $(Post_i \times G_i)$ is used to instrument for $(SLA_i \times G_i)$. Columns (4) to (6) re-estimate columns (1) to (3), restricting the sample to those who dropped out at age 18 or younger.

Column (2), which is consistent with Figure 3B, shows that the reform mitigated the genetic risks of developing ADRD. For those born right before September 1, 1957, a one standard deviation increase in the PGI increased the ADRD cumulative incidence by 0.24 percentage points. In contrast, for those born right after the cutoff birthdate, a one standard deviation increase in the PGI increased the ADRD cumulative incidence by 0.06 percentage points—a reduction of 0.18 percentage points (p-value 0.004). Our 95% confidence interval indicates that the school reform reduced the effect of the PGI on ADRD by at least 0.06

percentage points.[10] Column (6), which restricts the sample to those who left school at age 18 or younger, estimates that staying in school a year longer reduced the effect of the PGI on ADRD by 0.7 percentage points, with the lower bound of the 95% confidence implying a reduction of at least 0.08 percentage points. These are encouraging results, suggesting that ADRD incidence from genetic factors can be mitigated, and that changes in environmental circumstances, such as education, can reduce ADRD incidence even in a population with high incidence due to their genes.[11]

In principle, the relationship between dementia and the PGI, as captured by δ_3 and η_3 in equations (5) and (6), could be confounded by environmental factors. More specifically, imagine we ran the following regression:

$$ADRD_i = \kappa_0 + \kappa_1 G_i + \chi_i. \quad (7)$$

It would yield a biased estimate of the causal effect of the PGI on ADRD if the PGI was correlated for example with the socioeconomic circumstances into which one was born. However, due to the properties of Mendelian inheritance, the genes that one inherits are randomly assigned conditional on the genes of the one's parents (Spielman et al. 1993; Allison 1997; Young et al. 2022). Therefore, one could obtain an unbiased estimate of this causal effect by estimating the following alternative specification:

[10] Appendix Figure shows that these interaction effects are robust to bandwidth choice. When the bandwidth is significantly expanded, the estimated interaction effects become even larger and more statistically significant, possibly due to the accelerating age pattern in ADRD incidence—a trend that is not well captured by a simple linear or quadratic function.

[11] Appendix Table shows that a logit version of equation (5) still indicates a main effect of the reform on dementia, but the interaction with the PGI is no longer significant. This suggests that, in percentage terms, the reduction in dementia was similar for high- and low-PGI groups. While we believe the OLS model is the economically-relevant specification, we emphasize the importance of carefully considering the appropriate units of analysis in GxE models.

$$ADRD_i = \pi_0 + \pi_1 G_i + \mu_i + \varphi_i. \quad (8)$$

where μ_i is a fixed effect specific to individual i and individual i's full siblings. In equation (8), this fixed effect controls for the common parental genotypes for the siblings.

We leveraged this approach in Appendix Table 6 to investigate wether there is empricial support for the hypothesis that the relationship between dementia and the PGI that we have estimated was confounded by environmental factors. In particular, we estimated equation (7) and (8) using a subsample of UKB participants who are siblings. We find that the coefficients on the PGI are similar in the two specifications. We cannot reject the hypothesis that they are the same (p-value 0.402). We interpret this finding as suggestive evidence that the effects of the PGI shown in Figure 3 and in the bottom panel of Table 1 reflect causal genetic effects.

6. Potential Mechanisms

Because we have just one source of exogenous variation, we cannot quantify the relative importance of different mechanisms. Nevertheless, we can still investigate whether a proxy for a given channel was impacted by the school reform – a necessary condition for the potential mechanism to mediate the relationship between education and ADRD.

The UK Biobank contains rich data on health conditions considered risk factors for ADRD, including objective measures of obesity, hypertension, and diabetes (a HbA1c Test). Stroke, infarction, and chronic obstructive pulmonary disease (COPD) were identified from a combination of self-reports, hospitalization data, and death records and are measured as of December of 2022. All the other outcomes were measured at baseline when the analyzing sample was between 45 and 56 years of age.

Figure 4A shows intent-to-treat estimates of the effect of the policy on household income and on ADRD risk factors. Each row corresponds to a separate outcome (all effects are measured in percentage points). The markers show point estimates while the brackets show 95% confidence intervals.

Those affected by the school reform were 2.2 percentage points more likely to have an income of £31,000 or more (p-value 0.001); 0.45 percentage points less likely to have diabetes (p-value 0.045); and 0.59 percentage points less likely to have had a stroke or myocardial infarction (p-value 0.045). These results are consistent with other papers using the UKB data that show that the ROSLA had positive effects on health and SES (Davies et al. 2018; Barcellos et al. 2018).[12]

Figure 4B re-estimates the effects on these risk factors, separately for those in the bottom and top halves of the distribution of the ADRD genetic risk factor. Interestingly, the effects on diabetes and obesity are driven almost exclusively by the high-genetic-risk group. The school reform reduced the obesity rate and the diabetes prevalence of the group with high genetic risk by 1.64 (p-value 0.049) and 0.65 (p-value 0.035) percentage points, respectively. In contrast, the obesity rate and the diabetes prevalence for the group with low genetic risk reduced by 0.47 (p-value 0.584) and 0.1 (p-value 0.766) percentage points. The previous section showed that the reduction in ADRD incidence was larger for the high-genetic-risk group. The effects of the school reform on some of these mechanism-proxies was also larger for the high-genetic-risk group, providing additional suggestive evidence that these mechanisms are at play.

7. Conclusion

[12] Nevertheless, it is important to note that there is currently no consensus on whether education has a causal effect in health in general (Grossman 2015).

We found that the additional schooling induced by a natural experiment in the UK in the early 1970s subsequently reduced the cumulative incidence of ADRD and delayed ADRD onset. These results suggest that ADRD incidence can be modified by social policy, a welcome finding given the expected exponential growth in cases of dementia and their large costs. Encouragingly, we found that the school reform mitigated the genetic risk of developing ADRD – rejecting the common perception that the influence of genetics on diseases such as ADRD cannot be altered by environmental interventions.

Scholars have noted the need for high-quality evidence on which factors can reduce ADRD and delay its onset (Leshner et al. 2017; Leslie 2021). Such evidence is paramount for designing policies that can prevent and effectively treat dementia. Characteristics that are highly associated with ADRD risk have been deemed as risk factors for dementia, but there is limited evidence as to whether these characteristics causally affect ADRD (Leshner et al 2017; Østergaard et al. 2015).

Education is a case in point. While lower education has been singled out as a major risk factor for ADRD, there is limited evidence on the causal effect of education on dementia. While previous studies found evidence that education causally improves cognition and slows cognitive decline (Banks & Mazzonna 2012; Nguyen et al. 2016; Brenowitz et al. 2020; Fletcher et al. 2021), we are aware of only one other paper that studied the causal relationship between education and ADRD diagnosis using a natural experiment combined with dementia measures derived from administrative health records. Seblova et al. (2021) studied the effects of a compulsory schooling age reform in Sweden, exploiting temporal variation in when school districts implemented the policy: early-adopters implemented the reform as early as 1936 while late-adopters implemented it as late as 1953. Inpatient and death registries were used to measure

dementia diagnosis for over 1.3 million individuals. The study found no effect of the reform on ADRD diagnosis. It also found limited effects on socioeconomic outcomes such as income. One concern is that, because of the reform's staggered rollout over 17 years, students in early-adopter and late-adopter school districts may have had different ADRD risks even in the absence of the reform.

In contrast, this paper studied a natural experiment that lends itself to a compelling regression discontinuity design. Multiple studies have used this reform before, speaking to the widely accepted credibility of this natural experiment (Davies et al. 2018; Barcellos et al. 2018). To our knowledge, this is the first paper to document a causal relationship between education and ADRD diagnosis and to examine whether education can mitigate genetic risk for ADRD.

To translate this evidence into policy-relevant interventions, it is important to understand the channels through which education affects ADRD incidence. While the reform in Sweden studied by Seblova et al. (2021) seems to have had limited, if any, effects on socioeconomic outcomes, it is clear that the 1972 ROSLA improved socioeconomic status – *suggesting* that this may be one of the mechanisms through which education reduces ADRD incidence. The ROSLA may have also improved some health outcomes, reducing diabetes, obesity, stroke, and infarction, but much remains to be understood.

This study has several potential limitations. First, our results are specific to the natural experiment we studied and to the lower-education population affected by the ROSLA. Admittedly, the effects of education on ADRD may vary with the level of education and across contexts. Second, our results are specific to UKB participants, who tend to have higher socioeconomic status and better health than the general population (Fry et al. 2017). Moreover, the great majority of them are of European ancestries and results might not apply to more diverse

populations. Third, dementia outcomes identified using hospital admission records and death registries may misclassify some individuals with dementia as not having it. We note, however, that false positives are likely to bias our estimates towards zero, since the evidence suggests that they are inversely related with education (Rizzuto et al. 2018). It is also unclear why any misclassification would change discontinuously for individuals born after September 1, 1957. Finally, the cohort studied in this paper is relatively young; those born on September 1, 1957 were 65 years old in 2022. Although the ADRD prevalence in our sample was lower than 1%, we were still able to identify a clear reduction in ADRD incidence due to education. Follow-up with this cohort as ADRD prevalence increases will be important.

