Early-Life Determinants of Cognitive Decline and Dementia: The Role of Genetics, Education and Their Interaction

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Detailed Abstract

I. Introduction

Gains in life expectancy and population aging are driving a sharp rise in Alzheimer's Disease and Related Dementias (ADRD), with a predicted global prevalence of 65.7 million people by 2030.[1] In this context, it is crucial to understand what factors can modify ADRD risk and cognitive decline in older ages. Education has been identified as one potential modifier, as higher education is robustly associated with lower ADRD risk.[2,3] Studies in the US and other high-income countries suggest a recent decline in the incidence and prevalence of dementia coinciding with rising levels of education in more recent cohorts (National Institute on Aging Meeting Summary, 2016).[15]

Moreover, theory suggests a link between education and dementia. The cognitive reserve hypothesis, for example, suggests that people with high cognitive reserve (correlated with years of education) may be able to compensate for age-related brain damage and therefore stave off cognitive decline until later in life, compared to someone with low cognitive reserve or few years of education[16]. A person with high cognitive reserve may therefore face a lower lifetime risk of dementia and a longer cognitively healthy life expectancy.

Despite this evidence, little is known about how much of this association reflects a causal effect from education to cognition/ADRD risk and how much is driven by common third factors, such as genetics, that may confound and moderate this relationship. In addition, the relevance of factors beyond the *quantity* of education – in particular the importance of education *quality* as a driver of ADRD risk, as well as a moderator in the relationship between education and ADRD – are not well understood. Filling these knowledge gaps is essential to the design of effective policies aimed at improving cognitive health and reducing disparities in ADRD risk.

In this paper, we study how much of the association between education, cognition and ADRD risk in late-life is due to a causal effect running from education quantity and quality to cognition/ADRD risk. To deal with the fact that different people self-select into different types and quantities of schooling, we use two natural experiments: one school reform that affected education quantity (years of compulsory schooling) and another that affected quality (academic curriculum). We supplement existing datasets with the construction of polygenic indexes (PGIs) for educational attainment (EA) and for Alzheimer's Disease (AD), and by linking participants to local historic school quality measures such as pupil/teacher ratios and teacher pay. This allows

us to study the role of genetics and school quality in moderating the effects of both school reforms on ADRD.

In order to identify the causal effect of education *quantity* on ADRD outcomes in later life, we exploit UK's Raising of School Leaving Age (ROSLA) Order of 1972.[4–7] The ROSLA increased the minimum school-leaving age from 15 to 16 years for students born on or after September 1st 1957. We use data from the UK Biobank (UKB), a dataset with nearly 500,000 participants born between 1933 and 1970, and a Regression Discontinuity Design to investigate how the ROSLA affected ADRD outcomes in late-life. To estimate the causal effect of education *quality*, we exploit the Finnish comprehensive school reform of 1972-1977, which shifted the selection of students between vocational and academic tracks from age 11 to age 16.[8] For these analyses, we use a difference-in-differences strategy and data from FinnGen, which has over 350,000 participants.

Family genetic data provides us with an additional source of random variation in education. Due to Mendelian inheritance, we can exploit the "genetic lottery" at conception to evaluate the direct (causal) genetic effect of the EA PGI on ADRD outcomes. We can do this by conditioning the analyses on the PGIs of respondents' parents.[9] Previous studies have shown that the direct genetic effect of the EA PGI causes higher education.[10,11] We use this variation to investigate whether a higher EA PGI's direct effect (and consequent higher education) causally mitigates the polygenic risk of ADRD. In addition to UKB and FinnGen cohorts, who were fully genotyped and contain subsamples of related individuals, we will also use Dutch data from Lifelines, another large cohort that emphasized family connections in the sampling process, making it ideal for family-based genetic analyses.

Both the UKB and FinnGen samples are linked to administrative health records from hospital admissions, primary care visits, and death registries, that allow us to identify whether and when a participant was diagnosed with dementia. Currently there are 9,430 ADRD cases in the UKB and 8,030 in FinnGen and these numbers are expected to grow steeply as the cohorts age. Moreover, the UKB and Lifelines have a number of cognitive tests aimed at measuring numeric, visual and prospective memory, fluid intelligence, and processing speed. Finally, UKB, FinnGen, and Lifelines measured ADRD risk factors (e.g., BMI and smoking) that allows us to investigate the potential behavioral channels through which education affects ADRD. Having ADRD diagnosis, risk factors, and cognitive tests for these large samples is a strength of the current paper.

Our paper makes several contributions to the existing literature on the effects of education on ADRD risk. First, and most importantly, we use three sources of exogenous variation in education (one school reform that affected education quantity, another one that affected education quality, and family-based random variation in genetics) to study the causal effect of education on late-life cognition and ADRD risk. The use of a number of different sources of variation in education in three different national contexts (UK, Finland and the Netherlands) allows us to assess the relative importance of different aspects of education (e.g., quality versus quantity) and to gauge the generalizability of our results across aspects and settings.

Second, in addition to studying ADRD risk factors and survey measures of cognition, one of our main outcomes is actual ADRD diagnosis derived from administrative linkages to hospital inpatient data, primary care data, and death registries data, in addition to self-reported diagnosis. This is especially important in the context of studying dementia, a condition that is challenging to diagnose. Cognitive decline often progresses slowly, and the threshold of disability can be hard to distinguish reliably. Moreover, while brain pathology and cognition are correlated, there is no one-to-one correspondence between them.[18] The use of ADRD diagnoses from administrative health data and death records also helps with other challenges that plague survey-based ADRD measures, such as selective attrition (i.e., frail people are more likely to leave studies), survival bias, and the need for proxies when participants can no longer answer surveys for themselves. Moreover, the administrative-based data also allows us to study the effect of education on the age at ADRD diagnosis, since there are records of the date when a dementia diagnosis was first recorded for an individual in the data. Finally, such outcomes allow us to differentiate Alzheimer's disease, vascular dementia, frontotemporal dementia and other causes of dementia and analyze them separately.

Third, the use of three large aging cohorts – the UK Biobank, FinnGen and Lifelines – means we observe enough dementia cases to have well-powered analyses. The UK Biobank (UKB), for example, has over 500,000 participants born between 1937-1970 (who are currently 41-84 years old). There are approximately 10,000 dementia cases in the UKB currently and, given the cohort's age structure, we expect this number to increase steeply in next years.

Fourth, the three cohorts we use are genotyped which allow us to investigate the role of genetics in driving ADRD risk (using a subsample of related individuals) and in moderating the effects of the school reforms. ADRD has a strong genetic basis, with an estimated twin-based heritability of AD as high as 80%[19–21] and a SNP-heritability of 33%,[22] allowing us to use genetic data to identify individuals at risk. Importantly, we will be able to study whether the different sources of exogenous variation (generated by both the UK and Finnish school reforms but also by the within family "genetic lottery" in the UKB, FinnGen and Lifelines) in education reduce the association between polygenic risk for AD (AD PGI) and actual ADRD outcomes. A side benefit of studying those with a high AD PGI is increased power, since the high AD PGI population exhibits earlier onset and higher prevalence of ADRD when compared to the general population[23,24].

