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Higher educational attainment is associated with longer telomeres in midlife: Evidence from sibling comparisons in the UK Biobank

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ABSTRACT

Prior studies have established that higher educational attainment is associated with a longer telomere length (TL), a marker of cellular aging. However, it is unclear whether extant associations are causal, since they are likely confounded by unobserved genetic, early-life and family background factors that are correlated with education and TL. We leverage sibling differences in TL, education and measured genetics (polygenic scores for educational attainment and TL) to estimate associations between educational attainment and TL in midlife for European ancestry individuals in the UK Biobank, while controlling for unobserved confounders shared by siblings. After controlling for genetics and shared background between siblings, we find suggestive evidence that high school graduates have longer telomeres than high school dropouts, but we find no differences in TL between high school dropouts and college graduates.

1. Introduction

Telomeres are repetitive DNA-protein complexes capping the ends of chromosomes protecting them from degradation (Blackburn et al., 2015). Every time a cell divides, a portion of the telomeric DNA fails to replicate because of the end replication problem (Olovnikov, 1973). Telomere shortening is also linked to inflammation, oxidative and psychosocial stress (O'Donovan et al., 2011; Epel, 2009; vonZglinicki, 2002). When a critically short telomere length (TL) is reached, a cell loses its ability to divide. This ultimately means that as we age, we are less able to replace old or damaged cells, and this can increase the risk for age-related disease. A short TL, usually assessed in blood leukocytes, is associated with adult morbidity (Müezzinler et al., 2013; Wentzensen et al., 2011; Willeit et al., 2014) and mortality (Wang et al., 2018) independent of chronological age. Mendelian randomization studies have shown that robust genetic predictors of shorter TL are associated with higher odds of Alzheimer's disease (Zhan et al., 2015) and coronary artery disease (Codd et al., 2013). TL is thus a marker of cellular age and a predictor of aging-related diseases.

Educational attainment is viewed by some as a fundamental cause of health disparities (Phelan, Link, & Tehranifar, 2010) because of the multitude of social and behavioral mechanisms (e.g. access to health care, financial resources, social networks, social rank) through which it can affect health. It has also been hypothesized that low educational attainment may accelerate telomere attrition through oxidative stress stemming from psychological stress, worse environments, and unhealthy behaviors. Low educational attainment is associated with higher likelihoods of experiencing stress and negative life events (Baum et al., 1999; Lantz et al., 2005), as well as having fewer social networks and social support to cope with stress (Ajrouch et al., 2005; Shields & Price, 2005). Low educational attainment is associated with higher rates of obesity and smoking (Cutler & Lleras-Muney, 2010), which are both characterized by high oxidative stress and inflammation (Furukawa et al., 2017; Richards et al., 2011). Associations between educational attainment and TL could vary by an individual's age, sex, and ethnicity. Telomere attrition is very fast before 20 years of age, and relatively invariant thereafter (Benetos et al., 2013). Women have longer telomeres on average than men (Barrett & Richardson, 2011) as do African versus European descendant people (Hunt et al., 2008).

A small observational literature has estimated associations between educational attainment and TL. Early studies found somewhat mixed results—positive (Adler et al., 2013; Steptoe et al., 2011), null (Adams et al., 2007; Batty et al., 2009), and inverse associations (Woo et al., 2009) have all been reported. Robertson et al. (2013) meta-analyzed

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early studies and found a significant difference in TL between individuals with high and low educational attainment in a random effects model (standardized mean difference of 0.060). Two, more recent studies have found clearer evidence of a positive association between higher educational attainment and TL. Needham et al. (2013) found that the average TL of high school dropouts was 4% shorter than that of college graduates in mid-age (average age of 49 years), using the 1999–2002 waves of the National Health and Nutrition Examination Surveys (NHANES). The difference in TL between high school dropouts and college graduates corresponds to about 7 years of additional telomere aging. Using data on almost 85,000 non-Hispanic white participants in the Genetic Epidemiology Research on Adult Health and Aging (GERA) cohort, Alexeeff et al. (2019) reported that less than high school education was associated with a 0.14 standard deviation decrease in TL compared to college education. This is more than twice the effect size reported in the Robertson et al. (2013) meta-analysis. Interestingly, the average difference in standardized TL between high school dropouts and college graduates also translates into 7 years of additional telomere aging, similar to Needham et al. (2013).[1] These findings suggest that educational attainment could lead to health disparities by "getting under one's skin" through its effect on cellular aging.

