

Cross-national and cross-generational evidence that

educational attainment may slow the pace of aging in European-descent individuals

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Funding Details and Acknowledgements

This work was supported by the National Institutes of Health (R01AG073207, R01AG032282 and HD077482 to T.E.M. and A.C., R01AG060110 to E.M.C., and R01AG073402, R01AG066887, and R01AG061378 to D.W.B.); the UK Medical Research Council (MR/P005918/1, and G1002190); the New Zealand Health Research Council Programme (16-604); and the North Carolina Biotechnology Center (2016-IDG-1013). Support was also received from the Jacobs Foundation. Generation Scotland received core support from the Chief Scientist Office of the Scottish Government Health Directorates (CZD/16/6) and the Scottish Funding Council (HR03006) and is currently supported by the Wellcome Trust (216767/Z/19/Z). Genotyping of the GS:SFHS samples was carried out by the Genetics Core Laboratory at the Edinburgh Clinical Research Facility, University of Edinburgh, Scotland and was funded by the Medical Research Council UK and the Wellcome Trust (Wellcome Trust Strategic Award “STratifying Resilience and Depression Longitudinally” (STRADL) Reference 104036/Z/14/Z).

The DNA methylation profiling and analysis was supported by Wellcome Investigator Award (220857/Z/20/Z, 104036/Z/14/Z) and through funding from NARSAD (Ref: 27404) and the Royal College of Physicians of Edinburgh (Sim Fellowship). Understanding Society is an initiative funded by the Economic and Social Research Council and various Government Departments, with scientific leadership by the Institute for Social and Economic Research, University of Essex, and survey delivery by NatCen Social Research and Kantar Public. The research data are distributed by the UK Data Service. Fieldwork for the web survey was carried out by Ipsos MORI and for the telephone survey by Kantar. We would like to acknowledge the assistance of the Duke Molecular Physiology Institute Molecular Genomics Core for the generation of data for the manuscript.

Conflict of Interest

K. Sugden; A. Caspi; D. W. Belsky; D. L. Corcoran; R. Poulton; and T. E. Moffit and are listed as inventors on a Duke University and University of Otago invention that is licensed to a commercial entity. All other authors report no conflict of interest.

Author Contributions

K. Sugden planned the study, sourced data, generated measures, developed models and software code, performed data analysis, and wrote the paper. A. Caspi planned the study, supervised the data analysis, provided funding, and wrote the paper. T.E. Arpawong, R. Houts, and J. Wertz performed data analysis. D.W. Belsky sourced data. T.E. Moffitt, E.M. Crimmins, L. Arseneault, and R. Poulton provided funding for and supervised data collection. D.L. Corcoran, J.S. Mill, E. Hannon, and B.S. Williams generated data and measures used in the manuscript. All authors reviewed and revised the manuscript.

Abstract

Objectives

Individuals with more education are at lower risk of developing multiple, different age-related diseases than their less educated peers. A reason for this might be that individuals with more education age slower. There are two complications in testing this hypothesis. First, there exists no definitive measure of biological aging. Second, shared genetic factors contribute towards both lower educational attainment and the development of age-related diseases. Here, we tested whether the protective effect of educational attainment was associated with the pace of aging after accounting for genetic factors.

Methods

We examined data from five studies together totaling almost 17,000 individuals with European ancestry born in different countries during different historical periods, ranging in age from 16 to 98 years old. To assess the pace of aging, we used DunedinPACE, a DNA methylation algorithm that reflects an individual's rate of aging and predicts age-related decline and Alzheimer's Disease and Related Disorders (ADRD). To assess genetic factors related to education we created a polygenic score (PGS) based on results of a genome-wide association study (GWAS) of educational attainment.

Results

Across the five studies, and across the lifespan, higher educational attainment was associated with a slower pace of aging even after accounting for genetic factors (meta-analysis effect size=-0.20, 95%CI[-0.30- -0.10]; p -value = 0.006). Further, this effect persisted after taking into account tobacco smoking (meta-analysis effect size=-0.13, 95%CI[-0.21- -0.05]; p -value = 0.01).

Discussion

These results indicate that higher levels of education have positive effects on the pace of aging, and that the benefits can be realized irrespective of individuals' genetics.

Keywords: pace of aging, education, epigenetic clocks

Accepted Manuscript

Main article

Introduction

Individuals with more formal education are at lower risk than their less educated peers of developing multiple age-related diseases, including Type 2 Diabetes, hypertension, cardiovascular disease (Agardh et al., 2011; Degano et al., 2017; Dupre, 2007; Kubota et al., 2017) and Alzheimer's and related dementias (Sharp & Gatz, 2011; Xu et al., 2015). One reason for this may be that individuals with more formal education age slower. The geroscience hypothesis proposes that biological aging, conceptualized as the gradual and progressive deterioration of biological system integrity (Kirkwood, 2005), increases vulnerability to multiple age-related diseases (Kennedy et al., 2014). Thus, while all individuals age chronologically at the same rate, some individuals age much faster biologically. Since lower educational attainment is such a powerful predictor of multiple, different age-related diseases and early mortality, it is possible that education exerts its influence on age-related diseases not via disease-specific social and biological mechanisms but by accelerating whole-body biological aging. Accelerated biological aging would help to explain the wide-ranging health effects of education (Hahn & Truman, 2015; Zajacova & Lawrence, 2018)

A difficulty in evaluating the hypothesis that educational attainment is negatively associated with accelerated aging is that, at present, there is no widely accepted measure of biological aging (Cohen et al., 2020; Crimmins et al., 2021). But progress on this front is rapid, including efforts to measure individual differences in the pace of aging using -omics data (Rutledge et al., 2022), especially genome-wide methylation data. DNA methylation is an epigenetic mechanism by which specific points of the genome (cytosines) are chemically modified (methylated) and thereby influence gene regulation. Many efforts to develop measures of aging have focused on DNA methylation quantified in blood, in part because it is a biological substrate that is sensitive to age-related changes (Horvath & Raj, 2018; Levine, 2020). Using machine learning, these efforts involve developing algorithms to capture information about aging by combining measurements of DNA