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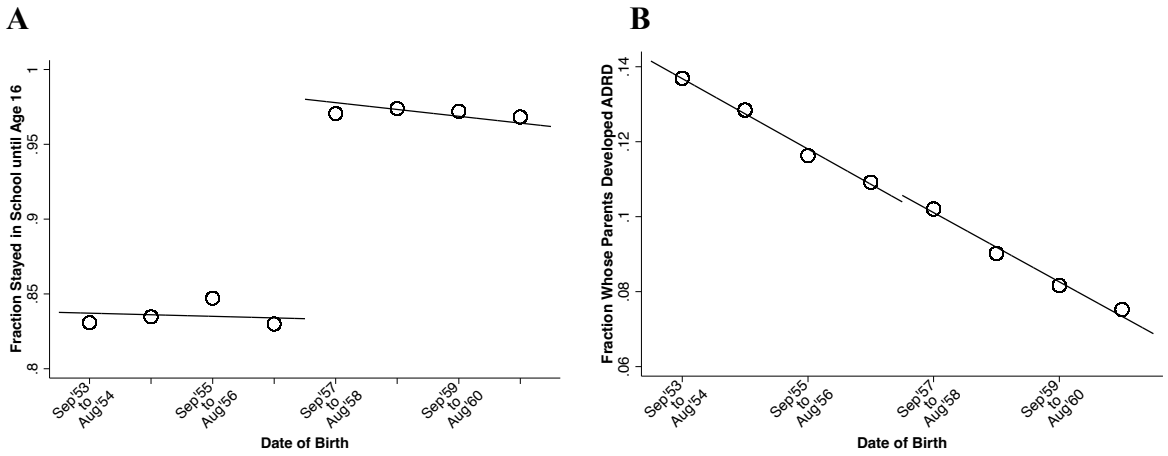
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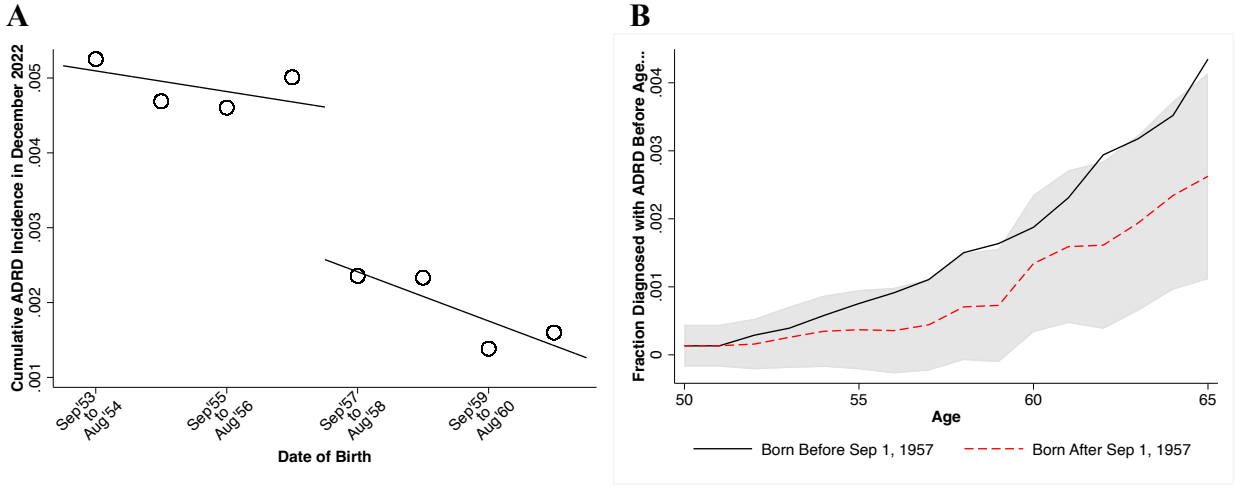
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Figure 1: The Natural Experiment



Notes: The figures plot (**A**) the fraction of each birth cohort who stayed in school until age 16 and (**B**) the fraction of each birth cohort whose parents developed ADRD. The cohort born between September 1, 1957 and August 31, 1958 was the first affected by the reform. The lines show linear trends in date of birth, which are allowed to be different for those born before and after September 1, 1957. Figure (A) shows that the reform generated a discontinuity in the relationship between education and date of birth. Figure (B) shows that *the parents* of those born right after September 1, 1957 are as likely to have ADRD as *the parents* of those born right before September 1, 1957. This illustrates that the latter provides a valid counterfactual of what would have happened to the former had they not been forced to stay in school until age 16. $N = 107{,}200$ (A) and 96,738 (B).

Figure 2. Education Reduces Cumulative Incidence of ADRD and Delays Onset



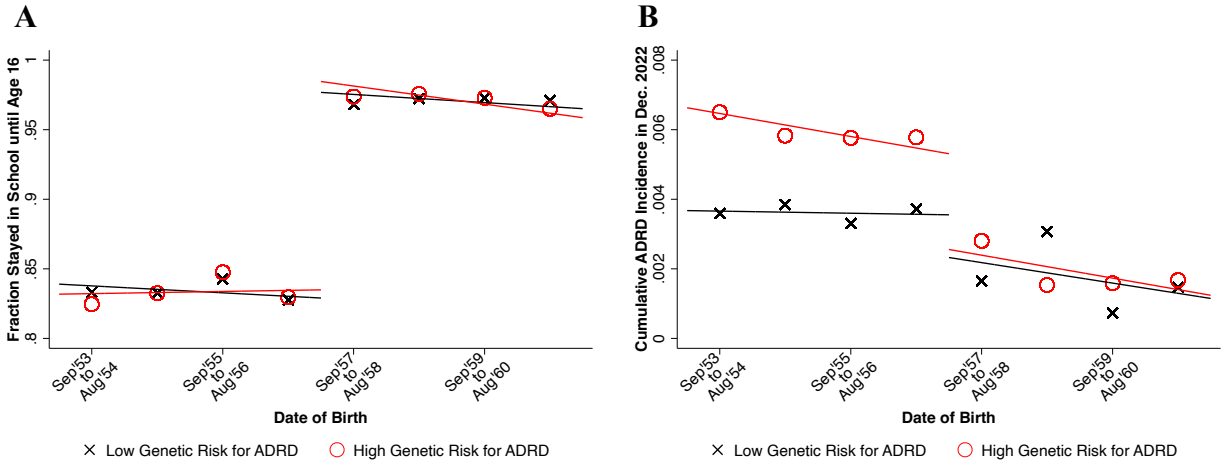
Notes: Figure (**A**) plots the fraction of each birth cohort diagnosed with dementia. The cohort born between September 1, 1957 and August 31, 1958 was the first affected by the reform. The lines show linear trends in date of birth, which are allowed to be different for those born before and after September 1, 1957. Figure (A) shows a sharp decline in the cumulative incidence of ADRD for those born after September 1, 1957, illustrating the causal effects of education on ADRD. Figure (A) shows the effect on cumulative incidence as of December of 2022, when individuals born on September 1, 1957 were 65 years old. Figure (**B**) shows the effect on cumulative incidence for other ages. It plots hazard rates of dementia diagnosis, separately for those born right before September 1, 1957 (solid black line) and for those born right after September 1, 1957 (red dashed line). The shaded area shows 95% confidence intervals for the difference between the two hazards; the difference is statistically significant at the 5% level when the solid black line is outside the shaded area. The figure suggests that education may delay the onset of ADRD. $N = 107{,}200$ (A) and 89,259 (B).

Table 1. Regression Estimates of the Effect of the Reform and the Effect of Education.