However, observational associations may reflect the influence of unobserved genetic, early childhood and family background factors that are correlated with education and TL rather than a causal relationship. TL is largely genetically determined with a heritability estimate of 70% (Broer et al., 2013), while educational attainment also has a high heritability estimate of 40% (Branigan et al., 2013). If there are genetic factors correlated with both TL and educational attainment, and these are not controlled for, then this would confound estimates. Newborn TL is influenced by maternal stress (Entringer et al., 2013) and smoking (Salihu et al., 2015) during pregnancy. A failure to control for maternal pregnancy characteristics could bias estimates as they affect TL and are likely correlated with unobserved mother characteristics (e.g., innate ability) which affects children's education. Early adversities, in the form of abuse, neglect, socioeconomic status, and other adverse experiences are associated with a shorter TL (Ridout et al., 2018) and lower educational attainment (Houtepen et al., 2020). Associations between educational attainment and TL could be due to reverse causality as there is some evidence that a shorter childhood TL is associated with childhood obesity (Clemente et al., 2019), which is associated with lower adult educational attainment.

We are aware of only one study that has attempted to estimate the causal effect of educational attainment on TL. Hamad et al. (2019) conducted a two-sample instrumental variable (IV) analysis using NHANES and the Health & Retirement Study (HRS). They estimated the effect of compulsory school leaving laws, which are likely orthogonal to unobserved genetic endowments and family environments, using the 5% 1980 US census sample. The first-stage census estimates were then linked to individuals in NHANES and the HRS to obtain the IV estimates. Ordinary Least Squares (OLS) estimates showed that an extra year of education increased TL by 1.4% in NHANES and 0.36% in the HRS. The IV estimates showed that an extra year of education decreased TL by 2.1% in NHANES and increased TL by 8.2% in the HRS, and both estimates were imprecise. Although the IV estimates were imprecise and are only relevant for low educated individuals, they cast doubt on the generally assumed causality of observational associations.

We contribute by providing new evidence on the relationship between educational attainment and TL for European ancestry individuals, using newly released large scale data from the UK Biobank (UKB). Importantly, we employ a sibling fixed-effects design which controls for shared family background and genetics that might otherwise confound observational associations. We further add polygenic scores (PGSs; summary measures of an individual's genetic predisposition) for educational attainment and TL in sibling fixed-effects models to control for unshared genetics between siblings.[2] We find suggestive evidence that TL differences between high school dropouts and high school graduates persist after controlling for shared family background and genetics. In contrast, we find no TL differences between high school dropouts and college graduates after controlling for shared family background and genetics.

2. Data

The UKB is a population-based prospective study of 502,499 individuals aged 40–69 years in 2006–2010 from across the UK. Participants were assessed between 2006 and 2010 in 22 centers. At the baseline appointment, participants gave informed consent and completed questionnaires on their lifestyle, environment, medical history, had a wide range of physical measures taken, and had samples of blood, urine and saliva collected.

TL was measured in DNA extracted from peripheral blood leukocytes using quantitative polymerase chain reaction (qPCR). The qPCR method is based on the principle that the abundance of telomere signal per genome measured represents the average TL in a given DNA sample. qPCR compares the telomere sequence copy number (T) to a single-copy gene copy number (S). The resulting T/S ratio is proportional to mean telomere length. Specific details about TL measurement are given in Codd et al. (2021). Valid TL measurements are available for 472,590 participants, and we standardized the T/S ratio to have a mean of 0 and standard deviation of 1.

To measure educational attainment we use responses to the question "which of the following qualifications do you have: college or university degree; A level/AS levels or equivalent; O levels/General Certificate of Secondary Education (GCSE) or equivalent/Certificate of Secondary Education (CSE) or equivalent; National Vocational Qualification (NVQ), Higher National Diploma (HNC), or equivalent; other professional qualifications (e.g., nursing, teaching); none of the above.[3] As in

[1] Although the results are strikingly similar in the GERA cohort and NHANES, the results are not directly comparable due to differences in study populations and TL measurements. Unlike NHANES, the GERA sample was non-representative, comprised of individuals with private health care provision. Moreover, in the GERA sample only 1.8% of participants were high school dropouts, whereas 32% were high school dropouts in NHANES. TL was measured from DNA extracted from whole blood in NHANES but from saliva in the GERA cohort. Though salivary TL is highly correlated with blood leukocyte TL is (r~0.61; Rej et al., 2021), it may be measuring different aspects of TL biology.

[2] PGSs are constructed using results from Genome Wide Association Studies (GWAS). In a GWAS, hundreds of thousands to millions of single nucleotide polymorphisms (SNPs) are tested for associations with an outcome. As an example, Lee et al. (2018) conducted a GWAS on a sample of 1.1 million individuals and identified 1271 SNPs as genome-wide significant predictors ($p < 5 \times 10^{-8}$), of educational attainment. The PGS for individual i is a weighted average across the number of SNPs (n) of the number of reference alleles A (0, 1 or 2) at that SNP: $PGS_i = \sum_{j=1}^{n} \beta_j A_{ij}$.