methylation at multiple sites across the genome. Such algorithms can be summarized in terms of developmental ‘generations’. The first generation of methylation algorithms was trained on chronological age in samples ranging in age from children to older adults. These algorithms identify patterns of methylation that vary by chronological age; however, if an individual’s score on such clocks is older than their actual age, it is inferred that they are biologically older. The first-generation algorithms include the “Hannum clock” (Hannum et al., 2013) and the “Horvath clock” (Horvath, 2013). The second generation of methylation algorithms included measures of people’s current physiological status in order to identify methylation patterns that account for variation in current health status and that predict mortality. These second-generation algorithms include PhenoAge (Levine et al., 2018) and GrimAge (Lu et al., 2019). In contrast to these earlier algorithms that relied on cross-sectional measures of current health to estimate relative biological age third-generation algorithm has been recently developed, DunedinPACE (**P**ace of **A**ging **C**alculated from the **E**pigenome), which is unique in predicting an individual’s rate of aging. Unlike the prior clocks, DunedinPACE was based on geroscience theory, which specifies the definition of aging as “the gradual, progressive, synchronized deterioration of function in multiple organ systems of the body over years of time.” No other measure of aging operationalizes this theory. The DunedinPACE algorithm was developed by first measuring people’s rate of physiological change over time and then identifying the methylation patterns that optimally captured individual differences in their age-related decline (Belsky et al., 2022). Specifically, age-related change in 19 cardiovascular, metabolic, renal, immune, dental, and pulmonary biomarkers among individuals of the same chronological age over a 20-year observation period in the Dunedin Longitudinal Study (Elliott et al., 2021) were measured. Methylation patterns at the end of the observation period were then identified that estimated how fast aging occurred during the years leading up to the point of measurement (Belsky et al., 2022). Thus, DunedinPACE distills multiple decades of longitudinal change in biomarker data to a single point-in-time measure and was designed to capture methylation patterns reflecting individual differences in age-related decline. This new measurement tool can now be exported to

diverse studies with DNA methylation data in order to test the hypothesis that lower educational attainment is associated with accelerated aging.

A challenge in testing this hypothesis is that lower educational attainment and greater susceptibility to age-related diseases share genetic risk factors (Boardman et al., 2015; Marioni et al., 2016; Wedow et al., 2018). Large-scale genome-wide association studies (GWAS) have uncovered many genetic variants (Single Nucleotide Polymorphisms; SNPs) that are associated with educational attainment (Lee et al., 2018). These SNPs can be condensed into a single metric of genetic likelihood of education, a 'polygenic score' (PGS). This PGS not only predicts how much education individuals attain, but is also statistically associated with many health outcomes such as metabolic dysregulation, coronary heart disease, and frailty (Ding et al., 2019; Huibregtse et al., 2021). Shared genetic etiology between educational attainment and age-related diseases raises the possibility that educational attainment is associated with accelerated aging not because formal education protects individuals from more rapid age-related decline, but because individuals who attain more education are genetically predisposed to better health more generally. The scientific, policy, and ethical implications of these alternative pathways are not inconsequential. They raise questions about whether improving access to formal education may slow the process of aging and protect people from disease (Zimmerman & Woolf, 2014) and they flag concerns about genetic essentialism and the geneticization of social and health inequalities (Shostak et al., 2009). These discussion points beg the important question: can education be a lever for reducing unhealthy population aging?

Here we leveraged data from five studies in developed nations to ask whether the protective effects of formal education against accelerated aging accrue despite differences between people in their education-related genetics. We tested this in three steps. First, in each study, we evaluated an individual's pace of aging by applying the DunedinPACE algorithm to their genome-wide DNA methylation data. We then tested if higher educational attainment was associated with slower pace of aging. Second, we used genome-wide SNP data to quantify each individual's education-related

genetics (as captured by a PGS). We then tested whether associations between higher educational attainment and slower pace of aging persisted irrespective of genetic differences between people and if higher educational attainment benefitted all individuals equally. Third, we tested whether the association between educational attainment and pace of aging was explained by tobacco smoking. Tobacco smoking is much more common among individuals who have not obtained high levels of education (Centers for Disease & Prevention, 2010), and exposure to tobacco smoking harms virtually every organ in the body. Tobacco smoking could thus be a potent mechanism by which low educational attainment accelerates whole-body aging. Beyond the negative biological impact of tobacco-related toxins, tobacco smoking captures many personological and psychosocial factors that antedate the completion of formal education and that put people at risk for faster aging. For example, adolescents who become lifelong tobacco smokers are characterized by high levels of negative emotionality (e.g., stress reactivity, aggression, and feelings of alienation) and low levels of behavioral constraint (e.g., greater risk-taking, impulsivity (Slutske et al., 2005), which portend later poor health and early mortality (Chiang et al., 2018; Jokela et al., 2013). Thus, controlling for tobacco smoking captures unmeasured confounding beyond the health effects of tobacco smoking.

The five studies included in this article represent almost 17,000 individuals born and raised in different countries and in different historical periods. By including people from different places and time, we test whether the protective effect of education generalizes across geographical and historical variation in educational and health-care practices and policies.

Methods

Data sources

We utilized data from five cohorts. These were (A) the Dunedin study (New Zealand, $N = 804$, 50.6% male, age = 45 years), (B) the Health and Retirement Study (U.S., $N = 2,311$, 43.2% male, mean(SD) age = 71.6(9.6)), (C) the Understanding Society study (UK, $N = 3,620$, 44.4% male,

mean(SD) age = 53.0(15.5)), (D) the Generation Scotland study (Scotland, $N = 8,613$, 40.9% male, mean(SD) age = 49.7(13.7), and (E) the E-Risk study (England and Wales, $N = 1,507$, 50.6% male, age = 18 years). Detailed descriptions and demographics of each study can be found in **Supplemental Figure 1** and **Supplemental Methods**.

Calculation of DNA methylation aging measures

For all studies, DunedinPACE was calculated using the *R* package ‘*DunedinPACE*’ as described in (Belsky et al., 2022) and publicly available on GitHub (<https://github.com/danbelsky/DunedinPACE>). Within each study, DunedinPACE values were standardized to mean = 0, SD = 1. All other DNA methylation measures were calculated using the online calculator found at <https://dnamage.genetics.ucla.edu/new>. Where appropriate, estimates of age advancement were derived from these values by residualizing for chronological age at the time of assessment.