	All			Dropped Out at Age 18 or Younger		
	School-Leaving Age (1)	*ADRD (in p.p.)* (2)	*ADRD (in p.p.)* (3)	*School-Leaving Age* (4)	*ADRD (in p.p.)* (5)	*ADRD (in p.p.)* (6)
Top Panel						
Born after	0.14	-0.20		0.32	-0.31	
	(0.04)	(0.08)		(0.02)	(0.12)	
School-Leaving Age			-1.44			-0.96
			(0.69)			(0.37)
Mean of Y among Those Born before	18.71	0.48	0.48	16.17	0.60	0.60
Bottom Panel						
Born after × Genetic Risk	0.004	-0.18		-0.01	-0.19	
	(0.02)	(0.06)		(0.01)	(0.08)	
School-Leaving Age × Genetic Risk			-1.38			-0.70
			(1.13)			(0.31)
Born after	0.14	-0.19		0.32	-0.29	
	(0.04)	(0.08)		(0.02)	(0.12)	
School-Leaving Age			-1.68			-0.97
			(0.94)			(0.38)
Genetic Risk	0.01	0.24	5.39	0.01	0.24	1.08
	(0.01)	(0.05)	(4.28)	(0.01)	(0.07)	(0.44)
Mean of Y among Those Born before	18.69	0.47	0.47	16.16	0.58	0.58

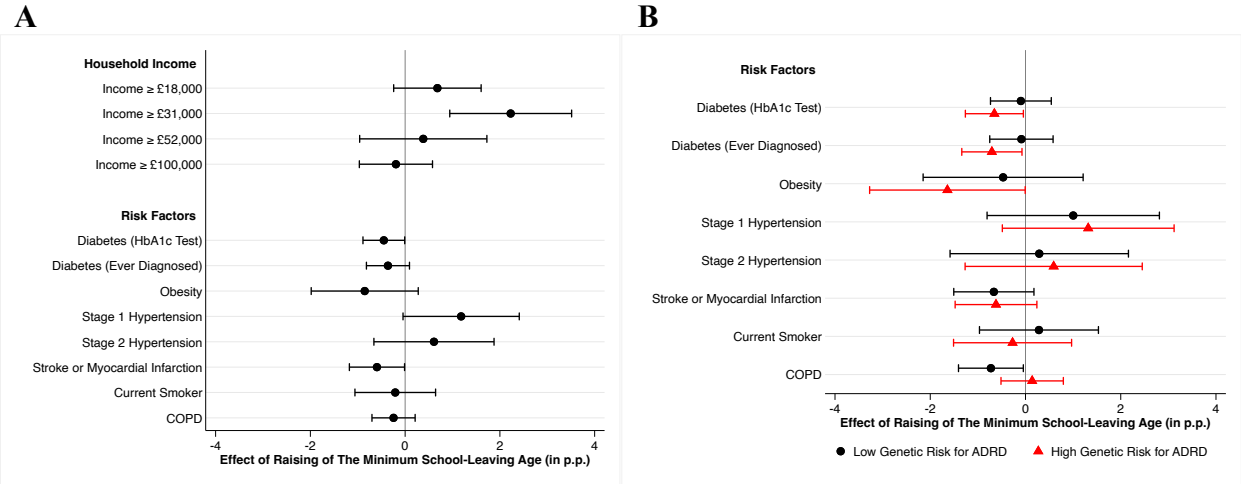
Notes: The dependent variables label each column. ADRD cumulative incidence is measured in percentage points. "Born after" is an indicator for being born on or after September 1, 1957. All regressions include linear trends in date of birth; those born before and after September 1, 1957 are allowed to have different trends. Columns (1), (2), (4), and (5) are OLS estimates. Columns (3) and (6) are estimated through two-stage least squares, where "Born after" is used to instrument for school-leaving age. In columns (4) to (6), the sample is restricted to individuals who dropped out at age 18 or younger. Regressions in Panel B include either an interaction of the genetic risk index with "Born after" (in columns (1), (2), (4), and (5)) or an interaction of the index with school-leaving age (in columns (3) and (6)); these regressions also control for the index. The ADRD genetic risk is standardized to have a standard deviation of one. The last row in each panel shows the mean of the dependent variable among those who were born before September 1, 1957. In Panel A, the number of observations is 89,259 for columns (1) to (3) and 49,457 for columns (4) to (6). In Panel B, the number of observations is 82,250 for columns (1) to (3) and 45,715 for columns (4) to (6). The number of observations is smaller in Panel B because the genetic risk index is not available for some participants. Robust standard errors between parentheses. While common to cluster standard errors on the running variable, we do not need to because our running variable is exact date of birth. Nevertheless, because the running variable is measured very finely, clustering on the running variable produces nearly identical standard errors.

Figure 3. Reduction in ADRD Cumulative Incidence Is Larger for Those with Greater ADRD Genetic Risk.



Notes: We measured one's genetic risk of developing ADRD by constructing an ADRD polygenic index that includes both a polygenic component and a person's APOE genotype. Separate results are shown for those in the bottom half (black) and in the top half (red) of the distribution of this index. The figures plot (**A**) the fraction of each birth cohort who stayed in school until age 16 and (**B**) the fraction of each birth cohort diagnosed with ADRD. The cohort born between September 1, 1957 and August 31, 1958 was the first affected by the reform. The lines show linear trends in date of birth, which are allowed to be different for those born before and after September 1, 1957. Figure (A) shows that the reform affected the education of the two groups similarly. Figure (B) shows that it had a larger effect on the prevalence rate of those in the top half. $N = 98{,}778$.

Figure 4. Potential Mediators: Income and Risk Factors.



Notes: The figure examines some potential channels through which the additional schooling may have affected ADRD incidence. It shows intent-to-treat estimates of the effect of the policy on the outcomes listed in the rows. Estimates are in percentage point units. The top panel of each figure estimates the effects on annual household income. The bottom panel estimates effects on various risk factors for ADRD. While (**A**) shows estimates for the entire sample, (**B**) estimates separate effects on those in the bottom half (black) and on those in the top half (red) of the distribution of the ADRD genetic risk index. The brackets show 95% confidence intervals. Robust standard errors. Depending on the variable, the number of observations varies from 80,259 to 89,259 in Figure 4A and from 74,493 to 82,250 in Figure 4B.

Supplementary Material for Education and Dementia Risk

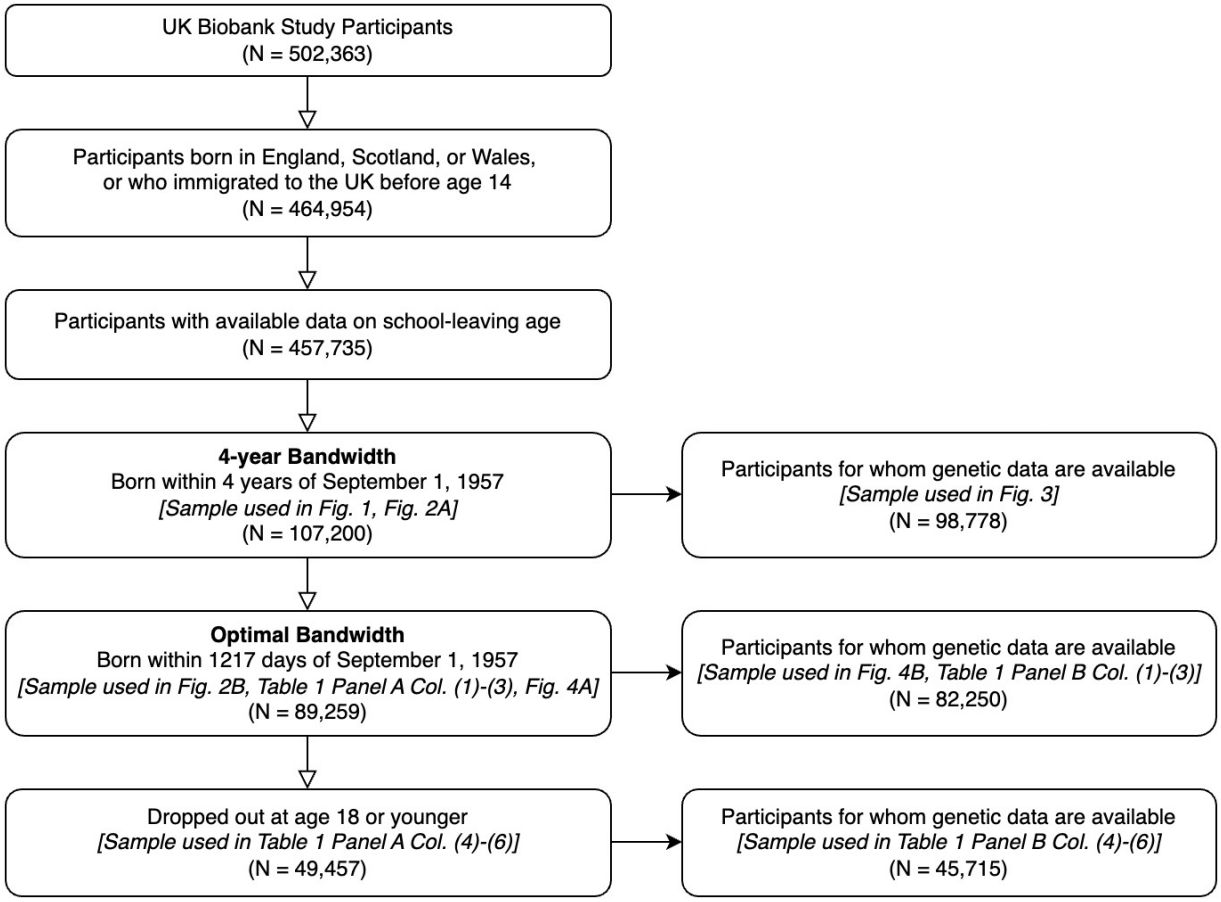
Silvia H. Barcellos, Leandro S. Carvalho, Kenneth Langa, Sneha Nimmagadda, and Patrick Turley

Corresponding author: Silvia H. Barcellos, barcellos@wisc.edu

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Appendix Figure 1. Sample. The figure shows the different sample restrictions, the size of the resulting samples, and the analyses in which these samples were used. The UK Biobank (UKB) sample is formed by 502,363 individuals. We made the following sample restrictions. First, we restricted the sample to UKB participants born in England, Scotland, or Wales or who immigrated to the UK when they were 14 years of age or younger. Second, we excluded from the sample participants for whom data on the age at which they left full-time education were missing. Third, we restricted the sample according to date of birth. In some analyses, we restricted to individuals who were born between September 1, 1953 and August 1, 1962 (i.e., within 4 years of September 1, 1957). In others, we restricted to participants born within 1,217 days of September 1, 1957, which is the optimal bandwidth determined by Calonico et al. (2014)'s optimal bandwidth selection procedure. Appendix Figure 6 shows that our results are robust to alternative bandwidth choices. In columns (4) to (6) of Table 1, we further restricted the sample to UKB participants who dropped out at age 18 or younger. In the analyses using genetic data, the sample was restricted to individuals who had been genotyped and who were of European genetic ancestries.