Finally, we study whether local measures of school quality moderate the relationship between education and ADRD outcomes. In particular, we link study participants to historic local school quality data around the time when they are in school, based on their locality of birth or residence when 10 years old (availability of data varies across the three cohorts). We then use these geographic measures of quality to investigate whether the effect of school reforms, and the direct (causal) effect of a polygenic index for educational attainment (EA PGI) on ADRD outcomes, vary for students in high- versus low-school quality localities. The seminal work by Card and Krueger[28] showed that geographic measures of quality, such as teacher/pupil ratios, term length and teacher pay, predicted higher earnings returns to education. We hypothesize that they also predict the effects of education on ADRD outcomes.

The research described here builds on a few papers that have used natural experiments to estimate the effects of education quantity on cognition later in life.[7,29,30] For example, ref. [31] finds that the extra education afforded by the 1947 ROSLA in the UK improved male's earnings and executive functioning at older ages. Similarly, ref. [32] uses variation in state-level school policies in the US jointly with HRS data and find that education has a protective effect on cognition. We advance our knowledge by using administrative-based measures of dementia diagnosis together with survey-based measures; using data from large-sample aging cohorts in three different countries; considering the importance of education measures beyond years of schooling; and investigating the role of genetics as a driver and mediator of ADRD outcomes.

II. Data

II.1. UK Biobank, FinnGen and Lifelines

We use data from three cohort studies: the UK Biobank, FinnGen and Lifelines. The UKB is a large, population-based prospective study initiated by the UK National Health Service.[36] Between 2006 and 2010, more than half a million individuals between the ages of 40 and 69 visited 22 centers throughout the UK. The center visit included the completion of a touchscreen questionnaire, a verbal interview, and collection of physical measures. All participants were genotyped. Moreover, the data was linked to administrative hospital data (ICD-coded diagnosis / OPCS-coded procedures), primary care data, and death registries. We will focus our analyses on cognition, ADRD diagnosis, and ADRD risk factors.

Survey-based measures of cognition in the UKB include reaction time, pairs-matching, fluid intelligence, the prospective memory, and the numeric memory tests. Moreover, UKB participants are linked to hospital in-patient data, coded primary care data, and death registry data, so that all conditions that lead to an interaction with UK's National Health Service are represented in the linked data, including dementia. We also use a number of algorithmically-defined outcomes for dementia derived from the linked data and a baseline verbal interview that contains self-reported dementia diagnosis.

The UKB is not a randomly-selected, nationally-representative dataset. Its sample is more educated, healthier and lives in less socioeconomically deprived areas than the overall population.[37] However, as argued in the *Limitations* section below, our results will still have internal validity.

FinnGen is a partnership of several public and private institutions, including six regional and three country-wide Finnish biobanks and data from previously established population and disease-based cohorts. Over 350,000 participants are linked to the national health registries (1969–2016), which track their information from birth to death on various health outcomes. The participants have a mean birth year of 1959 (s.d. of 19.26 years). Individuals with AD are identified by the ICD8, 9, or 10 code on their hospital discharge, or cause of death record.

Lifelines is a multi-generational prospective cohort study that includes over 10% (N=167,000) of the population of the Northern Netherlands. The study includes individuals of all ages and

consists of a baseline assessment at a Lifelines site conducted between 2007 and 2014, with ongoing repeated assessments every five years. These consists of various questionnaires, a verbal interview, and the collection of anthropomorphic measurements, a urine sample, and biological samples. Currently, over 50,000 Lifelines participants have genotyped data available, about 40,000 are currently being genotyped, and the remainder is expected to be genotyped in the next 1-2 years. Family connections were emphasized in the sampling process, such that Lifelines provides a unique data structure to estimate the prevalence of ADRD within families. At baseline, all participants took the Ruff figural fluency test (RFFT). In addition, all participants aged 65 and over took the Mini-Mental State Examination (MMSE). The MMSE was repeated during the second follow-up assessment (ten years after baseline) for 5,000 participants.

All three datasets contain detailed geographic identifiers for respondents at birth or during their school lives. We use these to link respondents to geographical historical measures of school quality, which allow us to test whether the effect of education on cognition and ADRD outcomes vary with local school quality measures.

II.2. Construction of Polygenic Indices and Parental Imputations

At a high level, a PGI for some phenotype is a composite measure meant to represent the portion of phenotypic variation that can be explained by a linear combination of common genetic variants called single-nucleotide polymorphisms (SNPs). PGIs are constructed by taking a weighted sum of an individual's genotypes for a set of observed SNPs. The weights that define the PGI are based on large genetic studies called genome-wide association studies (GWASs). GWASs measure the association between some phenotype and millions of SNPs. Using Bayesian methods that account for the correlation structure of the genome, these associations are transformed to PGI weights. In other words, each index is a weighted sum of SNP genotypes:

$$I_i = \sum_j g_{ij} w_j, \quad (1)$$

where I_i is the PGI for individual i, $g_{ij} \epsilon \{0,1,2\}$ is the count of the number of reference alleles for individual i at SNP j, and w_j is the weight for SNP j, derived from an existing GWAS.

The predictive power of a PGI depends on several factors, including the heritability of the phenotype in the GWAS and the prediction sample, and the size of the GWAS sample. We constructed PGIs for educational attainment (EA) and Alzheimer's disease (AD) for all participants in the three cohorts we study: UKB, FinnGen and Lifelines. The strongest PGIs for AD and EA have been shown to have predictive power of up to 2% and 17%, respectively, in European ancestry populations (measured by the variance explained, R^2, by the PGI). To produce the final weights, we transformed these summary statistics using a standard method, LDpred2.[41]

Interpreting results using PGIs is nuanced. Importantly, an individual's genes are not randomly assigned in a population, which means that a PGI may be correlated with other important nongenetic factors including their family background and ancestry. In all of the analyses that use PGIs, we restrict our sample to a subset that is classified as having European ancestries based on how closely related the sample is to the European-ancestry reference sample from the 1000 Genomes Project. We also include genetic principal components as covariates to (partly) control for any additional population stratification that exists within our sample. Despite

this, even these strategies for accounting for unobserved confounders have been shown to be insufficient; PGIs are still correlated with the PGIs of each individual's parents which may have an effect on the phenotype of the child. As a result, PGIs must be interpreted as a combination of both genetic and environmental effects (unless they are employed in a family design; see below).

Due to the process of Mendelian inheritance, PGIs are randomly assigned conditional on the average PGI of a person's parents. Therefore, if the average PGI of an individual's parents are included as covariates, the coefficient associated with the individual's own PGI can be thought of as the "causal effect of the PGI" in that it represents a weighted average of the causal effects of the SNPs included in the PGI or SNPs correlated with the PGI. This is especially interesting when studying the causal effect of education on ADRD outcomes, since, in this case, the causal effect of the EA PGI provides an additional source of exogenous variation in education.

In the datasets we use in this study, few individuals have both parents genotyped. However, using a novel method, we are able to impute the average PGI of a person's parents as long as one first-degree relative (e.g., a sibling or a parent) is available.[9] It has been shown that controlling for the imputed parental genotype is sufficient to produced unbiased estimates of the causal effect of the PGI.[9] Intuitively, this is because, at a minimum, all shared variants between the parent and child are included in the imputed parental PGI, and these shared variants are the source of confounding when they are omitted. In the UKB, FinnGen, and Lifelines, we observe or can impute the average parental PGI of 43,204; 47,062; and 71,952 individuals, respectively.