Education measurements

In each cohort, educational attainment was measured as the highest level of education on a 4-point scale, ranging from no school qualification to a university degree or higher. To aid cross-study comparisons, cohort-specific measures of educational attainment qualifications were binned into classes reflecting increasingly higher educational achievement, as follows:

Dunedin Study: 0=‘No school qualification’; 1=‘School certificate’; 2=‘High school graduate’;

3=‘University degree or higher’; HRS: 0=‘Less than high-school’, 1=‘General Educational

Development (GED) certificate’, 2=‘High-school graduate or some college’, 3=‘College and above’;

Understanding Society Study, 0=‘No Qualification’, 1= ‘GCSE etc.’/‘Other Qualification’, 2=‘A-level etc.’, 3=‘Degree’ /‘Other higher degree’; Generation Scotland Study: 0=‘No Qualification’,

1=‘Standard Grade/O Level/GCSE’/‘CSEs or equivalent’/‘School leavers certificate’/‘Other’,

2='NVQ/HND/HNC or equivalent'/'Higher Grade', 3='University degree or higher'/'College/University degree'/'Other professional or technical qualification'; and E-Risk: 0='No qualification', 1='GCSE grade D-G', 2='GCSE grade A*-C', 3='A level'. Across all cohorts, the four levels of educational achievement show a dose-response relationship with aging as measured by DunedinPACE (Figure 1); education was therefore analyzed as a continuous variable.

Polygenic score measurements

Polygenic scoring was conducted following the method described by Dudbridge (Dudbridge, 2013) using PRSice (Euesden et al., 2015). For each study, we used summary statistics from a GWAS of educational attainment (Lee et al., 2018) to compute PGS for educational attainment. We used all matched SNPs to compute PGS irrespective of nominal significance for their association with educational achievement. SNPs were not clumped or pruned for LD prior to analysis. To control for possible residual population stratification, scores were residualized for the first 10 principal components estimated from the genome-wide SNP data. Within each study, we standardized residuals (mean = 0, SD = 1) for analysis.

Tobacco smoking

Exposure to tobacco smoking was estimated from DNA methylation data following published guidelines (Sugden et al., 2019). Briefly, within each study DNA methylation values for 2,623 DNA methylation probes associated with tobacco smoking were weighted by the coefficient of association with smoking and summed to produce a smoking PolyEpiGenetic Score (smPEGS). This score was standardized to mean = 0, SD = 1. In addition, we also employed data on self-reported tobacco smoking (Generation Scotland: pack years smoked up to time of assessment (standardized to mean = 0, SD = 1); all other studies: current smoking at time of assessment; yes/no).

Data analysis and statistical methods

All data analyses were performed in the *R* statistical environment apart from the genetic sensitivity analysis (described later) which was conducted in *MPLUS*. For association analyses, we used linear regression models in the Dunedin, HRS and Understanding Society studies; for Generation Scotland and E-Risk, we used panel linear models with Huber-White robust standard errors (using *R* packages '*plm*' and '*lsmmeans*') to account for familial clustering. Models included covariates for sex, age (except for the Dunedin and E-risk studies where participants are the same age), and technical covariates consisting: in the Dunedin, HRS, and E-Risk studies of the first 32, 6, and 28 PCs from principal component analysis of methylation control probes, explaining 90% of variation; in Understanding Society and Generation Scotland of DNA methylation processing rank.

To perform t- and Z-ratio tests, we used the *R* packages '*lsmmeans*' and '*geepack*' (for the Generation Scotland and E-Risk studies). To perform meta-analysis and plot results, we used the *R* packages '*metagen*' (using the restricted maximum likelihood estimator, REML, the Knapp-Hartung adjustment, and the random-effects model) and '*forest*'. We used the *R* package '*Evalues*' to calculate E-values. To address potential population stratification, data from all five cohorts were restricted to participants with white ancestry. All analyses were performed in parallel by a second, independent researcher to confirm reproducibility.

Data availability

For the Dunedin and E-Risk studies, data may be accessed through agreement with the Study investigators (<https://moffittcaspi.trinity.duke.edu/research-topics/dunedin>; <https://moffittcaspi.trinity.duke.edu/research-topics/erisk>). For HRS, data may be accessed via the Health and Retirement Study (<https://hrs.isr.umich.edu/data-products>) with restricted health data available from NIAGADS. For Understanding Society, data may be accessed upon approval by the

study coordinators (<https://www.understandingsociety.ac.uk/documentation/health-assessment/accessing-data/genetics-application>). For Generation Scotland, data may be accessed upon approval by the study coordinators (<https://www.ed.ac.uk/generation-scotland/for-researchers/access>).

Results

Educational attainment is associated with the Pace of Aging

We first tested the association between educational attainment and the pace of aging in the **Dunedin Study**. Participants in the Dunedin Study were all born during the same year (1972-73) in the same city (Dunedin, New Zealand). As such, they had opportunities to interact with the same educational and health systems with minimal influence of temporal or geographical effects. Dunedin participants who attained more education aged at a significantly slower rate than participants who attained less education (b [95% CI] = -0.38 [-0.44 -0.31], **Table 1, Figure 1**). Individuals with the highest level of education aged 1.8 months/year more slowly than individuals with no education (Supplemental Table 1, Panel D).

Next, we turned to the **Health and Retirement Study (HRS)**, a population-representative cohort of 50+ year-olds from the United States limited to those of European ancestry for this analysis. This cohort represents individuals entering later life in a region with different educational and health systems than that of the midlife Dunedin Study members. HRS participants who attained more education aged at a significantly slower rate than participants who attained less education (b [95% CI] = -0.20 [-0.24 -0.16] , **Table 1, Figure 1**). Individuals with the highest level of education aged 1.32 months/year more slowly than individuals with no education (Supplemental Table 1, Panel D).

We next asked whether we could replicate this association across the lifespan. To do this, we turned to two independent studies. The **Understanding Society** study includes individuals ranging in

age from 16-98 (mean age = 53.0 years; SD = 15.5 years). The **Generation Scotland** study includes individuals ranging in age from 18-93 (mean age = 49.7 years; SD = 13.7 years). Individuals in each study were exposed to different educational and health opportunities related to the era in which they were born (between 1915 and 1990 for Understanding Society between 1914 and 1995 for Generation Scotland). Moreover, both Understanding Society (sampling England, Wales, Northern Ireland, and Scotland) and Generation Scotland (sampling Scotland) are based in the United Kingdom, and as such reflect educational and health practices that are not necessarily shared with New Zealand or the USA. Despite these differences, results across both studies were very similar and resembled those observed in Dunedin and HRS. Study participants who attained more education aged at a significantly slower rate than participants who attained less education (Understanding Society: b [95% CI] = -0.20 [-0.23- -0.17]; Generation Scotland: b [95% CI] = -0.20 [-0.22- -0.18]; **Table 1, Figure 1**). Individuals with the highest level of education aged 1.44 and 1.08 months/year more slowly than individuals with no education in the Understanding Society and Generation Scotland Studies, respectively (Supplemental Table 1, Panel D).