Appendix Table 1 gives details about the data. **Appendix Table 2** gives specific details about the main outcome of interest, dementia status. **Appendix Table 3** shows summary statistics.

Appendix Table 1. Data. The table shows the UK Biobank fields used to construct the data used in the main analyses. The UK Biobank Showcase gives more information about each field (see tab Notes and tab Resources). For survey questions, the table also shows the wording of the questions. Participants who answered that they had a college degree were not asked about their school-leaving ages. We assigned a school-leaving age of 22 to college graduates.

	UKB Field	Notes and *Survey Questions*
Registry Data		
Gender	31	Updated by participant if needed
Date of Birth	33	Updated by participant if needed
Survey Questions		
Educational Qualifications	6138	*Which of the following qualifications do you have?*
School-Leaving Age	845	*At what age did you complete your continuous full time education?*
Parents Developed ADRD	20107, 20110	*Has/did your father/mother ever suffer from Alzheimer's disease/dementia?*
Income Greater than £18,000	738	*What is the average total income before tax received by your HOUSEHOLD?*
Income Greater than £31,000	738	*What is the average total income before tax received by your HOUSEHOLD?*
Income Greater than £52,000	738	*What is the average total income before tax received by your HOUSEHOLD?*
Income Greater than £100,000	738	*What is the average total income before tax received by your HOUSEHOLD?*
Diabetes (Ever Diagnosed)	2443	*Has a doctor ever told you that you have diabetes?*
Current Smoker	1239	*Do you smoke tobacco now?*
Algorithmically-Defined Outcomes		
ADRD	42018	See UK Biobank 2022 Algorithmically-Defined Outcomes
Myocardian Infarction	42000	https://biobank.ndph.ox.ac.uk/showcase/ukb/docs/alg_outcome_main.pdf
Stroke	42006	
COPD	42016	
Physical Measures		
Obesity	21001, 23104	Average BMI from anthropometrics and BMI from impedance measurement
Stage 1 Hypertension	93, 94, 4079, 4080	Systolic ≥ 130 or Diastolic ≥ 80
Stage 2 Hypertension	93, 94, 4079, 4080	Systolic ≥ 140 or Diastolic ≥ 90
Biomarker		
Diabetes (HbA1c Test)	30750	HbA1c ≥ 6.5 https://biobank.ndph.ox.ac.uk/showcase/ukb/docs/serum_hb1ac.pdf

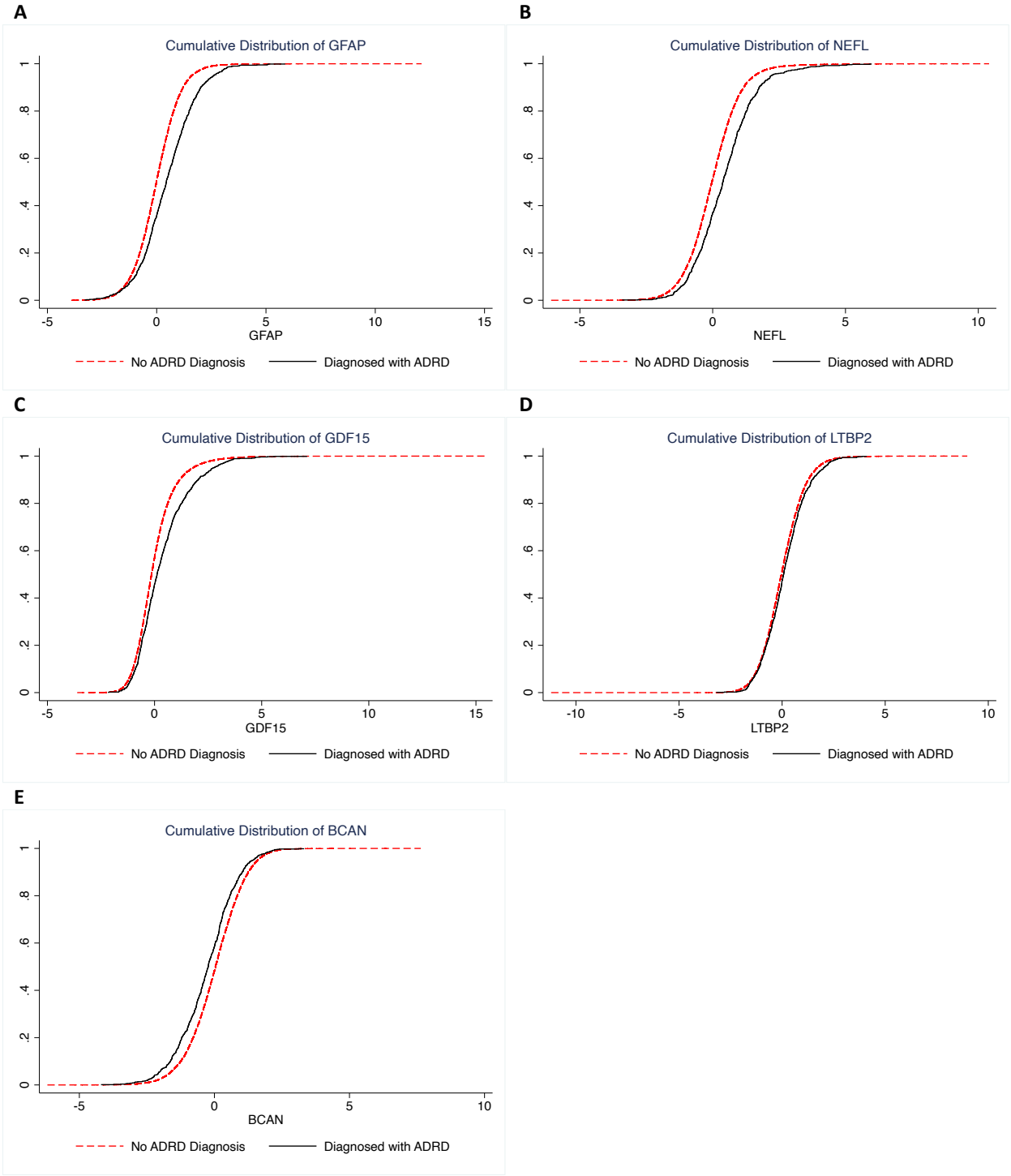
The UK Biobank Outcome Adjudication Group, in conjuction with clinical experts, developed algorithms that ascertain a given health outcome – e.g., ADRD – based on a list of clinical codes. For each individual, the algorithm takes the earliest recorded date in which one of these predefined codes show up in either hospital admission records or in death certificate records. Appendix Table 2 shows the ICD-9 and ICD-10 codes used to ascertain ADRD. In some cases, ADRD was ascertained from the participant's self-report of an ADRD diagnosis, in which case field 20008 is used to identify the date of diagnosis. Less than 2% of the dementia diagnoses in our data are ascertained from self-reports. Approximately 94% of the dementia diagnoses in our data come from hospital admission records. The reader is referred to the document "Algorithmically-defined outcomes" put out by the UK Biobank in January of 2022 (Version 2.0).

Appendix Table 2. Clinical Codes Used to Ascertain ADRD. The table shows the ICD 9 and ICD 10 codes used to ascertain ADRD status of UK Biobank participants.