[3] In the UK students enter secondary school at age 11 and take their school leaving exams at age 16. From 1965 to 1997 school leaving exams consisted of the O-Level and CSE exams. O-Level exams were taken by academically able students, while CSE exams were taken by less-academically-oriented students. Although CSE exams were less demanding than GCE O-Level exams, both were graded on the same scale. In 1988, the GCSE was introduced, which marked a turning point in the UK educational system. The GCSE is a single subject exam, and students usually take up to ten GCSE exams in different subjects. Students are given a letter score of A–G where A is the top grade. Although grades A–G are all officially pass grades, only grades A to C are generally regarded as equivalent to the "pass" grades in the previous O-level system. Once secondary schooling is completed, students can extend into further education by taking A/AS levels (subject based exams that are used for entry into university) or vocational qualifications such as NVQs/HNCs.

previous genomic studies of this phenotype in the UKB (Lee et al., 2018), we map each educational qualification to an International Standard Classification of Education (ISCED) category and impute years of education equivalent for each ISCED category. The imputed years of education for the educational qualifications are: no qualification = 7 years; CES/O levels/GCSEs or equivalent = 10 years; A level/AS levels or equivalent = 13 years; other professional qualification = 15 years; NVQ/HNC or equivalent = 19 years; and college or university degree = 20 years.

Fig. 1 shows the sample selection steps in arriving at our analytical sample. We limit our analysis to respondents of European descent (N = 408,956) due to the lack of portability of PGSs in non-European populations (Martin et al., 2017). We then drop individuals with missing education data (N = 3816) and with missing TL data (N = 12,924) leaving an analytical sample of 392,216 individuals.

Siblings are not identified in the survey, but relatedness among individuals can be inferred from the kinship coefficient— the probability that a random allele from an individual is identical by descent with an allele at the same locus from the other individual. We identified siblings using the UKB provided kinship file, listing all pairwise kinships among 100,000 pairs in the sample of nearly 500,000 individuals. We first choose pairs with kinship coefficient >0.2, which reflects first-degree biological relatives (parents/siblings). We then choose the remaining pairs who are <13 years apart in age, leaving ~22,000 sibling dyads. We then chose to keep only one dyad from any family with more than one dyad, leaving ~17,600 dyads. The number of dyads who also have non-missing TL and education is 15,351 (30,702 respondents).

Genetic associations for educational attainment were obtained from a recent GWAS which excluded UKB samples (Lee et al., 2018). We performed a GWAS for TL using 348,318 independent UKB samples of European descent, while controlling for sex, year of birth, genotyping array, and 20 genetic principal components. We excluded the participants who are recommended by UKB to be excluded, those with conflicting genetically-inferred and self-reported sex, those who withdrew from UKB, and all samples in our sibling analysis. We kept only SNPs with missing call rate below 0.01, minor allele frequency greater than 0.01, and with Hardy Weinberg equilibrium test p-value greater than 1.0e-6. After quality control, 6,957,330 SNPs remained in the GWAS. We clumped GWAS summary statistics using 1000 Genomes Project Phase III European samples as a reference for linkage disequilibrium (LD). We used an LD window size of 1 Megabase (Mb) and a pairwise r2 threshold of 0.1. We did not apply any p-value thresholding to select variants and used PRSice-2 to calculate the PGSs (Choi & O'Reilly, 2019). PGSs were generated for the full sibling samples and standardized to a mean of 0 and a variance of 1 in all analyses.

3. Empirical framework

To test whether higher educational attainment is associated with a longer TL, we use OLS and sibling fixed-effect regression models. In equation (1), the TL of sibling i in family f is a linear function of educational attainment, basic control variables (X_{if}) which consist of age, sex, and the first 20 genetic principal components, and an error term (v_{if}).

$$TL_{if} = \beta_0 + \beta_1 Education_{if} + X_{if}^{'}\Theta + v_{if} \quad (1)$$

OLS regression estimates of β_1 that use between family variation do not control for unobserved genetic and family factors that can confound estimates. To control for some of the confounding factors, we exploit differences between siblings by estimating the sibling fixed-effect regression equation (2) which contains indicator variables for each family (μ_f).