Even though family-based methods allow us to obtain causal estimates of the effect of a PGI, the causal mechanisms involved must still be interpreted with caution. For most behavioral phenotypes and many medical phenotypes, the causal pathways may operate through complicated and variable environmental mechanisms. As such, it would be incorrect to interpret even the causal component of a PGI as an "innate" or "immutable" component of the phenotype.

III. Methods

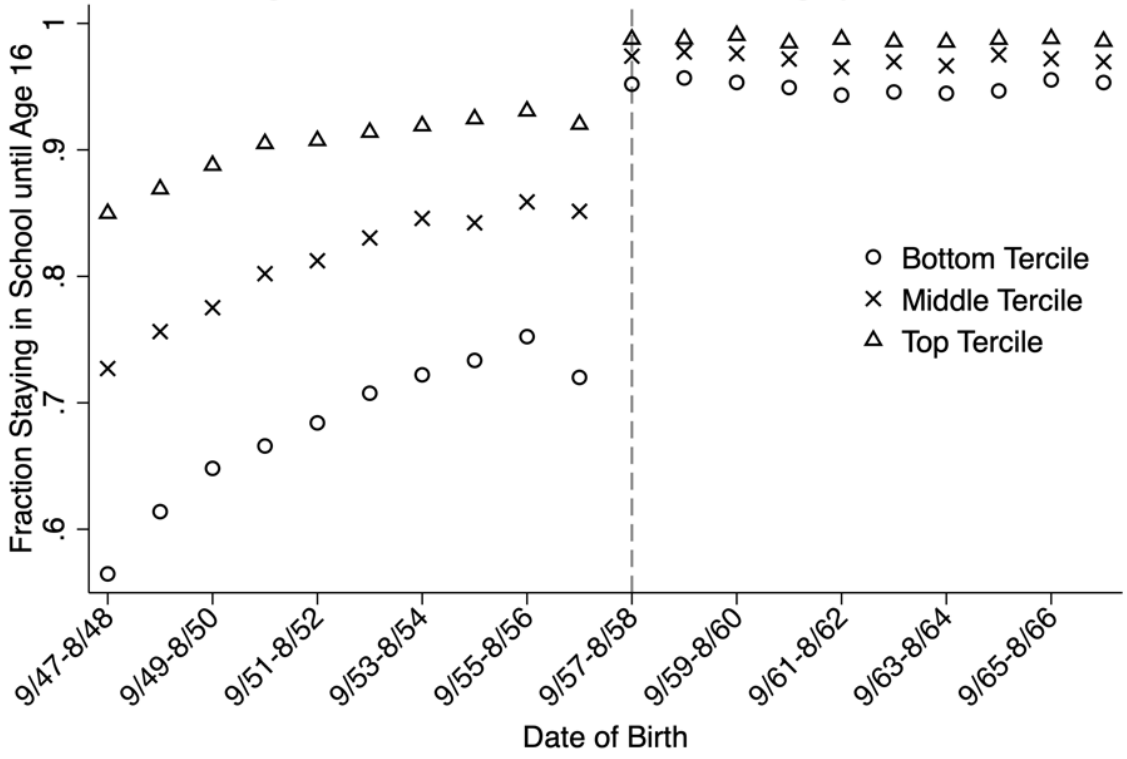
In order to overcome the endogeneity in schooling decisions and estimate the causal effect of education quantity and quality on cognition, ADRD risk factors and diagnosis, we use two different natural experiments. The first experiment, an increase in school leaving age in the UK, increased compulsory schooling by one year, but did not change other key aspects of the educational system (e.g., curriculum). The second experiment, a comprehensive school reform in Finland, replaced a two-track school system with a uniform nine-year comprehensive school and shifted the selection of students into vocational and academic tracks from age 11 to age 16. We argue that the first reform affected primarily the *quantity* of education students got, while the second reform affected the *quality* of education. We discuss below how these two reforms were implemented and the empirical methods we will use to uncover the causal effects of education quantity and quality on ADRD outcomes.

III.1 *UK's Raising of School Leaving Age (ROSLA) of 1972*

In 1972, England, Scotland and Wales passed the ROSLA legislation, which increased the minimum school-leaving age from 15 to 16 years of age (see [4–7] for a detailed discussion of the 1972 ROSLA). The change took effect in September 1, 1972, implying that those who were 15 or younger before that date (i.e., born on September 1, 1957 or later) had to stay in school until at least age 16 while those born before that date could still drop out at age 15. Infrastructure investments, such as school building to absorb the additional students, preceded the 1972 ROSLA, but key elements of the school system did not change with the reform.

The ROSLA generated a discontinuity in years of education by date of birth, with kids born within days of each other receiving different levels of schooling. Moreover, these effects differed by EA PGI. Figure 1 plots the fraction of study participants in the bottom, middle and top terciles of the EA PGI distribution who stayed in school until at least age 16. For example, the circles show the fraction of low-PGI individuals who stayed in school until age 16 by year of birth. The graph shows a sharp discontinuity in schooling at the vertical line, which marks the first birth cohort affected by the reform. Among cohorts born before 1957, those with low PGIs were less likely to stay in school until age 16. However, after the reform almost everyone stayed in school until age 16. Further, those with lower PGIs for EA were the most affected by the reform (a larger jump). The two-stage least squares (2SLS) estimates we propose to use take into account this difference in the likelihood of being affected by the reform.

Figure 1: Effect of ROSLA on Schooling by EA PGI



School reforms like the ROSLA Order provide a unique opportunity to study the causal effects of education because the exogenous variation in schooling generated by the reform is "as good as random."[34] The policy forced students who were born within days of each other, and *who would otherwise have had similar education and dementia risk*, to obtain different levels of education. Individuals born on August 31st 1957 provide a counterfactual of the levels of cognition that individuals born on September 1st 1957 would have had, *had they not been forced to stay in school until age 16*. The Regression Discontinuity Design (RDD), described in detail below, will estimate the causal effects of education on dementia and cognitive outcomes by comparing those born just before and just after September 1, 1957. Using the same research design and UKB data, past studies by our research group have shown that the extra education afforded by the ROSLA resulted in an increase in income, and a reduction in BMI later in life, especially for participants who had high PGI for obesity (see [11,33]).

We estimate how the effects of the ROSLA on ADRD outcomes vary by EA and AD PGIs, running the following RDD reduced-form model

$$ADRD_i = \beta_0 + \beta_1 After_i + \beta_2 After_i * I_i + \beta_3 I_i + g(DoB_i) + X_i \boldsymbol{\beta}_4 + \varepsilon_i \quad (2),$$

where $ADRD_i$ is a cognitive or dementia outcome for individual i (i.e., ADRD risk factors, diagnosis or age at diagnosis – all ADRD outcomes will be oriented so that a higher number means better cognitive health); $After_i$ is 1 if the individual was born on or after September 1st 1957 (0 otherwise); I_i is the EA or AD PGI constructed as in equation (1) above (i.e. we will run separate regressions for each PGI); DoB_i is the date of birth (measured in days); the vector X_i contains predetermined characteristics, such as gender, age at interview, and month-of-birth dummies (e.g., July), as well as the first 20 principal components of the genetic data to control for ancestry effects.[46] The function $g(\cdot)$ captures birth cohort trends in ADRD outcomes that are allowed to vary on both sides of the discontinuity. The coefficients of interest, β_1 and β_2, give the causal effect of the ROSLA on ADRD outcomes and whether it varies with the EA and/or AD PGIs.