ICD 10 Code	ICD 10 Text
A81.0	Sporadic Creutzfeldt-Jakob disease
F00	Dementia in Alzheimer's disease
F00.0	Dementia in Alzheimer's disease with early onset
F00.1	Dementia in Alzheimer's disease with late onset
F00.2	Dementia in Alzheimer's disease, atypical or mixed type
F00.9	Dementia in Alzheimer's disease, unspecified
F01	Vascular dementia
F01.0	Vascular dementia of acute onset
F01.1	Multi-infarct dementia
F01.2	Subcortical vascular dementia
F01.3	Mixed cortical and sub-cortical vascular dementia
F01.8	Other vascular dementia
F01.9	Vascular dementia, unspecified
F02	Dementia in other diseases classified elsewhere
F02.0	Dementia in Picks disease
F02.1	Dementia in Creutzfeldt-Jacob disease
F02.2	Dementia in Huntington’s disease
F02.3	Dementia in Parkinson’s disease
F02.4	Dementia in HIV disease
F02.8	Dementia in other specified diseases classified elsewhere
F03	Unspecified dementia
F05.1	Delirium superimposed on dementia
F10.6	Mental and behavioural disorders due to use of alcohol - amnesic syndrome
G30	Alzheimer’s disease
G30.0	Alzheimer’s disease with early onset
G30.1	Alzheimer’s disease with late onset
G30.8	Other Alzheimer's disease
G30.9	Alzheimer's disease unspecified
G31.0	Circumscribed brain atrophy
G31.1	Senile degeneration of brain
G31.8	Other specified degenerative diseases of nervous system
I67.3	Binswanger’s disease
ICD 9 Code	**ICD 9 Text**
290.2	Senile dementia, depressed or paranoid type
290.3	Senile dementia with acute confusional state
290.4	Arteriosclerotic dementia
291.2	Other alcoholic dementia
294.1	Dementia in other conditions classified elsewhere
331	Alzheimer's disease
331.1	Pick's disease
331.2	Senile degeneration of brain
331.5	Creutzfeldt-Jakob disease

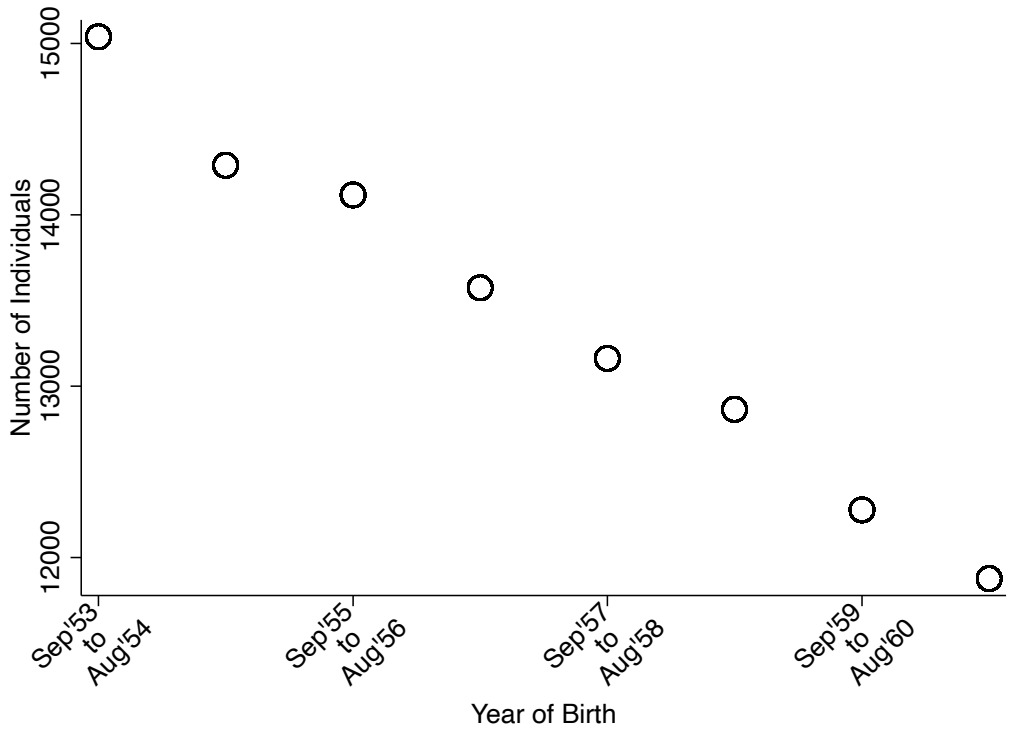
Appendix Table 3. Summary Statistics. This table shows summary statistics of the variables used to produce the results shown in the paper. The sample includes those born between September 1, 1953 and August 1, 1962 (i.e., within 4 years of September 1, 1957).

	All			Dropped Out at Age 18 or Younger		
	N	*Mean*	*SD*	*N*	*Mean*	*SD*
	(1)	(2)	(3)	(4)	(5)	(6)
Male	107,200	0.44	0.50	59,342	0.43	0.50
Year of Birth	107,200	1957	2.33	59,342	1957	2.33
Born after September 1, 1957	107,200	0.47	0.50	59,342	0.47	0.50
Stayed in School until Age 16	107,200	0.90	0.30	59,342	0.82	0.39
School-Leaving Age	107,200	18.79	2.97	59,342	16.32	1.05
Parents Developed ADRD	96,738	0.11	0.31	52,316	0.10	0.30
Diagnosed with ADRD	107,200	0.004	0.06	59,342	0.004	0.06
Age at Time of ADRD Diagnosis	375	61.32	5.17	251	61.21	5.38
Genetic Risk for ADRD	98,778	0.00	1.00	54,843	0.00	1.00
High Genetic Risk for ADRD	98,778	0.50	0.50	54,843	0.50	0.50
Income Greater than £18,000	96,292	0.87	0.34	51,504	0.82	0.39
Income Greater than £31,000	96,292	0.68	0.47	51,504	0.57	0.50
Income Greater than £52,000	96,292	0.38	0.48	51,504	0.25	0.43
Income Greater than £100,000	96,292	0.08	0.27	51,504	0.03	0.17
Diabetes (HbA1c Test)	100,116	0.03	0.16	55,265	0.03	0.18
Diabetes (Ever Diagnosed)	106,958	0.03	0.18	59,167	0.04	0.19
Obesity	106,763	0.25	0.43	59,080	0.29	0.45
Stage 1 Hypertension	107,034	0.68	0.47	59,237	0.70	0.46
Stage 2 Hypertension	107,034	0.37	0.48	59,237	0.40	0.49
Stroke or Myocardian Infarction	107,200	0.05	0.23	59,342	0.06	0.24
Current Smoker	107,136	0.12	0.33	59,302	0.15	0.36
COPD	107,200	0.03	0.18	59,342	0.05	0.21

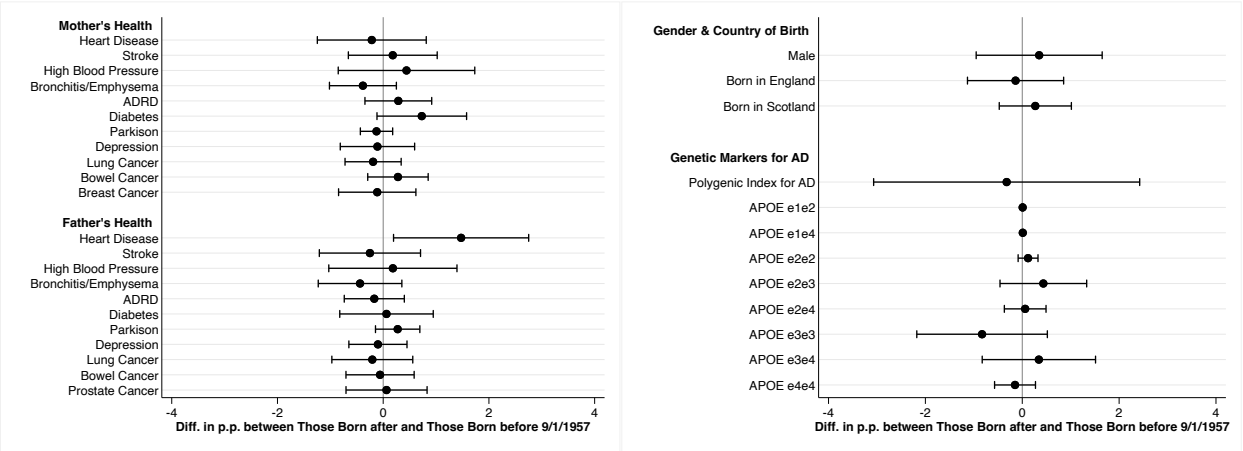


Appendix Figure 2. Dementia Outcome is Associated with Plasma Proteins. The figure shows cumulative distribution functions (CDFs) of five plasma proteins – GFAP (**A**), NEFL (**B**), GDF15 (**C**), LTBP2 (**D**), and BCAN (**E**) – that have been implicated in ADRD (Guo et al. 2024). Separate CDFs are shown for those who had been diagnosed with dementia by December of 2022 (solid black) and for those who had not been diagnosed (dashed red). The plasma proteins were measured at baseline between 2006 and 2010. Contrary to the other four plasma proteins, BCAN is protective against ADRD. The UK Biobank chose a random sample of its participants and made the proteomic data available for this random sample. That is the sample we use in these analyses. It includes people born