Due to nationwide social policy changes, access to education and health care can vary for different generations of individuals born in the same country. These generational differences might alter the patterns of association between educational attainment and aging. To test this possibility, we subset the Understanding Society and Generation Scotland data into five groups each to capture individuals who were born within the same 15-16-year age bands. Analysis of the association between pace of aging and educational attainment within each of these age groups showed that, in both studies, individuals with the highest level of education had the slowest pace of aging regardless of how old they were or when they were born. An exception to this was among the very oldest group of individuals in each of the two studies (**Figure 3**); this may reflect selective participation and selective mortality, combined with a small sub-sample size. In general, the positive effects of education on pace of aging are experienced across the lifespan and are not restricted to individuals who were born and raised during specific time periods.

Lastly, we tested the link between educational attainment and the pace of aging in a contemporary cohort of young individuals who were currently in the process of realizing their educational potential. We turned to the **E-Risk study**, which includes individuals born in the United Kingdom in 1994-95. Study members were assessed at age 18, at which point we measured how far they had advanced in the UK educational system. This cohort offered the opportunity to test whether educational attainment was associated with early whole-body aging, years before the typical hallmarks of aging are manifest. E-Risk participants who attained more education aged at a significantly slower rate than participants who attained less education (b [95% CI] = -0.17 [-0.21 - -0.12]; **Table 1, Figure 1**). Individuals with the highest level of education aged 0.48 months/year more slowly than individuals with no education (Supplemental Table 1, Panel D).

Genetics of educational attainment are associated with the Pace of Aging

In each of the five cohorts, we calculated each individual's PGS for educational attainment. In each cohort, individuals with higher polygenic scores attained significantly more education (**Figure 2**). The education PGS accounted for 9-13% of the variance in educational attainment across the cohorts, a finding that is consistent with published estimates (Lee et al., 2018). Mean differences in PGSs between individuals with the lowest vs. highest level of education in each study were substantial, ranging from 0.69 SD units in Understanding Society to 0.97 SD units in the Health and Retirement Study (**Supplemental Table 1**).

Consistent with evidence that educational attainment and aging-related health are influenced by similar genetic factors, we found individuals with a higher educational attainment PGS also aged at a significantly slower pace in all five cohorts (**Figure 2**). Mean differences in PGS between individuals who were aging slowest vs. fastest (bottom and top quartiles of the DunedinPACE distribution) in each study were substantial, ranging from 0.26 SD units among the

young participants in the E-Risk study to 0.50 SD units among middle-aged Dunedin Study participants.

Do the beneficial effects of education on slower aging persist after taking education-related genetic differences into account?

To answer this, we repeated tests of association between educational attainment and pace of aging, controlling for education PGS. Across all five cohorts, individuals who attained more education aged at a significantly slower rate than participants who attained less education even after controlling for an individual's PGS (**Table 1**). This effect was observed in middle-aged New Zealanders (Dunedin Study, b [95% CI] = -0.36 [-0.43- -0.29]), older-aged Americans (HRS, b [95% CI] = -0.18 [-0.22- -0.13]), British and Scottish individuals of varied age (Understanding Society and Generation Scotland, b [95% CI] = -0.16 [-0.20- -0.13] and b [95% CI] = -0.17 [-0.19- -0.15], respectively) and British teenagers (E-Risk, b [95% CI] = -0.16 [-0.21- -0.11]).

Next, we tested whether the benefits of more education accrue equally to individuals at different levels of the PGS distribution, from low to high. In each of our 5 cohorts, we subset individuals into quintiles according to their PGSs (from lowest 20% to highest 20%). Analysis of the association between educational attainment and pace of aging showed that, in all studies, individuals with higher levels of education had the slowest pace of aging regardless of their location on the education polygenic-score distribution (**Supplemental Figure 2**). Further, the magnitude of association between educational attainment and pace of aging within each PGS quintile was not significantly different from that of any other quintile within each cohort. The association between higher educational attainment and slower pace of aging does not differ across the distribution of education-related genetic differences.

In summary, higher educational attainment was associated with slower pace of aging irrespective of genetic differences related to education, and this effect was seen across individuals from different geographical regions, born during different eras, and, in the case of the E-Risk Study, still accumulating their educational achievements. Higher education has the potential to benefit all individuals irrespective of genetic differences between them that predict how much education they are likely to attain.

Meta-analysis of the association between educational attainment and the Pace of Aging

We performed a meta-analysis of the results in the five cohorts (N=16,855) to establish the overall effect size of the association between educational attainment and the pace of aging after controlling for each individual's PGS for educational attainment. The overall effect size was significantly different from zero (effect size = -0.20, 95%CI [-0.30 -0.10]). We noted significant heterogeneity in the estimates across the 5 cohorts ($I^2 = 87\%$, heterogeneity $\chi^2 = 29.64$, **Figure 4A**). Heterogeneity statistics may be biased upward with only 5 studies (von Hippel, 2015). Nevertheless, we re-performed the meta-analysis after removing the largest estimate, from the Dunedin Study; heterogeneity was no longer significant ($I^2 = 0\%$, heterogeneity $\chi^2 = 0.35$, $p = 0.95$), and the overall effect size was little changed (effect size = -0.17, 95%CI [-0.18 -0.16]).

Robustness to sources of confounding and bias

Is the association between educational attainment and Pace of aging explained by tobacco smoking? To test whether tobacco smoking accounts for the link between low educational attainment and accelerated aging, we repeated all preceding analyses controlling for each individual's exposure to tobacco smoking. To ensure that consistent measures of smoking were used across the various studies, we utilized a Smoking PolyEpiGenetic Score (smPEGS) that indexes

tobacco exposure via variation across smoking-associated DNA methylation sites (Sugden et al., 2019). Importantly, smPEGS indexes cumulative lifetime exposure to tobacco smoking, not only current smoking. After controlling for smoking, educational attainment remained significantly associated with the pace of aging in all five cohorts (**Table 1**). Meta-analysis estimated that tobacco smoking attenuated the association between educational attainment and pace of aging by one-third, but the association remained significantly different from zero (effect size = -0.13, 95%CI [-0.21 - -0.05], $I^2 = 81\%$, heterogeneity $\chi^2 = 20.83$, **Figure 4B**), even after we removed the largest Dunedin Study estimate from the meta-analysis (effect size = -0.09, 95%CI [-0.11 - -0.08], $I^2 = 0\%$, heterogeneity $\chi^2 = 1.45$). Furthermore, these patterns remained consistent if instead we controlled for self-reported tobacco smoking (**Supplemental Table 2**) rather than smPEGS. Tobacco smoking does not fully explain the association between higher educational attainment and slower pace of aging.