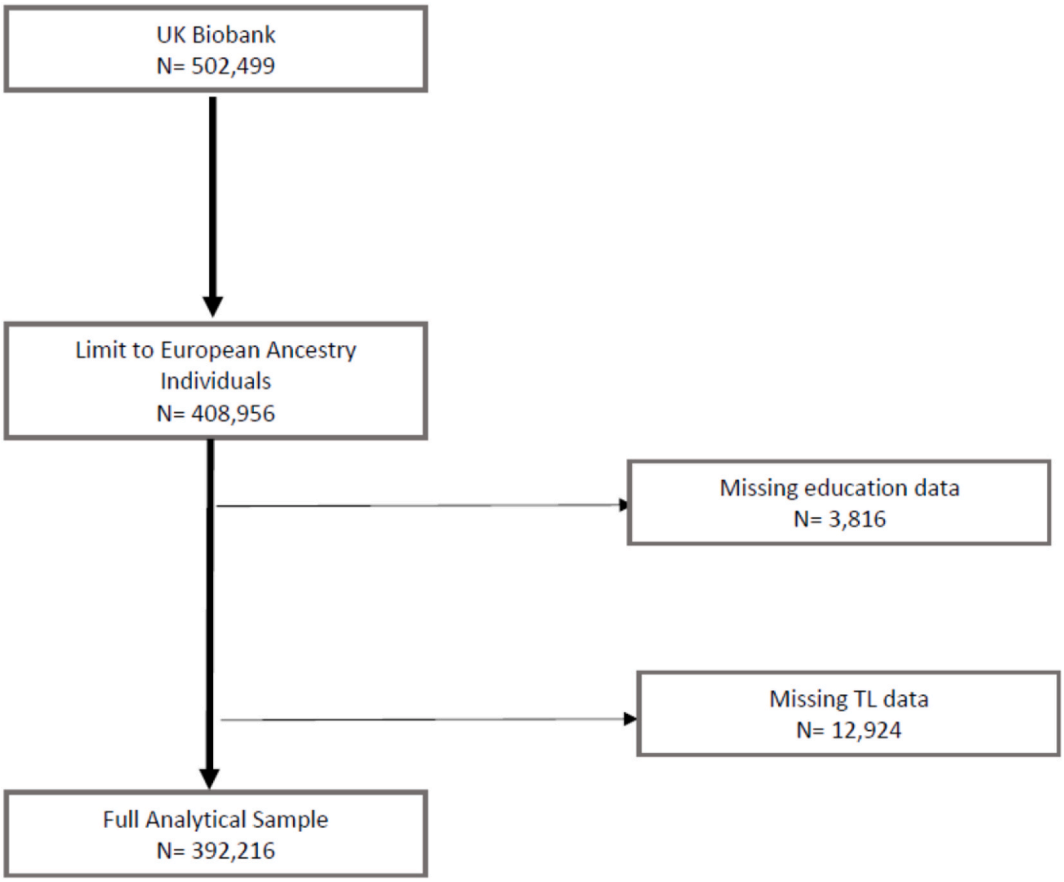

Fig. 1. Flowchart of sample selection criteria for full analytical sample.

$$TL_{if} = \beta_0 + \beta_1 Education_{if} + X'_{if}\Theta + \mu_f + v_{if} \quad (2)$$

Equation (2) is equivalent to relating differences in TL between siblings to differences in educational attainment and the control variables. A sibling fixed-effects model improves upon OLS because it controls for shared background factors that are difficult to measure. As siblings share 50% of their genes, sibling fixed-effect does not fully control for sibling-specific genetic differences. We therefore add PGSs for TL and educational attainment as additional covariates (equation (3)) to control for unshared genetic differences between siblings.

$$TL_{if} = \beta_0 + \beta_1 Education_{if} + X'_{if}\Theta + \mu_f + \beta_2 \text{PGS\_TL}_{if} + \beta_3 \text{PGS\_Education}_{if} + v_{if} \quad (3)$$

4. Results

Descriptive statistics for our analysis samples are shown in Table 1. In the full estimation sample (column 1) the average age is 57 years and 54% are female. The average years of education is 13.8; 18% have no qualification (equivalent to high school dropout in the US context) and 31% are college graduates. The summary statistics for the sibling pairs sample (column 3) are similar to those for the full sample. Absolute within-sibling differences are shown in columns 4 and 5. The absolute difference in age is 4 years and 45% of sibling pairs are mixed-sex (brothers and sisters). The absolute within-sibling pair difference of standardized TL is 0.94. There is a fair amount of within-sbling variation in educational attainment. The mean absolute within-sibling difference in education is 4.15 years, and 85% of sibling pairs are discordant on college degree. Table 2 provides more detailed information on educational attainment differences between siblings. It shows that within-sibling education differences are distributed throughout the education distribution. For example at the low end of the education distribution, 10% of sibling pairs have no qualification vs GCSE, which is equivalent to high school dropout vs high school graduate in the US context. At the upper end of the education distribution, 7% of sibling pairs have a difference of A/AS level vs college degree.