As an additional more nonparametric specification, we create a set of indicator variables of whether an individual has a PGI in the lowest, middle, or highest third of the sample. In this specification, I_i will be a vector composed of the full set of binary variables defined above, omitting the lowest category.

The ROSLA did not induce students to stay in school past age 18,[5,11] therefore we restrict the sample to individuals who left school at age 18 or younger to increase the precision of our estimates.[31,47] We run two alternative specifications: a 10-year bandwidth with quadratic trends in date of birth and a 4-year bandwidth with linear trends. We use triangular weights, giving greater weight to participants close to the cutoff.

The identifying assumption is that the unobserved determinants of health, i.e., ε_i, are a smooth function of date of birth. We partially test this assumption by running specifications similar to (2) with predetermined characteristics, such as gender, place of birth, and genetic makeup, as the dependent variable. Results support the hypothesis that the identification assumption is valid.[33]

We also estimate two-stage least squares (2SLS) models in order to estimate the effect of one additional year of schooling on the ADRD outcomes of "compliers" (i.e., those who were affected by the ROSLA)

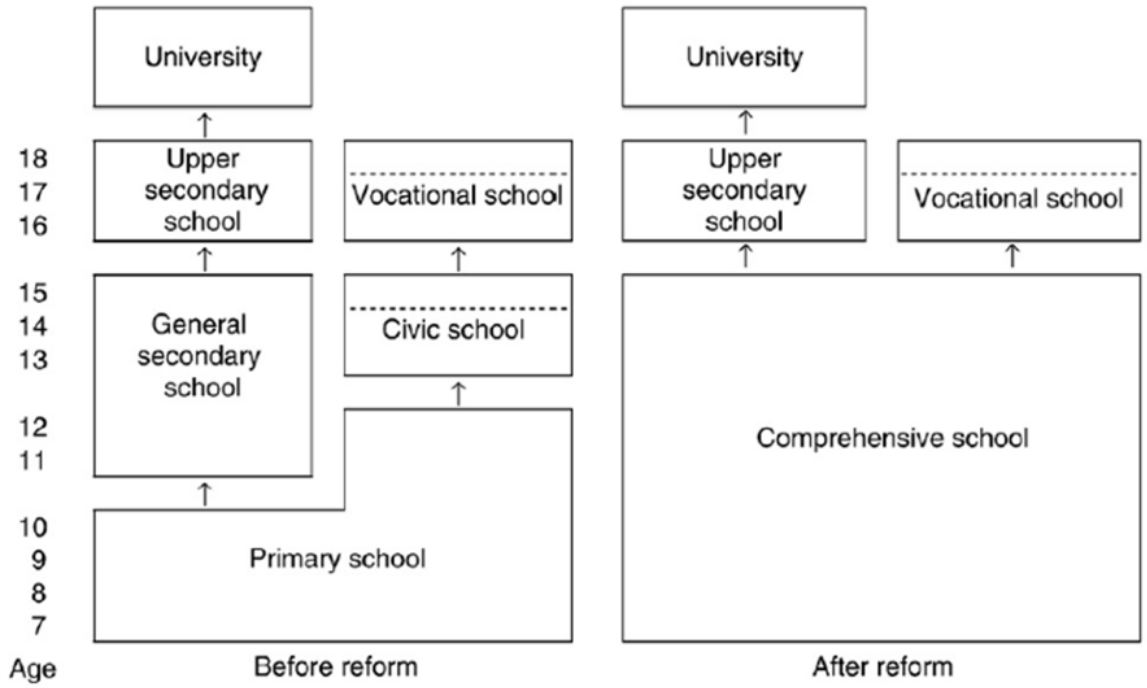
$$ADRD_i = \lambda_0 + \lambda_1 Educ_i + \lambda_2 Educ_i * I_i + \lambda_3 I_i + h(DoB_i) + \lambda_4 Age_i + X_i \boldsymbol{\lambda}_5 + \epsilon_i \quad (3),$$

where $Educ_i$ is school leaving age and we use $After_i$ and $After_i * I_i$ to instrument for $Educ_i$ and $Educ_i * I_i$. We also run the terciles specification mentioned above. Given the robust association between years of education and (better) dementia outcomes, we hypothesize that $\lambda_1 > 0$ (ADRD is oriented so that higher number means better health), meaning that at least part of this association reflects a causal effect running from more education to better cognition. We also expect that this effect will be higher among those with a high AD PGI ($\lambda_2 > 0$ when I_i corresponds to the AD PGI)—this would be in line with findings in our previous work for BMI[33] and consistent with the fact that individuals with high AD risk may have more room for improvement. However, a-priori the sign of λ_2 is less obvious when the EA PGI is used. In other previous work, we found that the income returns to education were higher among those with a high EA PGI;[11] therefore, we hypothesize that $\lambda_2 > 0$ in the EA PGI specification. However, it is also possible that no interaction, or a negative interaction, exists.

III.2 *Finland's Comprehensive School Reform of 1972-1977*

While the ROSLA provides an excellent natural experiment to study the causal effects of education *quantity*, it says little about the potentially equally, if not more, important effect of education *quality*. For this reason, we also study the effects of another educational reform: Finland's comprehensive school reform of 1972-1977. This reform is representative of European educational reforms after WWII with the objective of enhancing equality of economic opportunities, irrespective of place of residence or social background.[35]

Figure 2: Finnish School System, Before and After 1972-1977 Comprehensive Reform



This comprehensive school reform transformed the Finnish educational system from a selective to a comprehensive one. Figure 2, reproduced from ref. [8], illustrates the structure of the system before and after the reform. Under the pre-reform system, students were tracked into academic and vocational tracks by age 11. These tracks differed in the content of education and in the eligibility they provided for further education. The reform postponed this choice to age 16. After the reform, all students received nine years of common education according to a uniform curriculum as opposed to being taught together only for four years in the old system. The reform led to an increase in the academic content of the curriculum and in the quality of the peer group for those students who would have otherwise attended the vocational track in the old system, likely students from poorer families. Under the new system, the curriculum had a larger share of mathematics and sciences, as well as compulsory study of one foreign language. On the other hand, students who would have chosen the academic track in the old system ended up with, on average, a less gifted peer group, leading to a potential decrease in educational quality. In fact, [8] shows that the Finnish comprehensive school reform increased intergenerational income mobility.

In 1968, the parliament approved legislation regulating that the two-track school system would be gradually replaced with a nine-year comprehensive school, starting in 1972. The order in which the municipalities adopted the reform was determined geographically. A regional implementation plan divided the country into six implementation regions and dictated when each region would adopt the new system.