Selection bias. Selection into research studies as well as dropout from studies may exert a biasing effect on both genetic and phenotypic associations. It is increasingly appreciated that these problems characterize many large publicly available studies (Tyrrell et al., 2021). In contrast, both the Dunedin and E-Risk studies represent the populations from which they were drawn and have high retention rates with no evidence of selective attrition in relation to genetic and exposure variables (see **Supplemental Figure 3**). Since we observed similar patterns of association in these two studies versus in the three other studies we included where endogenous selection bias (Akimova et al., 2021) and healthy volunteer bias (Brayne & Moffitt, 2022) are thought to exist (for example, see Lynn & Borkowska, 2018; Michaud et al., 2011; Smith et al., 2013), it is unlikely that selection bias accounts for the associations reported here.

Genetic sensitivity analysis. We used PGS for educational attainment to test if genetic differences between individuals could explain the association between an individual's educational attainment and their pace of aging. However, PGS explain only a portion of the heritability of educational attainment and as such controlling for the PGS alone may not capture all genetic

confounding (Pingault et al., 2022). For context, in the present study the education PGS explains 9-13% of the variation in educational attainment, whereas the SNP heritability of educational attainment has been estimated between ~15-21% (Davies et al., 2016; Pingault et al., 2021). Unmeasured genetic confounding could be present.

To test if additional genetic confounding might explain the association between educational attainment and pace of aging, we performed genetic sensitivity analyses across all five studies using GsensX (Pingault et al., 2021), a method to adjust associations for the presence of unidentified genetic factors influencing both risk factor and outcome. First, using a previously-reported SNP heritability estimate of 14.7% (Pingault et al., 2022), we calculated total effect size, effect size of genetic confounding, and adjusted effect size of the association between educational attainment and DunedinPACE (controlling for education PGS) across the five studies. Next, we performed meta-analysis of these effect sizes to calculate combined estimates for the total effect size, proportion of genetic confounding, and adjusted effect size (**Supplemental Figure 4A-C**). The portion of the combined effect explained by genetic confounding was -0.06 (95% CI [-0.09, -0.02], $p=0.01$, **Supplemental Figure 4B**), corresponding to 25.7% of the total effect size. After taking this genetic confounding into account, higher educational attainment remained significantly associated with slower pace of aging, although the effect was reduced (estimate = -0.16, 95% CI [-0.28, -0.05], $p=0.02$), **Supplemental Figure 4C**). Higher educational attainment is associated with slower pace of aging, even after taking both measured (via educational attainment PGSs) and unmeasured genetic confounding into account.

Unobserved heterogeneity/confounding bias. To ascertain the robustness of the association between educational attainment and DunedinPACE to other unmeasured confounding, we computed E-values for the estimate generated through meta-analysis. E-values represent the magnitude of association necessary between an unmeasured confounder and both exposure and

outcome to fully account for observed associations (Haneuse et al., 2019; VanderWeele & Ding, 2017).

The E-value for the meta-analysis of the association between educational attainment and the pace of aging after controlling for both education PGS and tobacco smoking (**Figure 4B**) was 1.69; that is, unmeasured confounder(s) would need to increase the probability of having a faster versus slower pace of aging 1.69 times the reported estimate to fully explain the observed associations. E-values for associations between DunedinPACE and education for each individual study are reported in **Supplemental Table 3**.

Sensitivity analysis: Patterns of association with earlier generations of DNA methylation clocks.

To test the specificity of the pattern of associations between DunedinPACE and educational attainment, we repeated the primary analyses substituting alternate DNA methylation measures of accelerated aging (the first-generation clocks from Horvath (Horvath, 2013) and Hannum (Hannum et al., 2013), and the second-generation clocks PhenoAge (Levine et al., 2018) and GrimAge (Lu et al., 2019)). Of these four measures, only GrimAge showed similar patterns of association with education to that of DunedinPACE (Supplemental Table 4). This observation mirrors what is increasingly observed in other studies (e.g. Graf et al., 2022; Reed et al., 2022): whereas the Horvath, Hannum, and PhenoAge measures are yielding null, weak, and inconsistent associations in various validity tests, GrimAge and DunedinPACE are yielding robust associations. Of note, it is observed that GrimAge tends to be more strongly associated with tobacco smoking than DunedinPACE (e.g., Kankaanpää et al., 2022) and this is evidenced here by the greater attenuation of associations with education after controlling for smoking. An explanation for this could be that GrimAge is comprised of data about packyears of tobacco smoking in its construction, meaning it is less likely to be independent of tobacco's effects.

Discussion

Higher educational attainment is robustly associated with both better brain health and better physical health across the life span. But it is less clear if attaining more formal education is also associated with slower cognitive and physical aging. In fact, in the realm of cognitive aging, evidence suggests that the association between education and age-related cognitive decline might be negligible (Lovden et al., 2020). Here we leveraged a novel approach to measuring whole-body biological pace of aging using a DNA methylation algorithm harmonized across multiple different cohorts to test if education is associated with slower physical aging across the lifespan.

Across five studies totaling almost 17,000 individuals, we demonstrate that higher educational attainment was associated with slower pace of aging, and that this persisted after accounting for an individual's education-related genetics. This finding was observed in middle-aged individuals from New Zealand (Dunedin study), older-aged individuals from the United States (Health and Retirement Study), individuals of different ages in the United Kingdom (Understanding Society and Generation Scotland Studies), and British teens (E-Risk Studies). Across different ages and geographical regions, higher educational attainment predicted slower pace of aging irrespective of genetic differences that are known to confer advantages in Western educational systems.

There are several strengths to the study. First, the finding that higher education predicts slower aging after accounting for genetic differences in the propensity to attain more education was replicated across five independent samples. Second, we replicated the association in samples from different populations born during different time periods. Our studies sampled populations resident in New Zealand, the United States, and the United Kingdom, countries with independent education and health systems. The five studies included individuals from 16-years to 98-years old; the wide age-range of our samples means that individuals have been exposed to very different health or education policies throughout their life. Taken together, this suggests that associations are not specific to certain sociological or economic factors that advantaged certain generations of

individuals in terms of education or health. The beneficial effect of education on the pace of aging over and above genetic inheritance was present regardless of when or where individuals were born.