The main results are presented in Table 3. OLS estimates for the full sample in column 1 show that an additional year of aging is associated with a 0.022 standard deviation decrease in TL, being female is associated with a 0.18 standard deviation increase in TL, and that an extra year of education is associated with a 0.007 increase in TL. The protective association of an additional year of education is relatively small. The estimates imply that an additional year of education is associated with 0.32 (0.007/0.022) fewer years of telomere aging. Column 2 gives OLS estimates where educational attainment is specified as a series of indicator variables for each educational qualification with no qualification (high school dropout) as the reference category. There are much larger protective associations of education in this nonlinear specification. The TL of individuals with GCSEs (high school graduates) is on average 0.055 of a standard deviation longer compared to individuals with no qualification, which translates into 2.5 (0.055/0.022) fewer years of telomere aging. The largest difference in TL is seen between individuals with no qualifications and individuals with college degrees, where the difference in TL is 0.13 of a standard deviation, or equivalently 6 years in telomere aging. This is similar to US results in Needham et al. (2013) and Alexeeff et al. (2019) who report a gap of 7 years in telomere aging between high school dropouts and college graduates. Columns 3 and 4 provide OLS estimates for the sibling pairs subsample, which are similar in magnitude to the OLS estimates for the full sample. The only exception is that there is no difference in TL between individuals with NVQ/HNC qualifications and individuals with no qualifications in the sibling pairs sample, whereas there is a difference of 0.03 of a standard deviation in the full sample.

Sibling fixed-effect estimates are shown in columns 5 and 6. The association between age and TL is slightly larger in sibling fixed-effect models. An additional year of aging is associated with a 0.37 standard deviation decrease in TL. The implied sex differences in TL from sibling fixed-effect models is similar to OLS models. Findings for educational attainment differ according to the specification of educational attainment. There is no association between years of education and TL in column 5, suggesting that OLS associations are entirely driven by unobserved confounders shared by siblings. Sibling fixed-effect estimates in column 6 suggest that TL differences between individuals with no qualifications and GCSEs persist after controlling for shared genetics and family background. Specifically, the difference in TL between individuals with no qualifications and with GCSEs is reduced by 33% from 0.066 in column 4 to 0.046 in column 6. Though the latter estimate is imprecise, this translates into 1.2 (0.046/0.037) fewer years of telomere aging. Similarly, the difference in TL between individuals with no qualifications and with A/AS level (other professional qualifications) is reduced by 38% (20%) from 0.091 (0.084) in column 4 to 0.056 (0.067) in column 6. However, differences in TL between individuals with no qualifications and with college degrees are completely eliminated after controlling for shared genetics and family background—the difference in TL falls by 84% from 0.117 in column 4 to 0.019 in column 6. The estimates suggest an inverse U pattern, where higher educational qualifications have smaller associations with TL compared to low/middle educational qualifications. Columns 7 and 8 add the TL and educational attainment PGSs to control for unobserved sibling-specific genetic differences. The TL PGS, as one would expect, is a significant predictor of TL. A one standard deviation increase in the TL PGS increases TL by 0.064 of a standard deviation. The educational attainment PGS does not predict TL—the point estimate is close to zero. The sibling fixed-effect estimates on years of education and the educational qualification indicators are not altered by controlling for the PGSs.

We conducted two other analyses. First, given that women have a longer TL on average than men, we tested for sex differences in associations between educational attainment and TL by interacting educational attainment with the female dummy variable in OLS and sibling fixed-effect regressions. We did not find any consistent evidence that the associations differed by sex (see appendix Table A1). Second, previous research has shown that the relationship between educational attainment and mortality is nonmonotonic (Backlund et al., 1999).[4] We examined whether there is a nonmonotonic relationship between educational attainment and TL through linear spline regressions (see appendix Table A2). The spline regression estimates also suggest an inverse U pattern in the association between educational attainment and TL, consistent with the results from the nonlinear specification in Table 3.

5. Conclusion

Higher educational attainment has been linked with longer telomeres, a marker of cellular aging. Understanding whether education affects cellular aging and gets “embedded under the skin” is important because education disparities in chronic disease and mortality have widened over recent decades. However, few studies have attempted to estimate the causal effect of education on TL. We fill this gap by using sibling fixed-effect models along with measured genetics (PGSs) to estimate associations between educational attainment and TL in midlife while controlling for genetics and shared family background. We find that there is no association between years of education and TL after controlling for genetics and shared family background. However, specifying educational attainment as years of educations masks important

[4] Backlund, Sorlie, and Johnson (1999) found that the relationship between educational attainment and mortality among US working aged adults in the 1980s was best depicted with a discontinuous functional form, with education categorized as less than a high school diploma, a high school diploma but no college degree, college degree or more.