Whether a student transitioned into the new system also depended on the grade in which the student was when her region of residence started implementing the reform. In each region, the five lowest primary school grades were to start in the comprehensive school immediately in the fall term of the year stated in the regional implementation plan. After this, each incoming cohort of first graders would start their schooling in the comprehensive school. Students that were already above the 5th grade in the year when the reform was first implemented would complete their schooling according to the pre-reform system. The fact that the Finnish comprehensive school reform was implemented at different times in different municipalities makes it a promising natural experiment to study the impacts of school quality. It allows us to use a differences-in-differences approach that controls for time trends and regional differences in cognitive and dementia outcomes, as we describe in detail below.

In order to estimate the causal effect of education quality we apply a difference-in-differences empirical strategy that uses students who were not affected by the reform as a counterfactual for students who were affected.[8] We will estimate

$$ADRD_{ji} = \alpha_0 + \alpha_1 T_{ji} + \alpha_2 T_{ji} * I_i + \alpha_3 I_i + \boldsymbol{X}_{ij}\boldsymbol{\beta} + \varepsilon_i \quad (4),$$

where j indexes region of residence and t indexes birth cohort. T_{ji} is a dummy variable equal to 1 if the participant was in the relevant age group at the time when the reform took place in her region of residence. X_{ij} is a full set of controls including genetic principal components, interactions of the principle components with T_i, region and cohort fixed effects, and interactions of these fixed effects with the polygenic index. The remaining variables are defined as above. Our main ADRD outcomes here are ADRD diagnosis, age at diagnosis and risk factors (all oriented so that higher numbers mean better health), since we do not have cognitive functioning measures in FinnGen. The models will be run separately with the EA and the AD PGIs. The coefficients of interest, α_1 and α_2, estimate whether the reform affected ADRD outcomes and whether these effects differed by genetic makeup.

The main identifying assumption of the model in equation 3 is that, conditional on the PGI, changes in ADRD outcomes unrelated to the reform are not systematically related to the implementation timing of the reform across regions. In order to check whether the treated group is a good counterfactual for the untreated group, we show that the parallel trends assumption holds. That is, we will verify that difference in the rates of ADRD diagnoses between regions are similar for individuals born in the years leading up to the reform.

We hypothesize that the overall increase in school quality resulting from the reform had a positive effect on ADRD outcomes ($\alpha_1 > 0$). Using data for pre-reform cohorts, we check whether those with low EA PGIs were more likely to go to Civic school (i.e., the less academic track) than those with high EA PGIs (we believe this is likely to be the case). Since students who, before the reform, chose the Civics' track were more likely to experience a significant increase in school quality as a result of the reform, we expect the reform to have a larger benefit for those with low EA PGIs ($\alpha_2^{EA} < 0$). In contrast, we expect those who are more genetically vulnerable to AD to see the largest benefits from increased education quality ($\alpha_2^{AD} > 0$).

The analyses described in equations (2)-(4) above have strong internal validity, but they ultimately only estimate the effect of education on ADRD for compliers (i.e., those who would have dropped out of school before age 16 in the UK or who would have followed the civic school track at age 11 in Finland). Therefore, we also use genetic data on related individuals to explore a source of random variation that influences a much wider spectrum of the education distribution. By imputing and conditioning on the PGI of parents, we estimate the direct (causal) effect of one's own AD and EA PGIs, and also investigate the interaction of the direct EA PGI effect and the direct AD PGI effect. Such interaction allows us to investigate how being predicted to go farther in school based on one's genes affects the relationship between the direct AD PGI effect and actual ADRD outcomes. In other words, this "genetic lottery" offers us another way to investigate whether education mitigates the polygenic risk of ADRD, parallel to estimating β_2 in equation (2) and α_2 in equation (4).

In contrast to the British and Finnish reforms, the direct EA PGI is not a valid instrument for education because, given the many unknowns about the complex ways in which genetics influences phenotypes, it is unlikely that the EA PGI affects ADRD outcomes exclusively through educational attainment. However, we believe that it is safe to assume that, if we do find a relationship between the direct EA PGI effect and ADRD, *at least part* of that effect will be operating through more education, offering evidence of a causal effect of education on ADRD outcomes. We start by estimating

$$Educ_i = \mu_0 + \mu_1 I_i^{EA} + \mu_2 I_i^{EA,P} + \varepsilon_i \quad (5),$$

where $Educ_i$ is a measure of education for individual i (such as school leaving age), I_i^{EA} is her EA PGI, and $I_i^{EA,P}$ is the EA PGI for individual $i's$ parents. In this case, μ_1 estimates the direct (causal) genetic effect of the EA PGI on education. We show in the preliminary results section below that, using a subsample of the UKB, a 1 standard deviation increase in the direct effect of the EA PGI causes an increase in school leaving age of 0.49 years.[11]

Given these "first stage" estimates, we will run "reduced form" models of the direct effect of the EA PGI and the AD PGI on ADRD outcomes, as well as a full model with their interaction. Formally, we estimate

$$ADRD_i = \delta_0 + \delta_1 I_i^{EA} + \delta_2 I_i^{AD} + \delta_3 I_i^{EA} * I_i^{AD} + \theta(I_i^{EA}, I_i^{EA,P}, I_i^{AD}, I_i^{AD,P}) + \varepsilon_i \quad (6),$$

where, $\theta = \delta_4 I_i^{EA,P} + \delta_5 I_i^{AD,P} + \delta_6 I_i^{EA} * I_i^{AD,P} + \delta_7 I_i^{EA,P} * I_i^{AD}$, are the terms that allow us to interpret the coefficients in equation (6) as direct effects. Our coefficients of interest are δ_1, δ_2, and δ_3. The first two coefficients measure, respectively, the direct (causal) effect of the EA and the AD PGIs on ADRD outcomes. We hypothesize that, consistent with the (non-causal) relationships between EA and the AD PGIs and ADRD outcomes, we will find $\delta_1 > 0$ and $\delta_2 < 0$. Moreover, we expect that $\delta_3 > 0$, meaning that the higher EA PGI would *counteract* the polygenic risk for AD, decreasing the relationship between the AD PGI and AD risk. Estimating such models in three different national contexts, will inform how general results are.