There are some caveats. First, the study populations we analyzed are white and we are unable to extrapolate the findings to populations of other ethnicities. Individuals from non-white populations have unequal access to both education and health care. In addition, the education PGS that we employed here was developed in white individuals; patterns of genetic linkage differ between ethnic groups, and there is mixed evidence as to the applicability of this score in non-white populations (Lewis & Vassos, 2020). Furthermore, there is evidence that non-white underprivileged individuals who achieve high levels of education age *faster* and have *poorer* health outcomes than both white individuals (Shuey & Willson, 2008) and their non-educated peers, and that the advantages of educational mobility on slower aging seen for white individuals are not evident for black individuals (Graf et al., 2022). These findings suggest the mechanisms defining the link between education and aging might not operate in the same way across all ethnic groups. Second, our studies all sampled individuals from developed nations. Globally, these countries are among the most privileged in terms of access to both health and educational resources. We are therefore unable to test whether our findings are applicable to situations where education and health resources are scarcer. More studies sampling low- and middle-income countries are necessary to test the implications of our findings on a global level. Third, apart from genetic differences in the propensity to educational attainment, we did not rule out other potential confounds of the association between educational attainment and slower aging. For example, it has been demonstrated that there are strong links between parental genetic and non-genetic factors that contribute to both the health and educational attainment of offspring (e.g., Wang et al., 2021). Using data on cross-generational factors and within-family designs will be crucial to investigate these factors; however, those data are not yet widely available along with data on DNA methylation and genetics that would enable us to test this. Despite this, our tests of unmeasured confounding suggest the associations we report are likely to be robust. Fourth, apart from smoking, we did not

evaluate the intervening social and biological pathways that may account for the link between educational attainment and slower aging (Oblak et al., 2021; Raffington & Belsky, 2022). It will be especially important to evaluate these pathways via models that test the timing of risk in the life course (Chumbley et al., 2021). Fifth, the association between education and the pace of aging suggests that it is not simply that truncated education hastens aging or that a university education slows aging, it is that the non-genetic association between education and the pace of aging appears to operate in a graded fashion. This suggests that education may impart benefits across different levels of education, although it is not known whether the mechanisms are the same throughout the gradient.

Taken together, these results suggest that higher levels of education have positive effects on the pace of aging, and that the benefits can be realized irrespective of an individual's genetic endowment. Improving access to education has the potential to benefit all strata of society and could contribute to a healthier aging population.

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Table 1: Association between education polygenic scores (PGS), educational attainment, and DunedinPACE. For these analyses, education (reported as highest educational achievement) is treated as a continuous variable. Across all five studies, individuals with high education PGS (**A**) and high educational attainment (**B**) had the slowest pace of aging (DunedinPACE). Further, an individuals' genetic propensity to higher educational attainment (PGS) did not explain the association between education and DunedinPACE; education remained significantly associated with DunedinPACE even after controlling for PGS (**C**). Effect sizes after adjusting for tobacco smoking (using the DNA methylation-derived PolyEpiGenetic score, smPEGS) for each study are also shown. DunedinPACE, PGS and education are standardized to mean = 0, SD=1. All models include sex as a covariate. Additional covariates to control for confounders (e.g., age, batch) are also included when appropriate. To account for non-independence of observations in the Generation Scotland and E-Risk studies, we report p-values associated with Huber-White robust standard error correction.

| Study | A | | B | | C | | | |
|------------------------------|----------------------|----------|----------------------|----------|----------------------|----------|----------------------|-----------|
| | Education PGS | | Education | | Education PGS | | + | Education |
| | <i>b</i> [95% CI] | <i>p</i> | <i>b</i> [95% CI] | <i>p</i> | <i>b</i> [95% CI] | <i>p</i> | <i>b</i> [95% CI] | <i>p</i> |
| Dunedin | -0.17 [-0.24- -0.10] | <0.001 | -0.38 [-0.44- -0.31] | <0.001 | -0.08 [-0.15- -0.01] | 0.022 | -0.36 [-0.43- -0.29] | <0.001 |
| adjusted for smoking | -0.12 [-0.18- -0.06] | <0.001 | -0.26 [-0.33- -0.20] | <0.001 | -0.06 [-0.13-0.00] | 0.048 | -0.25 [-0.31- -0.18] | <0.001 |
| HRS | -0.13 [-0.17- -0.09] | <0.001 | -0.20 [-0.24- -0.16] | <0.001 | -0.08 [-0.12- -0.04] | <0.001 | -0.18 [-0.22- -0.13] | <0.001 |
| adjusted for smoking | -0.10 [-0.1- -0.07] | <0.001 | -0.14 [-0.18- -0.10] | <0.001 | -0.07 [-0.11- -0.03] | <0.001 | -0.12 [-0.16-0.08] | <0.001 |
| Understanding Society | -0.18 [-0.21- -0.15] | <0.001 | -0.20 [-0.23- -0.17] | <0.001 | -0.14 [-0.17- -0.11] | <0.001 | -0.16 [-0.20- -0.13] | <0.001 |
| adjusted for smoking | -0.13 [-0.15- -0.10] | <0.001 | -0.11 [-0.14- -0.08] | <0.001 | -0.11 [-0.14- -0.08] | <0.001 | -0.08 [-0.11- -0.06] | <0.001 |
| Generation Scotland | -0.15 [-0.17- -0.13] | <0.001 | -0.20 [-0.22- -0.18] | <0.001 | -0.10 [-0.12- -0.08] | <0.001 | -0.17 [-0.19- -0.15] | <0.001 |

| | | | | | | | | |
|----------------------|----------------------|--------|----------------------|--------|----------------------|--------|----------------------|--------|
| adjusted for smoking | -0.10 [-0.11- -0.08] | <0.001 | -0.11 [-0.13- -0.09] | <0.001 | -0.07 [-0.09- -0.05] | <0.001 | -0.09 [-0.11- -0.07] | <0.001 |
| E-Risk | -0.08 [-0.13- -0.03] | 0.007 | -0.17 [-0.21- -0.12] | <0.001 | -0.03 [-0.08- -0.02] | 0.293 | -0.16 [-0.21- -0.11] | <0.001 |
| adjusted for smoking | -0.05 [-0.10- -0.01] | 0.057 | -0.12 [-0.17- -0.07] | <0.001 | -0.03 [-0.08- -0.02] | 0.368 | -0.11 [-0.16- -0.06] | <0.001 |

b = standardized regression coefficient, CI = Confidence Interval, *p* = *p* value

Figure Legends

Figure 1: Distribution of DunedinPACE values across categories of educational attainment in (A) the Dunedin Study, (B) the U.S. Health and Retirement Study (HRS), (C) the Understanding Society Study (D) Generation Scotland Study, and (E) the E-Risk Study. DunedinPACE values are standardized within study to mean = 0, SD = 1. Educational categories are 0 = no qualification, 1 = School Certificate, 2 = High School Grad, 3 = University degree or higher for figures **A, B, C, and D** and 0 = no qualification (reference category), 1 = GCSE D-G, 2 = GCSE A*-C, 3 = A level for the E-Risk study, figure **E**. Boxes represent interquartile range (IQR), the line represents median and the whiskers represent 1.5*IQR beyond upper and lower quartile. For comparison purposes, y-axis limits are standardized across plots.