Table 1
Descriptive statistics for full analytical sample and sibling pairs subsample.

	Full Sample		Sibling Pairs Sample		Absolute Within-Sibling Differences	
Variable	Mean (SD)	Min (Max)	Mean (SD)	Min (Max)	Mean (SD)	Min (Max)
	(1)	(2)	(3)	(4)	(4)	(5)
Age	56.89 (7.99)	39 (73)	57.13 (7.28)	39 (73)	4.28 (2.74)	0 (12)
Female	0.54 (0.50)	0 (1)	0.57 (0.50)	0 (1)	0.45 (0.50)	0 (1)
Years of education	13.77 (5.12)	7 (20)	13.54 (5.09)	7 (20)	4.15 (4.23)	0 (13)
No qualifications	0.18 (0.38)	0 (1)	0.19 (0.39)	0 (1)	0.92 (0.28)	0 (1)
GCSEs or equivalent	0.28 (0.45)	0 (1)	0.29 (0.45)	0 (1)	0.88 (0.32)	0 (1)
A/AS level or equivalent	0.11 (0.32)	0 (1)	0.11 (0.31)	0 (1)	0.98 (0.14)	0 (1)
NVQ/HNC or equivalent	0.05 (0.22)	0 (1)	0.05 (0.23)	0 (1)	0.99 (0.06)	0 (1)
Other professional qualification	0.07 (0.25)	0 (1)	0.07 (0.26)	0 (1)	0.99 (0.09)	0 (1)
College degree	0.31 (0.46)	0 (1)	0.29 (0.45)	0 (1)	0.85 (0.36)	0 (1)
Standardized T/S Ratio	−0.028 (0.99)	−15.28 (12.14)	−0.018 (0.99)	−6.01 (10.60)	0.94 (0.75)	0.00 (10.53)
Standardized TL PGS	–	–	0.00 (0.99)	−10.59 (12.89)	0.76 (0.58)	0.00 (4.25)
Standardized Education PGS	–	–	−0.00 (0.99)	−4.52 (3.90)	0.78 (0.60)	0.00 (4.34)
N	392,216		30,702		30,702	

Table 2
Within-sibling variation in highest educational attainment.

Educational Attainment Difference	Number of Sibling Pairs (%)
(1)	(2)
No Difference in highest qualification	5853 (38%)
No qualification vs GCSE or equivalent	1483 (10%)
No qualification vs A/AS level or equivalent	319 (2%)
No qualification vs NVQ/HNC or equivalent	311 (2%)
No qualification vs Other professional qualification	622 (4%)
No qualification vs College degree	476 (3%)
GCSEs or equivalent vs A/AS level or equivalent	999 (7%)
GCSEs or equivalent vs NVQ/HNC or equivalent	471 (3%)
GCSEs or equivalent vs Other professional qualification	658 (4%)
GCSEs or equivalent vs College degree	1749 (11%)
A/AS level or equivalent vs NVQ/HNC or equivalent	167 (1%)
A/AS level or equivalent vs Other professional qualification	185 (1%)
A/AS level or equivalent vs College degree	1121 (7%)
NVQ/HNC or equivalent vs Other professional qualification	140 (1%)
NVQ/HNC or equivalent vs College degree	445 (3%)
Other professional qualification vs College degree	352 (2%)

nonlinearities. We find suggestive evidence that higher educational attainment is associated with longer telomeres when using a series of dummy variables for highest educational attainment. In particular, individuals with GCSEs or equivalent (high school graduates) have 1.2 fewer years of telomere aging compared to individuals with no qualifications (high school dropouts). However, we find no difference in TL between high school dropouts and college graduates after controlling for genetics and shared family background. Our finding that conclusions differ depending on the functional form of educational attainment are consistent with some twin studies in the education-health literature. For example, Fujiwara and Kawachi (2009) and Lundborg (2013) both estimate associations between educational attainment and health using identical twins in the Midlife in United States Development Study. Both studies find no associations between years of education and self-reported health. Lundborg (2013) does however uncover large differences in self-reported health between high school graduates and high school dropouts, and college graduates and high school dropouts in a nonlinear specification. Other studies though have found similar results using both linear and nonlinear representations of educational attainment (Amin et al., 2015; Behrman et al., 2011).