Previous work has highlighted the importance of school quality by showing that the earnings return to education varies with local measures of quality such as pupil-teacher ratios, teacher pay, and term length.[28] In the last part of the paper, we investigate this issue in the

context of ADRD by exploring whether our three different sources of variation in education (the ROSLA, the Finnish Comprehensive School Reform and family-based random genetic variation) affect ADRD outcomes differently for individuals who went to school in districts with high versus low average school quality. We will aggregate our measures of education quality into a single quality index Q_i. For example, using the ROSLA as an instrument, we estimate the following 2SLS regression

$$ADRD_i = \zeta_0 + \zeta_1 Educ_i + \zeta_2 Educ_i * Q_i + \zeta_3 Q_i + h(DoB_i) + \zeta_4 Age_i + X_i \boldsymbol{\zeta}_5 + \epsilon_i \quad (7),$$

Our main coefficient of interest, ζ_2, will estimate whether the returns to an extra year of education in terms of better ADRD outcomes are larger for students who went to secondary school in high quality school districts. Similarly, we estimate the following equation for the Finnish comprehensive reform

$$ADRD_{ji} = \eta_0 + \eta_1 T_{ji} + \eta_2 T_{ji} * Q_{ji} + \eta_3 Q_{ji} + D_j \boldsymbol{\eta_4} + D_t \boldsymbol{\eta}_5 + \varepsilon_i \quad (8),$$

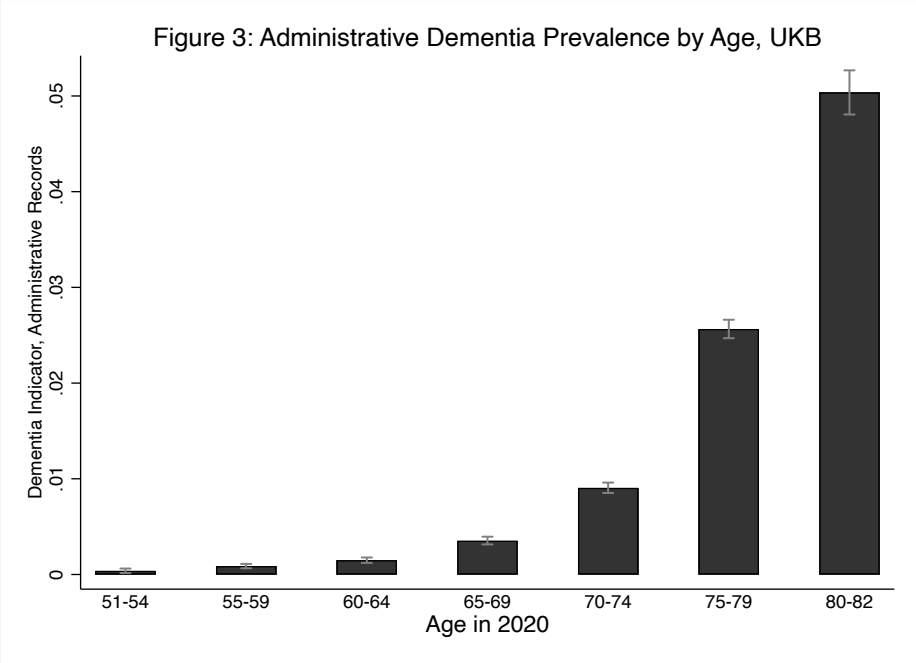
and for the family-based genetic variation in the UK, Finland and the Netherlands

$$ADRD_i = \sigma_0 + \sigma_1 I_i^{EA} + \sigma_2 Q_i + \sigma_3 I_i^{EA} * Q_i + \sigma_4 I_i^{EA,P} + \sigma_5 I_i^{EA,P} * Q_i + \varepsilon_i \quad (9).$$

We also separately estimate the interaction model given in equation (6) separately for individuals who completed their education in above- and below-median quality districts. Our hypothesis is that the direct genetic effect of the EA PGI will be larger for students from places with higher average education quality ($\sigma_3 > 0$). Moreover, we expect that the interaction between the EA PGI direct effect and the AD PGI direct effect will also be larger for students who went to school in above-median quality districts.

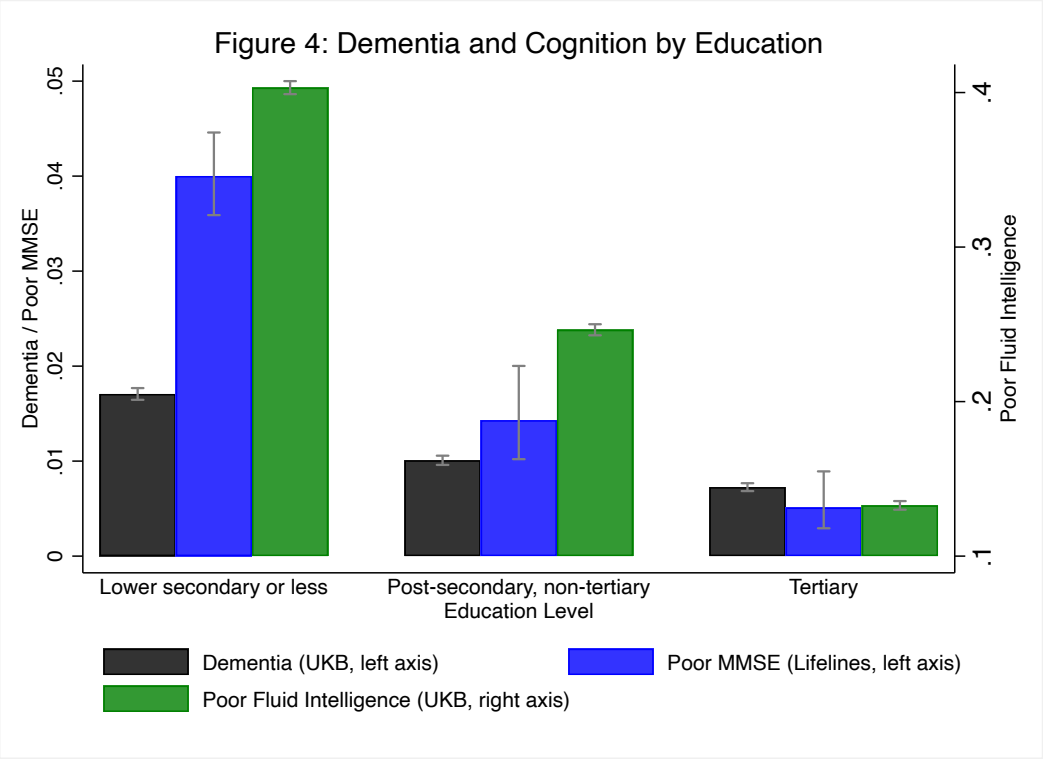
IV. Preliminary Results

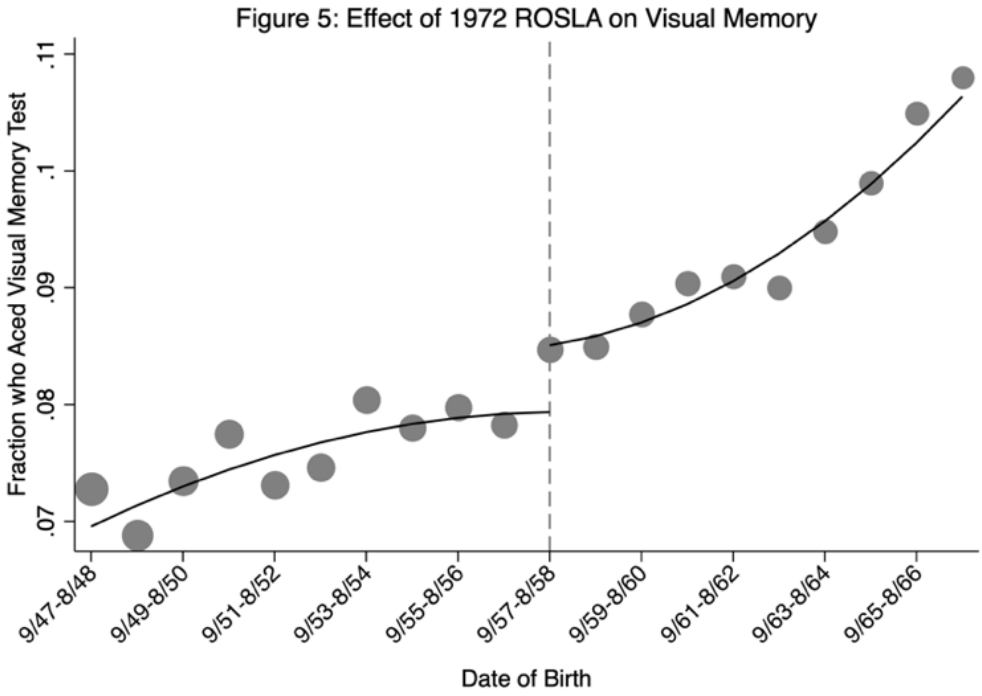
We start by potting the prevalence of all-cause dementia by age based on administrative records (participants are currently 51-82 years old) in the UK Biobank; see Figure 3. While the overall prevalence is lower than in studies that use survey-based information to assess cognition, the sharp age gradient is comparable.[39]