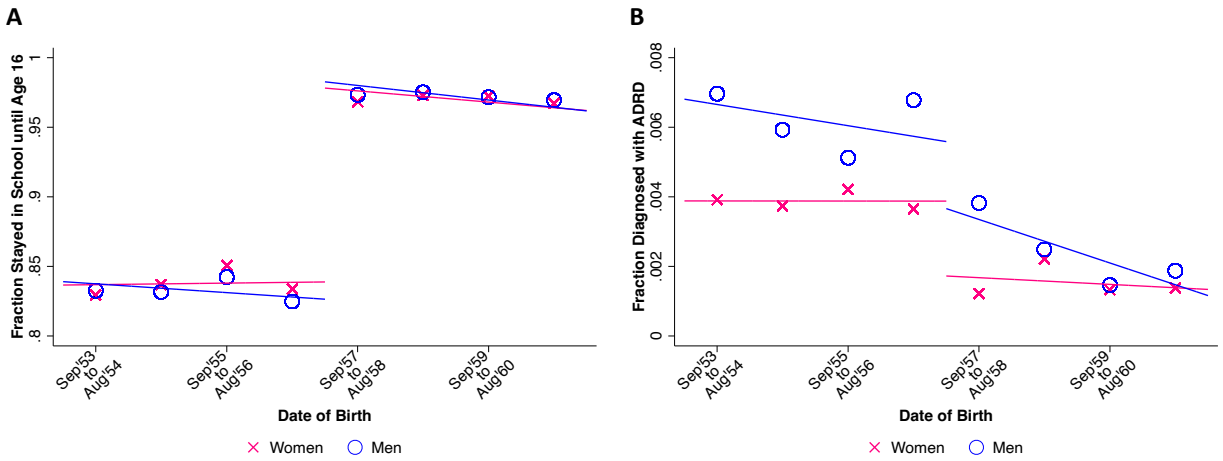
outside our optimal bandwidth and people born outside England, Scotland, and Wales who immigrated after age 14. After being adjusted for age, the outcomes were standardized to have a mean of 0 and a standard deviation of 1.



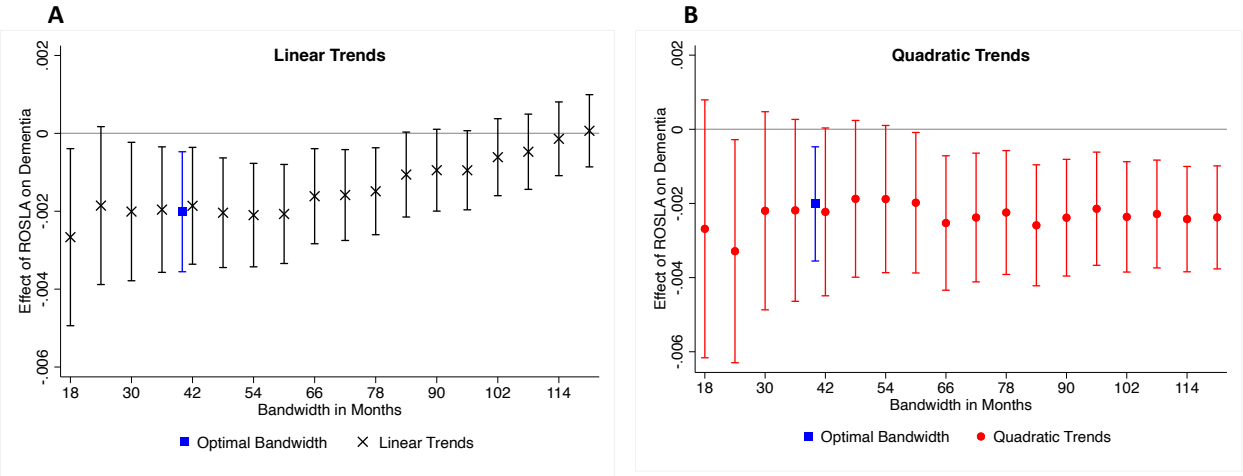
Appendix Figure 3. McCrary Test. The figure shows that we pass the McCrary Test. It shows the number of study participants by year of birth. Year of birth runs from September 1 of a given year to August 31 of the following year. Cohorts born before Year 0 had to stay in school until age 16 while cohorts born before could leave at age 15. The estimated discontinuity of the density is -0.04 with a standard error of 0.024. N = 107,200.



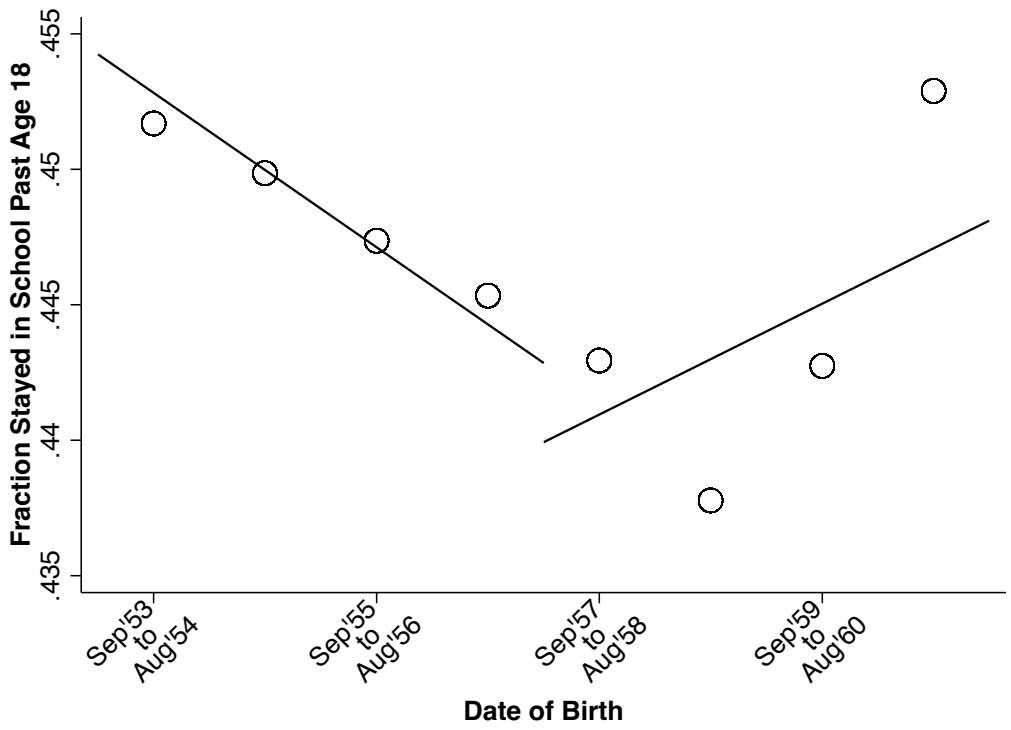
Appendix Figure 4. Balance Test. This figure provides evidence indicating that individuals born right before and right after September 1, 1957 are comparable in terms of pre-reform characteristics. Each row corresponds to a separate regression of the dependent variable listed in the row on an indicator for being born on or after September 1, 1957. All regressions also include exact date of birth to control for birth cohort trends. Separate birth cohort trends are estimated for those born before and those born after September 1, 1957. The markers show point estimates, that is, the coefficient on the indicator for being born on or after September 1, 1957. The brackets show 95% confidence intervals. The sample is restricted to those born within 1,217 days of September 1, 1957 – that is the optimal bandwidth determined by Calonico et al. (2014)'s optimal bandwidth selection procedure. Sample sizes vary between 81,167 and 89,259 depending on the specific dependent variable. The polygenic index for AD, which is the only continuous variable, is normalized to have a standard deviation of one. These results are obtained by estimating a specification akin to the one in equations (1) and (2) above.