Better health and healthier behaviors is hypothesized as a mechanism through which education may protect against telomere attrition. The evidence on increasing education at the lower tail of the education distribution on health is somewhat mixed. Davies et al. (2018) used the 1972 Raising of the School Leaving Age from 15 to 16 in the UK as a natural experiment to estimate the causal effect of education on health. They find that UKB participants affected by the reform were less likely to have ever-smoked, had reduced risks of diabetes and mortality. Barcellos et al. (2019) find that the reform decreased body size but increased blood pressure among affected UKB participants. Avendano et al. (2020) find that the reform did not affect mental health of UKB participants, but worsened mental health of participants in other datasets.[5] Our finding that TL differences between high school dropouts and graduates persist after controlling for genetics and shared family background, would be consistent with high school graduation being associated with a better body size and lower likelihood of smoking, which both protect against telomere shortening. On the other hand, more education may increase telomere attrition if it worsens mental health. We find that there is no difference in TL between high school dropouts and college graduates after controlling for shared confounders between siblings. This is an odd finding especially given that TL differences between high school dropouts and high school graduates persists in sibling fixed-effect models. In our analysis, only 3% of sibling pairs (476 pairs) are discordant on high school dropout vs college graduation. Thus, one possibility is that the comparison of high school dropouts and college graduates is rare in families. These families may also be different than other families that have smaller education differences. Another possibility is that this is consistent with telomere biology. Benetos et al. (2013) propose that the main determinant of adult TL are TL at birth and its attrition during the first 20 years of life. College education is typically completed in one's 20s. Thus, college education may not be associated with TL because there is not much telomere attrition after age 20, even if there are causal effects of education on health and psychosocial stress.

There are limitations with our study. First, sibling fixed-effect estimates are unlikely to reflect causal estimates. The key assumption for causality is that within-sibling differences in education are uncorrelated with unobserved factors related to education and TL. This is unlikely to hold because we cannot fully control for sibling-specific factors that are correlated with education and TL. For example, siblings may differ in neuroticism during childhood, which is correlated with lower educational attainment (Almulund et al., 2011) and shorter telomeres (van Ockenburg et al., 2014). Parents will notice if a child in a sibling pair has a lower propensity for education/learning and potentially channel additional resources to that child or direct resources away from the high propensity to the low propensity child. Such compensatory behavior likely results in smaller education differences between siblings, possibly leading to smaller TL differences and smaller associations. Although, we

[5] They find that the reform increased the probability of having depression/anxiety in the Annual Population Survey, a survey of 150,000 households and 350,000 respondents per year in the UK.

Table 3
OLS and sibling fixed-effect associations between educational attainment and standardized TL.

Sample	Full	Full	Sibling	Sibling	Sibling	Sibling	Sibling	Sibling
Fixed-Effects	None	None	None	None	Family	Family	Family	Family
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Age	−0.022***	−0.022***	−0.023***	−0.022***	−0.037***	−0.036***	−0.037***	−0.037***
	(0.000)	(0.000)	(0.001)	(0.001)	(0.002)	(0.002)	(0.002)	(0.002)
Female	0.178***	0.173***	0.181***	0.175***	0.174***	0.172***	0.175***	0.173***
	(0.003)	(0.003)	(0.011)	(0.011)	(0.014)	(0.014)	(0.014)	(0.014)
Years of Education	0.007***		0.006***		−0.001		−0.001	
	(0.000)		(0.001)		(0.002)		(0.002)	
No qualification		REF		REF		REF		REF
GCSE or equivalent		0.055***		0.066***		0.046*		0.045*
		(0.005)		(0.017)		(0.024)		(0.024)
A/AS level or equivalent		0.103***		0.091***		0.056*		0.054*
		(0.006)		(0.021)		(0.030)		(0.030)
NVQ/HNC or equivalent		0.065***		0.084***		0.067*		0.068*
		(0.008)		(0.027)		(0.035)		(0.035)
Other professional qualification		0.030***		0.000		0.012		0.010
		(0.007)		(0.024)		(0.030)		(0.030)
College degree		0.129***		0.117***		0.019		0.016
		(0.005)		(0.017)		(0.027)		(0.027)
TL PGS							0.064***	0.064***
							(0.010)	(0.010)
Education PGS							0.003	0.002
							(0.010)	(0.010)
N	392,216	392,216	30,702	30,702	30,702	30,702	30,702	30,702

Notes: All regressions additionally control for the first 20 genetic principal components. Standard errors clustered at the family level in columns 3–8. ***significant at 1% **significant at 5% *significant at 10%. REF: reference category.