Figure 2: Distribution of Education Polygenic Score (PGS) values across categories of educational attainment (left-hand column) and association with DunedinPACE (right-hand column) in (A) the Dunedin Study, $N = 804$, (B) the U.S. Health and Retirement Study (HRS), $N = 2,311$, (C) the Understanding Society Study, $N = 3,620$, (D) Generation Scotland Study, $N = 8,797$, and (E) the E-Risk Study, $N = 1,507$. Both PGS and DunedinPACE values are standardized within study to mean = 0, SD = 1. Educational categories are 1 = School Certificate, 2 = High School Grad, 3 = University degree or higher for figures **A, B, C, and D**, and 0 = no qualification (reference category), 1 = GCSE D-G, 2 = GCSE A*-C, 3 = A level for the E-Risk study, figure **E**. Boxes represent Interquartile range (IQR), the line represents median and the whiskers represent 1.5*IQR beyond upper and lower quartile. For comparison purposes, y-axis limits are standardized across plots. The linear regression is shown in blue (with surrounding confidence intervals in gray), and the Pearson's correlation coefficient is denoted by r and associated p-value by p .

Figure 3: Association between DunedinPACE and education within age group quintiles in the

Understanding Society (A) and Generation Scotland Study (B). In both cohorts, individuals were

binned into one of five groups on the basis of age, each group representing a 15-16 year age span.

Barcharts show the distribution of DunedinPACE values across categories of educational attainment

in each of the five age-groups. On average, pace of aging increases across the age-groups, but within

each age group higher education predicts slower pace of aging. For each study, the upper table

reports within-group values for the number of individuals per group (N), mean and SD of

DunedinPACE, and slopes of the association between educational attainment and DunedinPACE

(adjusted for sex and technical covariates). The lower table reports the t- (Understanding Society) or

Z- (Generation Scotland) ratios comparing the slopes between educational attainment and

DunedinPACE for different age groups. Values in **bold** are significant at the $p < 0.05$ level. Overall,

higher education predicts slower pace of aging across all age groups, although not significantly so

among the very old.

Figure 4: Forest plots of the association between educational attainment and DunedinPACE after

controlling for the genetics of educational attainment and tobacco smoking. (A) shows meta-

analysis of the association between educational attainment and DunedinPACE controlling for the

education PGS (and technical covariates), and **(B)** shows meta-analysis of the same model after the

addition of exposure to tobacco smoking (smPEGS). The effect size estimate [\pm 95% CI] of the

meta-analysis result is shown by the pale blue diamond, and the estimated prediction interval is

shown by the red bar.