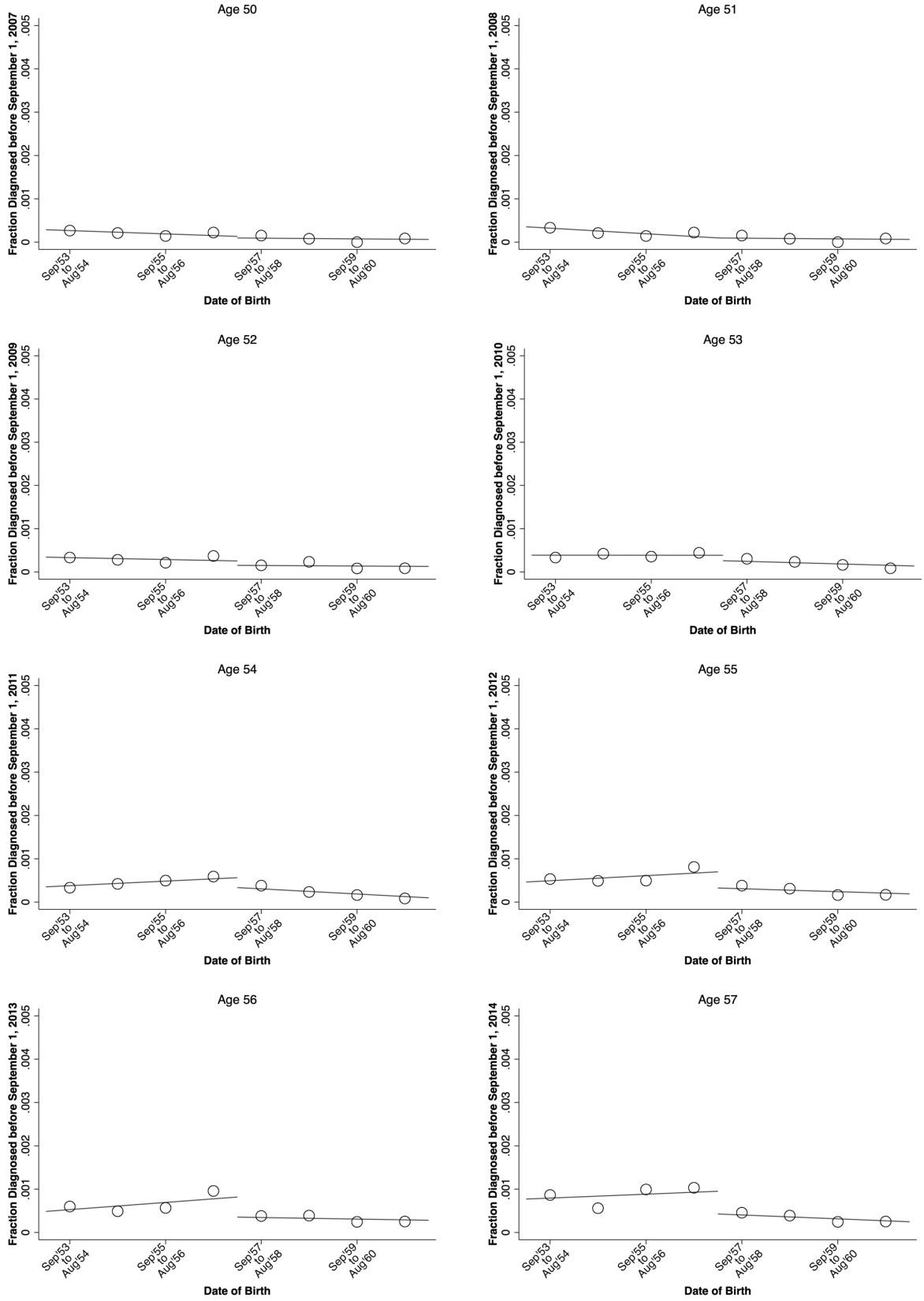
Appendix Figure 5. Similar Reduction in ADRD Risk for Men and Women. Separate results are shown for women (pink) and men (blue). The figures plot (**A**) the fraction of each birth cohort who stayed in school until age 16 and (**B**) the fraction of each birth cohort who was diagnosed with ADRD. The cohort born between September 1, 1957 and August 31, 1958 was the first affected by the reform. The lines show linear trends in date of birth, which are allowed to be different for those born before and after September 1, 1957. Figure (A) shows that the reform affected the education of the two groups similarly. Figure (B) shows that the effect on prevalence was similar for men and women.



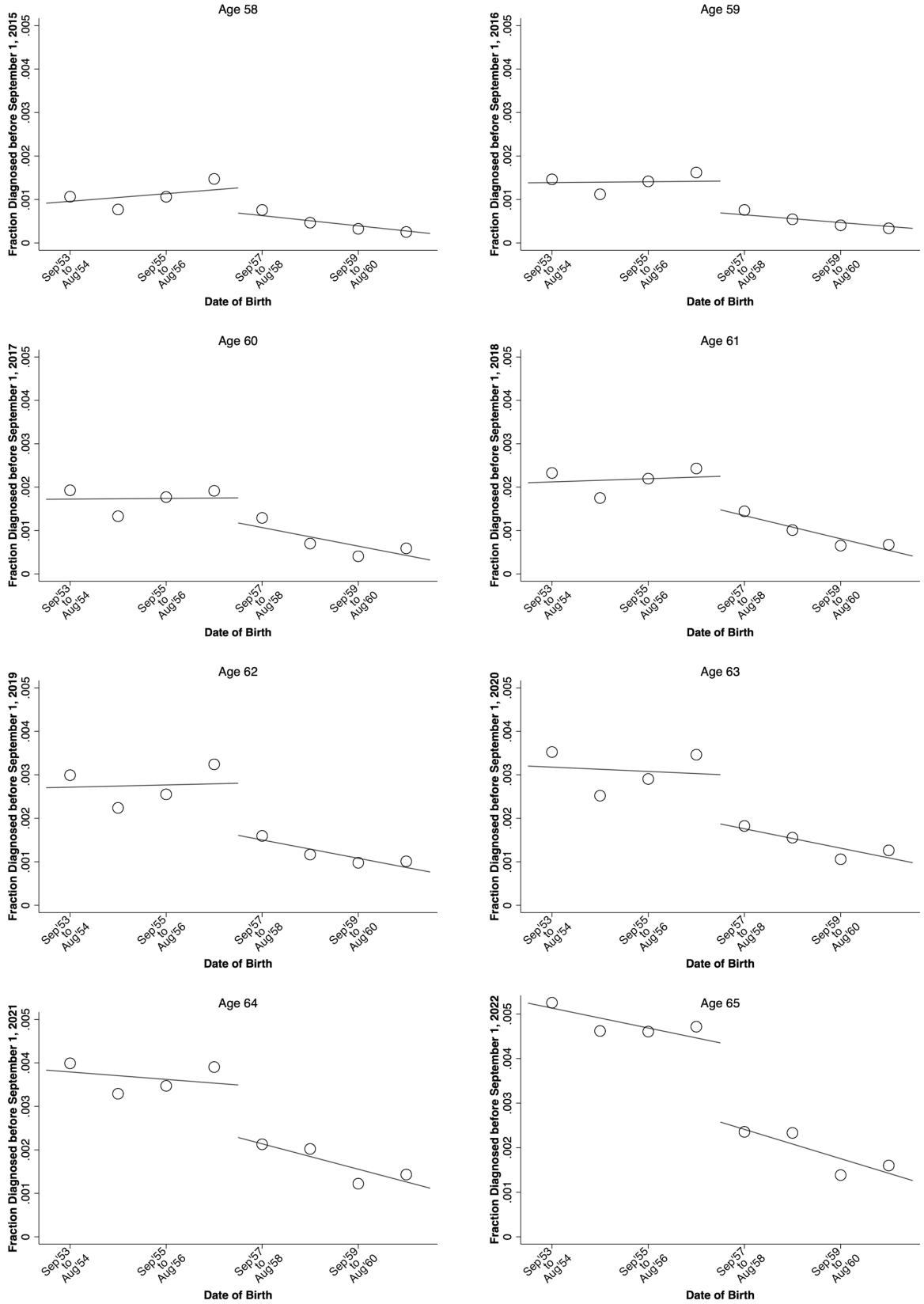
Appendix Figure 6. Bandwidth Sensitivity. The figure investigates whether the effects of the reform on ADRD risk vary with the bandwidth size (in months). These estimates correspond to equation (2) above and to the model estimated in column (2), top panel of Table 1. The markers show the coefficient on the indicator for being born on or after September 1, 1957. The brackets show 95% confidence intervals. Appendix Figure 6A shows estimates from a model with linear trends, as in equation (2). The blue square shows the estimate with the optimal bandwidth. Appendix Figure 6B shows estimates from a model with quadratic trends in exact date of birth. *N* varies from 40,519 (18-month bandwidth) to 280,463 (120-month bandwidth).



Appendix Figure 7. Reform Had No Effect on Fraction Staying in School Past Age 18. The figure shows that the reform had no effect on the fraction of students staying in school past age 18, which justifies the sample restriction in columns (4) to (6) of Table 1. It shows the fraction of study participants who stayed in school until *at least* age 19 by year of birth. Year of birth runs from September 1 of a given year to August 31 of the following year. Those born in Year 0 were born between September 1, 1957 and August 31, 1958. Cohorts born after Year 0 had to stay in school until age 16 while cohorts born before could leave at age 15. The lines show linear trends in date of birth, which are allowed to be different for those born before and after September 1, 1957. The point estimate is -0.0024 with a standard error of 0.0066 and a p-value of 0.714. The number of observations is 89,259.