Next, we document the education gradient in cognition and dementia in the UKB and Lifelines (Figure 4). For the UKB we show a dementia indicator based on administrative records (in black, left axis) and the fraction who scored in the bottom quartile of the (overall sample) fluid intelligence distribution (in green, right axis). For Lifelines we show the fraction who scored below 20 in the mini-mental state examination (MMSE) cognitive test, a threshold indicative of severe or moderate cognitive impairment (in blue, left axis). All three measures show a clear education gradient. Dementia prevalence is 2.5 times higher among those with less than lower secondary education (1.7% prevalence) than among those with tertiary education or higher (0.7%). The contrast is even starker for survey-based measures of cognition. While 40% of those with lower secondary education or less exhibit poor fluid intelligence, only 13% of those with tertiary education do. These numbers are 4% versus 0.9% for poor MMSE.

This paper studies how much of these gradients is due to a causal effect of education on cognition/dementia, as opposed to a reverse effect of cognition on education or an effect driven by a third factor, such as genetics. We explore the 1974 ROSLA as a natural experiment to investigate whether education quantity has an effect on cognition later in life. Figure 5 provides preliminary evidence that it does. It shows the fraction of individuals who aced a the "pairs matching test" by date of birth. There is a sharp discontinuity for those born after 1957. We estimate that students who stayed one more year in school are 4.2 percentage points more likely to ace the visual memory test (p-value of 0.06). These results are consistent with previous work.[31]





Further, we use family-based random genetic variation to estimate the causal effect of the EA and AD PGIs on ADRD outcomes. Table 1 provides some preliminary results by estimating equation (5) with education and other ADRD outcomes as dependent variables using data from the UKB. It shows that the EA PGI has a causal effect on years of schooling and on fluid intelligence. A one standard-deviation increase in the EA PGI causally increases school-leaving

age by approximately half a year (column 1). Moreover, the EA PGI also reduces the probability of scoring in the bottom quartile of the fluid intelligence distribution by 5 percentage points.

Table 1: Direct EA PGI Effects on Education and Cognition

	School- Leaving Age	Bottom Quartile Fluid Intelligence
EA PGI	0.49***	-0.05***
	(0.030)	(0.007)
Parents EA PGI	0.64***	-0.03***
	(0.026)	(0.007)
Constant	18.2***	0.23***
	(0.014)	(0.004)
Observations	42,617	12,870
R-squared	0.127	0.037

Robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

V. Limitations

Our ADRD measures, though widely used, have limitations. For cognitive tasks, more educated people may be better at, and more familiar with, completing such tests. This would lead to an underestimate of the rate of "true" cognitive problems among more educated individuals. Further, in the case of diagnosis from medical records, more educated people may have better access to doctors which may allow them to be diagnosed earlier and at higher rates, even if actual brain health is the same (Petersen JD et al 2021). This would, in turn, lead to an underestimate of the rate of diagnosed AD among less educated individuals. Ultimately, these issues are shared by the whole literature that investigates the relationship between education and cognitive functioning/ADRD measures. Nevertheless, these need to be kept in mind when interpreting our results.

Like all studies using changes in laws, our estimates of the British and Finnish reforms will have a local average treatment effect (LATE) interpretation that might not be generalizable to other cohorts and educational levels. LATE is a relevant estimate from a policy perspective because it is informative of the effects for the subpopulation affected by changes in the reforms. A strength of the use of natural experiments is their ability to establish causal effects, yet their lack of generalizability is a limitation. We also present estimates exploiting family-based random genetic variation, which influences a much wider spectrum of the education distribution.

There is some degree of sample selectivity in all three samples we will use. However, the large sizes and diversity of the samples allow us to construct inverse probability weights such that each

sample matches key moments of nationally representative samples (van Alten et al. 2022). Internal validity is less of an issue even in these selected samples, as long as the identifying assumptions of the regression discontinuity design (RDD) and of the difference-in-differences (DiD) model are satisfied. Our previous work suggests such assumptions are satisfied in the UK Biobank, we will run similar analyses on the other datasets.

Finally, because our cohorts are relatively young, we are well-powered to study the relationship between education and cognitive functioning at these (relatively) young ages. If the causal effect of education on ADRD is different at older ages (when prevalence is higher) our current project will not capture that. We can partially inform this question by estimating how the effect of the education reforms on ADRD changes as the cohorts age.

VI. Note to the Committee

I wrote this detailed abstract based on documents from a recently awarded NIA R01 (Barcellos). The analyses mentioned here are extensive and I don't expect we will have them all ready for presentation by the summer. I am confident, though, that we will have a number of results from the UK analyses and maybe some preliminary results from FinnGen also (hopefully enough for an interesting presentation!). I am submitting this abstract because this project would greatly benefit from early feedback from the NBER/CEPRA Aging group.