cannot control for all sources of biases in sibling fixed-effect models, associations that remain after controlling for shared genetics and early-life factors may increase the confidence of identifying causal relations. Second, our results are not generalizable. Our analysis does not contain diverse populations; it is limited to European ancestry individuals due to poor portability of PGSs in non-European populations. The UKB cohort is healthier (lower levels of mortality and lower rates of morbidity-increasing behaviors such as smoking) and more educated than the wider UK population (Fry et al., 2017). This means that less educated people who likely have shorter telomeres are under-represented which would attenuate associations to null. Third, we do not have repeated TL measurements, so we cannot examine whether higher educational attainment reduces telomere attrition. Fourth, TL was measured using qPCR, which is less precise compared to alternative assay methods such as Southern blots (Aviv et al., 2011). However, qPCR is the only feasible method for large population studies given the low cost and small starting amount of DNA needed.

Despite the limitations, our study suggests there may be a possible causal relationship between educational attainment and cellular aging. More research is needed to estimate causal effects of education on TL and other markers of cellular aging (e.g., epigenetic clocks) and to understand the mechanisms.

Ethics approval

This research has been conducted using the UK Biobank Resource under Application 57284 and undergone IRB approval at University of Wisconsin-Madison.

Author statement

Vikesh Amin: Conceptualization; methodology; writing—original draft; writing—review and editing; funding acquisition.

Jason M Fletcher: Conceptualization; data curation; formal analysis; writing—original draft; writing—review and editing; funding acquisition.

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Declaration of competing interest

None.

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Appendix

Table A1
Sex Differences in Associations between Educational Attainment and Standardized TL

Sample	Sibling	Sibling
Fixed-Effects	Family	Family
	(1)	(2)

(*continued on next page*)

Table A1 (*continued*)

Sample	Sibling	Sibling
Fixed-Effects	Family	Family
	(1)	(2)
Age	−0.037***	−0.037***
	(0.002)	(0.002)
Female	0.131***	0.200***
	(0.040)	(0.033)
Years of Education	−0.003	
	(0.002)	
Years of Education * Female	0.003	
	(0.003)	
No qualification		REF
GCSEs or equivalent		0.084**
		(0.034)
A/AS level or equivalent		0.089**
		(0.045)
NVQ/HNC or equivalent		0.113**
		(0.056)
Other professional qualification		0.030
		(0.041)
College degree		0.008
		(0.036)
No qualification*Female		REF
GCSEs*Female		−0.063
		(0.042)
A/AS level*Female		−0.059
		(0.054)
NVQ/HNC*Female		−0.073
		(0.069)
Other professional qualification*Female		−0.038
		(0.058)
College degree*Female		0.016
		(0.041)
TL PGS	0.064***	0.064***
	(0.010)	(0.010)
Education PGS	0.003	0.002
	(0.010)	(0.010)
N	30,702	30,702

Notes: All regressions additionally control for the first 20 genetic principal components. Standard errors clustered at the family level. ***significant at 1% **significant at 5% *significant at 10%. REF: reference category.

Appendix

Table A2
OLS and Sibling Fixed-Effect Associations Between Educational Attainment and Standardized TL from Regressions with Linear Splines

Knot	10 Years of Education			13 Years of Education			15 Years of Education			19 Years of Education		
Sample	Full	Sibling	Sibling	Full	Sibling	Sibling	Full	Sibling	Sibling	Full	Sibling	Sibling
Fixed-Effects	**None**	**None**	**Family**	**None**	**None**	**Family**	**None**	**None**	**Family**	**None**	**None**	**Family**
	(1)	**(2)**	**(3)**	**(4)**	**(5)**	**(6)**	**(7)**	**(8)**	**(9)**	**(10)**	**(11)**	**(12)**
Years of Education < Knot	0.019***	0.022***	0.017**	0.014***	0.014***	0.010**	0.011***	0.011***	0.008**	0.004***	0.002	0.002
	(0.002)	(0.005)	(0.008)	(0.001)	(0.003)	(0.005)	(0.001)	(0.003)	(0.004)	(0.001)	(0.002)	(0.002)
Years of Education ≥ Knot	−0.013***	−0.019**	−0.020**	−0.011***	0.014***	−0.018**	−0.008***	−0.012*	−0.020**	0.042***	0.049***	−0.037
	(0.002)	(0.006)	(0.008)	(0.001)	(0.005)	(0.007)	(0.002)	(0.006)	(0.008)	(0.006)	(0.021)	(0.026)
N	392,216	30,702	30,702	392,216	30,702	30,702	392,216	30,702	30,702	392,216	30,702	30,702

Notes: All regressions control for age, an indicator for being female, and the first 20 genetic principal components. Standard errors clustered at the family level in the sibling sample. ***significant at 1% **significant at 5% *significant at 10%.

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