Figure 1

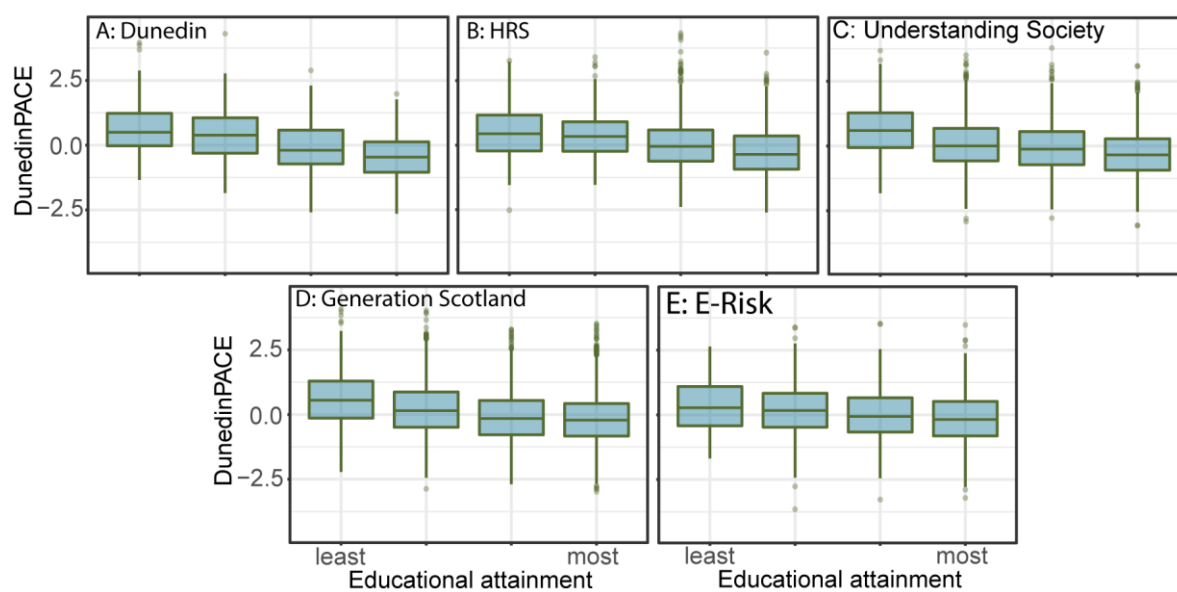


Figure 2

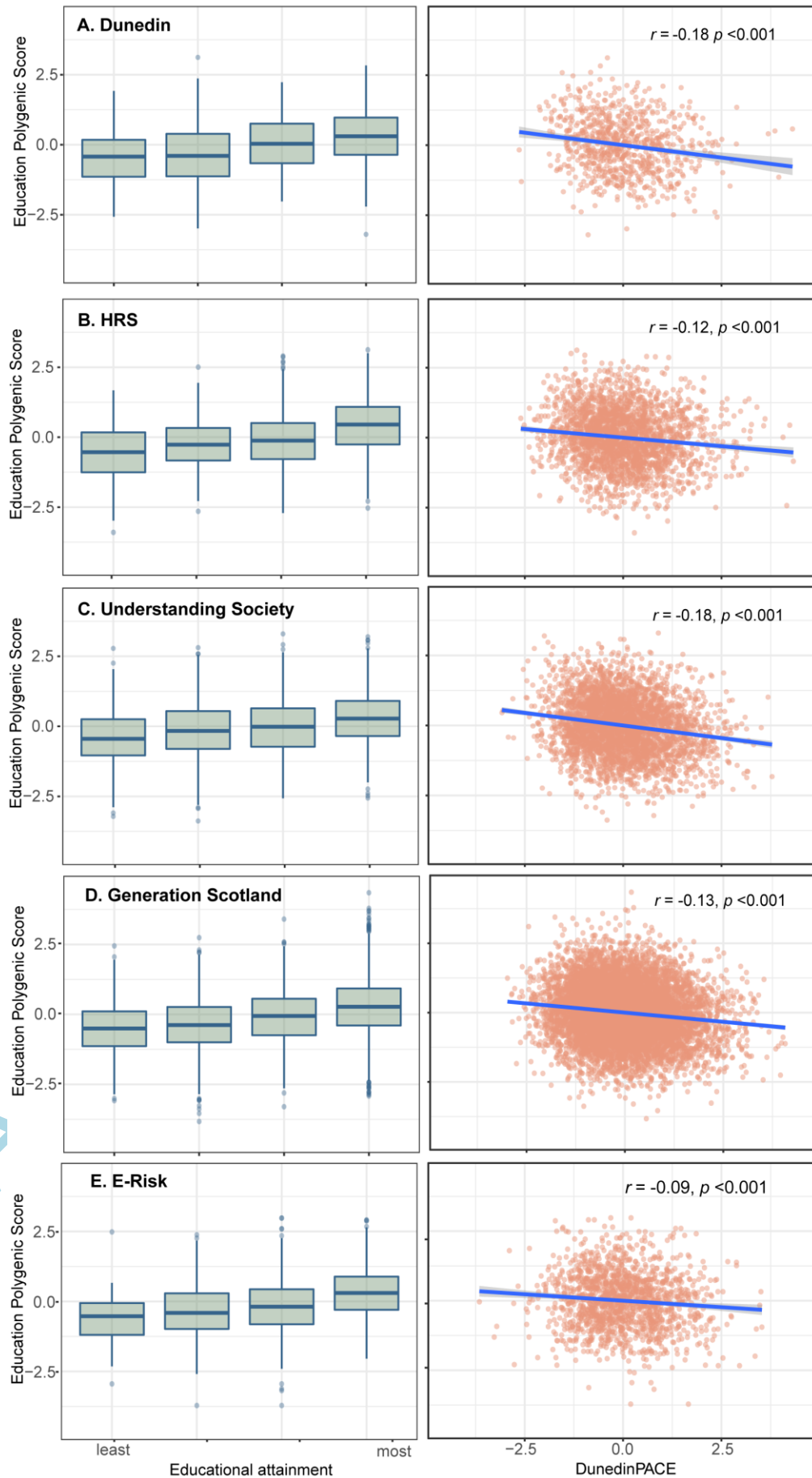
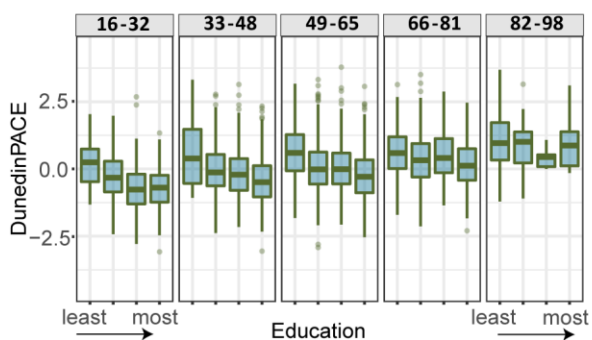


Figure 3

A. Understanding Society

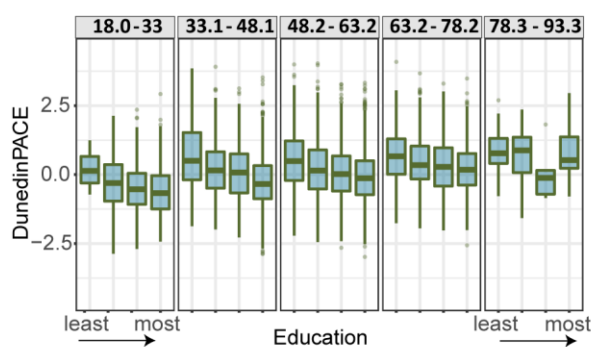


| Age quintile | N | mean(SD) DunedinPACE | slope[95% CI] |
|--------------|-------|----------------------|-------------------|
| 16-32 | 393 | -0.56(0.86) | -0.24[-0.35-0.13] |
| 33-48 | 1,038 | -0.19(0.93) | -0.22[-0.29-0.16] |
| 49-65 | 1,344 | -0.03(0.98) | -0.22[-0.27-0.17] |
| 66-81 | 780 | 0.40(0.97) | -0.13[-0.19-0.07] |
| 82-98 | 65 | 0.90(1.07) | -0.08[-0.30-0.15] |

t-ratio between slopes

| Age quintile | 33-48 | 49-65 | 66-81 | 82-98 |
|--------------|-------|-------|-------|-------|
| 16-32 | -0.21 | -0.31 | -1.71 | -1.29 |
| 33-48 | | -0.13 | -2.11 | -1.26 |
| 49-65 | | | -2.25 | -1.23 |
| 66-81 | | | | -0.45 |

B. Generation Scotland



| Age quintile | N | mean(SD) DunedinPACE | slope[95% CI] |
|--------------|-------|----------------------|-------------------|
| 18.0-33 | 1,204 | -0.52(0.88) | -0.19[-0.26-0.13] |
| 33.1-48.1 | 2,254 | -0.05(1.00) | -0.27[-0.31-0.22] |
| 48.2-63.2 | 3,918 | 0.06(0.98) | -0.18[-0.22-0.15] |
| 63.2-78.2 | 1,137 | 0.37(0.96) | -0.16[-0.21-0.11] |
| 78.3-93.3 | 100 | 0.74(0.88) | -0.05[-0.19-0.10] |

Z-ratio between slopes

| Age quintile | 33.1-48.1 | 48.2-63.2 | 63.2-78.2 | 78.3-93.3 |
|--------------|-----------|-----------|-----------|-----------|
| 18.0-33 | 1.73 | -0.24 | -0.81 | -1.80 |
| 33.1-48.1 | | -2.97 | -3.24 | -2.83 |
| 48.2-63.2 | | | -0.89 | -1.82 |
| 63.2-78.2 | | | | -1.44 |

Figure 4