VII. References

1. Prince, M. *et al.* The global prevalence of dementia: a systematic review and metaanalysis. *Alzheimer's Dement.* **9**, 63–75 (2013).
2. Sharp, E. S. & Gatz, M. The relationship between education and dementia an updated systematic review. *Alzheimer Dis. Assoc. Disord.* **25**, 289 (2011).
3. Maccora, J., Peters, R. & Anstey, K. J. What does (low) education mean in terms of dementia risk?: a systematic review and meta-analysis highlighting inconsistency in measuring and operationalising education. *SSM-Population Heal.* 100654 (2020).
4. Clark, D. & Royer, H. *The effect of education on adult health and mortality: Evidence from Britain*. (National Bureau of Economic Research, 2010).
5. Clark, D. & Royer, H. The Effect of Education on Adult Mortality and Health: Evidence from Britain. *Am. Econ. Rev.* **103**, 2087–2120 (2013).
6. Grenet, J. Is extending compulsory schooling alone enough to raise earnings? Evidence from French and British compulsory schooling laws. *Scand. J. Econ.* **115**, 176–210 (2013).
7. Davies, N. M., Dickson, M., Smith, G. D., Van Den Berg, G. J. & Windmeijer, F. The causal effects of education on health outcomes in the UK Biobank. *Nat. Hum. Behav.* (2018). doi:10.1038/s41562-017-0279-y
8. Pekkarinen, T., Uusitalo, R. & Kerr, S. School tracking and intergenerational income mobility: Evidence from the Finnish comprehensive school reform. *J. Public Econ.* **93**, 965–973 (2009).
9. Young, A. I. *et al. Mendelian imputation of parental genotypes for genome-wide estimation of direct and indirect genetic effects*. *BioRxiv* (2020). doi:10.1101/2020.07.02.185199
10. Lee, J. J. *et al.* Gene discovery and polygenic prediction from a 1.1-million-person GWAS of educational attainment. *Nat. Genet.* **50**, 1112–1121 (2018).
11. Barcellos, S. H., Carvalho, L. & Turley, P. *The Effect of Education on the Relationship between Genetics, Early-Life Disadvantages, and Later-Life SES*. (National Bureau of Economic Research, 2021).
12. Prince, M. J. *et al.* World Alzheimer Report 2015-The Global Impact of Dementia: An analysis of prevalence, incidence, cost and trends. (2015).
13. Livingston, G. *et al.* Dementia prevention, intervention, and care. *Lancet* **390**, 2673–2734 (2017).
14. Wong, W. Economic burden of Alzheimer disease and managed care considerations. *Am. J. Manag. Care* **26**, S177–S183 (2020).
15. Crimmins, E. *et al.* The Effect of Education on Recent Dementia Trends: A Look Forward Meeting Summary. (2016).
16. Stern, Y. Cognitive reserve and Alzheimer disease. *Alzheimer Dis. Assoc. Disord.* **20**, 112–117 (2006).
17. Becker, J. *et al.* Resource profile and user guide of the Polygenic Index Repository. *Nat. Hum. Behav.* (2021). doi:10.1038/s41562-021-01119-3

18. Buchman, A. S. *et al.* Brain pathology contributes to simultaneous change in physical frailty and cognition in old age. *Journals Gerontol. Ser. A Biomed. Sci. Med. Sci.* **69**, 1536–1544 (2014).

19. Gatz, M. *et al.* Role of genes and environments for explaining Alzheimer disease. *Arch. Gen. Psychiatry* **63**, 168–174 (2006).

20. Bird, T. D. Genetic factors in Alzheimer's disease. *N. Engl. J. Med.* **352**, 862–864 (2005).

21. Breteler, M. M. B. Vascular risk factors for Alzheimer's disease:: An epidemiologic perspective. *Neurobiol. Aging* **21**, 153–160 (2000).

22. Ridge, P. G., Mukherjee, S., Crane, P. K. & Kauwe, J. S. K. Alzheimer's disease: Analyzing the missing heritability. *PLoS One* (2013). doi:10.1371/journal.pone.0079771

23. Leonenko, G. *et al.* Identifying individuals with high risk of Alzheimer's disease using polygenic risk scores. *Nat. Commun.* **12**, 1–10 (2021).

24. Leonenko, G. *et al.* Polygenic risk and hazard scores for Alzheimer's disease prediction. *Ann. Clin. Transl. Neurol.* **6**, 456–465 (2019).

25. Baumgart, M. *et al.* Summary of the evidence on modifiable risk factors for cognitive decline and dementia: a population-based perspective. *Alzheimer's Dement.* **11**, 718–726 (2015).

26. Bellou, V. *et al.* Systematic evaluation of the associations between environmental risk factors and dementia: an umbrella review of systematic reviews and meta-analyses. *Alzheimer's Dement.* **13**, 406–418 (2017).

27. National Academies of Sciences and Medicine, E. Preventing cognitive decline and dementia: A way forward. (2017).

28. Card, D. & Krueger, A. B. Does school quality matter? Returns to education and the characteristics of public schools in the United States. *J. Polit. Econ.* **100**, 1–40 (1992).

29. Seblova, D. *et al.* Does prolonged education causally affect dementia risk when adult socioeconomic status is not altered? A Swedish natural experiment in 1.3 million individuals. *Am. J. Epidemiol.* **190**, 817–826 (2021).

30. Gorman, E. Schooling, occupation and cognitive function: evidence from compulsory schooling laws. *SocArXiv. Oct.* **23**, (2017).

31. Banks, J. & Mazzonna, F. The effect of education on old age cognitive abilities: evidence from a regression discontinuity design. *Econ. J.* **122**, 418–448 (2012).

32. Nguyen, T. T. *et al.* Instrumental variable approaches to identifying the causal effect of educational attainment on dementia risk. *Ann. Epidemiol.* **26**, 71–76 (2016).

33. Barcellos, S. H., Carvalho, L. S. & Turley, P. Education can reduce health differences related to genetic risk of obesity. *Proc. Natl. Acad. Sci.* **115**, E9765 (2018).

34. Lee, D. S. & Lemieux, T. Regression Discontinuity Designs in Economics. *J. Econ. Lit.* **48**, 281–355 (2010).

35. Leschinsky, A. & Mayer, K. U. *The Comprehansive School Experiment Revisited: Evidence from Western Europe*. (1990).

36. Sudlow, C. *et al.* UK Biobank: An Open Access Resource for Identifying the Causes of a Wide Range of Complex Diseases of Middle and Old Age. *PLoS Med.* **12**, e1001779 (2015).

37. Fry, A. *et al.* Comparison of Sociodemographic and Health-Related Characteristics of UK Biobank Participants with Those of the General Population. *Am. J. Epidemiol.* **186**, 1026–1034 (2017).

38. UK Biobank. First Occurrence of Health Outcomes Defined by 3-character ICD10 code. (2019).

39. Crimmins, E. M., Kim, J. K., Langa, K. M. & Weir, D. R. Assessment of cognition using surveys and neuropsychological assessment: the Health and Retirement Study and the Aging, Demographics, and Memory Study. *Journals Gerontol. Ser. B Psychol. Sci. Soc. Sci.* **66**, i162–i171 (2011).

40. Cao, Q. *et al.* The prevalence of dementia: A systematic review and meta-analysis. *J. Alzheimer's Dis.* **73**, 1157–1166 (2020).

41. Privé, F., Arbel, J. & Vilhjálmsson, B. J. LDpred2: better, faster, stronger. *Bioinformatics* **36**, 5424–5431 (2020).

42. Okbay, A. *et al.* Genome-wide association study identifies 74 loci associated with educational attainment. *Nature* **533**, 539–542 (2016).

43. Lee, J. J. *et al.* Gene discovery and polygenic prediction from a genome-wide association study of educational attainment in 1.1 million individuals. *Nat. Genet.* **50**, 1112–1121 (2018).

44. Kunkle, B. W. *et al.* Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates Aβ, tau, immunity and lipid processing. *Nat. Genet.* **51**, 414–430 (2019).

45. Harmon, C. & Walker, I. The returns to the quantity and quality of education: evidence for men in England and Wales. *Economica* **67**, 19–35 (2000).

46. Price, A. L. *et al.* Principal components analysis corrects for stratification in genome-wide association studies. *Nat. Genet.* **38**, 904–909 (2006).

47. Banks, J., Carvalho, L. S. & Perez-Arce, F. Education, decision making, and economic rationality. *Rev. Econ. Stat.* **101**, 428–441 (2019).