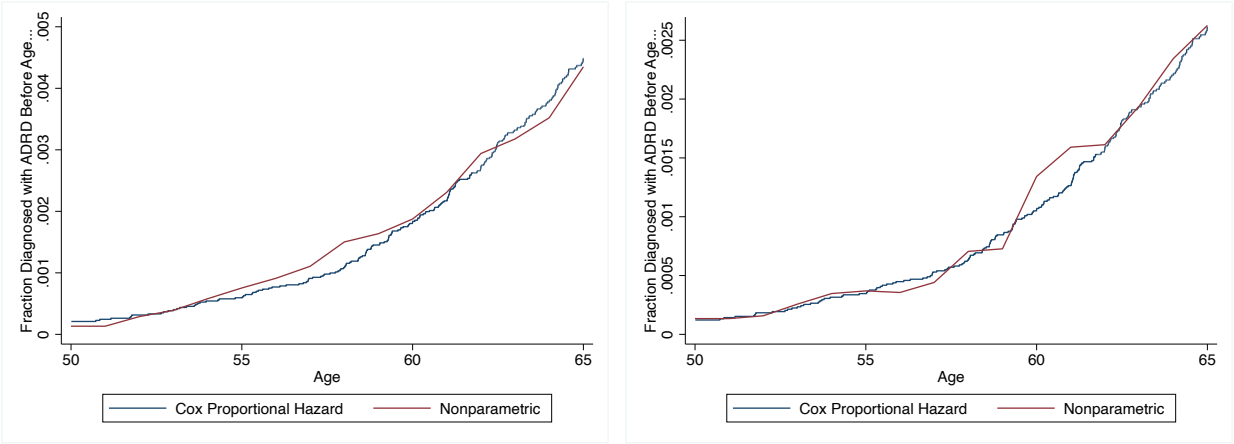


Appendix Figure 8. Hazard Estimates. The fraction diagnosed by 9/1 of year 1957 + "age" is shown, separately by date of birth. The graph title is the age those born on 9/1/1957 were at the time. The lines show estimates of equation (6), which are used in turn to construct Fig. 2B. In particular, the solid black line in Fig. 2B corresponds to θ_0^{age} while the dashed black line corresponds to $\theta_0^{age} + \theta_1^{age}$. The shaded area in Fig. 2B showing 95% confidence intervals corresponds to $\theta_0^{age} + \theta_1^{age} \pm [1.96 \times \text{SE}(\theta_1^{age})]$. The sample is restricted to those born within 4 years of Sep 1, 1957. N = 107,200.



Appendix Figure 8. Hazard Estimates. The fraction diagnosed by 9/1 of year 1957 + "age" is shown, separately by date of birth. The graph title is the age those born on 9/1/1957 were at the time. The lines show estimates of equation (6), which are used in turn to construct Fig. 2B. In particular, the solid black line in Fig. 2B corresponds to θ_0^{age} while the dashed black line corresponds to $\theta_0^{age} + \theta_1^{age}$. The shaded area in Fig. 2B showing 95% confidence intervals corresponds to $\theta_0^{age} + \theta_1^{age} \pm [1.96 \times \text{SE}(\theta_1^{age})]$. The sample is restricted to those born within 4 years of Sep 1, 1957. $N = 107{,}200$.

A. Born before September 1, 1957 **B. Born after September 1, 1957**



Appendix Figure 9. Survival Analysis. The figures compare the survival curves implied by the Cox Proportional model (solid blue line) to the survival curves originating from the nonparametric model (solid red line) described in equation (6) above. The left panel compares the curves for those born before September 1, 1957. The right panel compares the curves for those born after September 1, 1957. The results of the nonparametric model are shown in Figure 2B of the paper. The Cox Proportional model includes three independent variables: the indicator for being born after September 1, 1957; date of birth in days; and the interaction of these two variables. Our estimate of interest in the coefficient on the first variable. Its point estimate is 0.582 with a standard error of 0.141 and a p-value of 0.025.

Appendix Table 4. Mortality and Selection. This table shows that selective mortality does not drive our results. The 1972 ROSLA may have affected the likelihood of death, which is a potential concern because individuals who live longer are more likely to be diagnosed with ADRD. To investigate this issue, columns (1) and (2) estimate a multinomial logit that distinguishes between three possible outcomes: (a) being alive and having not been diagnosed with ADRD; (b) having died with no ADRD diagnosis; and (c) having been diagnosed with ADRD (the participant may have been alive or not as of December of 2022). Column (1) shows that we still find evidence that those born after September 1, 1957 are less likely to be diagnosed with ADRD. The point estimate in column (2) suggests that those individuals are less likely to have died, but this effect is not statistically significant. Column (3) estimates a regular logit where the omitted group includes both (a) and (b). The comparison of column (3) to column (1) shows that taking selective mortality into account does not affect our main estimate of interest. Columns (1) and (3) show the effects on ADRD risk. Column (2) shows the effect on likelihood of death. "Born after" is an indicator for being born on or after September 1, 1957. All regressions control for date of birth in days and its interaction with the "Born after" indicator variable. Robust standard errors between parentheses. N = 89,259.

	Multinomial Logit		**Logit**
	ADRD	*Dead*	*ADRD*
	(1)	(2)	(3)
Born after	-0.55	-0.05	-0.55
	(0.24)	(0.07)	(0.24)

Appendix Table 5. ADRD Risk from Genetic Factors. The table shows the association of different genetic measures with ADRD risk. The genetic measures are a polygenic index for AD, indicators for having different APOE genetic markers, and the composite measure that includes both this polygenic component and the APOE genetic markers. This composite measure was constructed based on the results shown in column (3). The AD PGI and the composite measure are standardized to have a standard deviation of one. Columns (1) to (4) show results for study participants born more than 1,217 days before September 1, 1957 (N = 273,712). Columns (5) to (8) show results for our analyzing sample, who were born within 1,217 days of September 1, 1957 (N = 82,250). To construct our composite PGI which also incorporates the effect of the the APOE region of the genome, we first follow the approach of Lumsden et al. (2020) to call the APOE variant for each person in the full UKB sample. We then regress our measure of ADRD onto the PGI and indicator variables for each person's APOE variant (e.g., ε3ε3, ε3ε4, ε2ε4, etc.) for the individuals in the UKB that are not in the UKB analysis sample. The coefficients from this regression along with the PGI and APOE variant calls are then used to produce the composite PGI in the analysis sample.

	Born Earlier than Optimal Bandwidth				**Born within Optimal Bandwidth**			
	ADRD (in p.p.)				*ADRD (in p.p.)*			
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
AD PGI	1.55		0.49		0.09		0.009	
	(0.04)		(0.04)		(0.02)		(0.03)	
Composite Measure				2.16				0.15
				(0.06)				(0.03)
ε1ε2		-1.98	-2.21			-0.29	-0.30	
		(0.04)	(0.04)			(0.03)	(0.04)	
ε1ε4		-1.98	-3.25			-0.29	-0.31	
		(0.04)	(0.20)			(0.03)	(0.07)	
ε2ε2		-0.53	-0.34			0.11	0.12	
		(0.29)	(0.29)			(0.28)	(0.29)	
ε2ε3		-0.35	-0.25			-0.08	-0.08	
		(0.08)	(0.08)			(0.05)	(0.05)	
ε2ε4		1.33	0.83			0.10	0.09	
		(0.22)	(0.22)			(0.14)	(0.14)	
ε3ε4		3.10	2.50			0.15	0.13	
		(0.09)	(0.10)			(0.05)	(0.06)	
ε4ε4		11.41	10.22			0.97	0.94	
		(0.42)	(0.43)			(0.25)	(0.26)	
R^2	0.0080	0.0150	0.0160	0.0160	0.0002	0.0010	0.0010	0.0010

Appendix Table 6. Causal Genetic Effects. This table shows that the associations between dementia and genetic risk shown in Figure 3 and in the bottom panel of Table 1 can be given a causal interpretation. In principle, the association between dementia and genetic risk could be confounded by omitted environmental factors associated with both. However, one can exploit that the genetic variation across (full) siblings is random to isolate causal genetic effects. In order to exploit this variation, this exercise is conducted with UK Biobank participants whose siblings also participated in the study (to maximize statistical power, we include participants born outside our optimal bandwidth). Column (1) estimates the association between dementia (measured in percentage points) and our measure of one's genetic risk factor for developing ADRD, the AD polygenic index (PGI). Column (2), which includes family fixed effects, estimates the causal effect of the AD PGI (also known as "direct genetic effects") on dementia. The last column of the table formally tests whether the coefficient on the genetic risk in column (2) is statistically different from the coefficient on the genetic risk estimated in column (1). We cannot reject the hypothesis of equality, which leads us to conclude that the associations between dementia and genetic risk shown in Figure 3 and in the bottom panel of Table 1 can be given a causal interpretation. Robust standard errors in column (1). In column (2), standard errors clustered at the family level.

	ADRD (in p.p.)		P-Value Test
	(1)	(2)	(1) = (2)
Genetic Risk	1.13	0.99	0.402
	(0.10)	(0.16)	
Constant	1.86	1.85	-
	(0.07)	(2.2E-3)	
Family Fixed Effects?	No	Yes	
Mean of Dependent Variable	1.84	1.84	
Number of Individuals	38,518	38,518	
Number of Families	-	19,029	

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