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HUMAN DEVELOPMENT, BIRTH TO DEATH

Moffitt & Caspi
Genes
Environment
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Concept Paper Form

Provisional Paper Title: Do genetics drive the positive effect of education on slower aging? Or is there evidence that education has a social effect on aging?
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Please describe your proposal in 2-3 pages with sufficient detail for helpful review.

Objective of the study:

Lower educational attainment (for example, fewer years of education) predicts lower life expectancy, higher rates of disease and self-reported poor health [1,2]. Recently, a large-scale Genome-Wide Association Study identified many SNPs associated with educational attainment [3]; these SNPs can be condensed into a single metric of genetic propensity to education, a 'Polygenic score' (PGS), that predicts associations with outcomes related to cognitive performance [3]. Subsequently, associations between educational attainment PGS and health-related outcomes have been suggested [4], and claims of shared genetic etiology between educational attainment and health have been made [5]. However, these observations beg the question: how does the link between education and health manifest? Could it be that an individual's genetic propensity for education is shared with a genetic propensity for more favorable health outcomes irrespective of education? Or might individuals who achieve higher education experience better health outcomes irrespective of their genetic endowment?

Here, we aim to test the hypothesis that associations between education PGS and health are primarily directed through provision of education. We will test this hypothesis by using two indices of accelerated aging. The first is 'Pace of Aging', a composite measure comprised of information from 18 biomarkers that capture the rate at which multiple bodily systems are declining over time [6]. The second is a novel biomarker of health-related decline that we have termed 'DunedinPoAm'[7]. This biomarker—recently developed by our team--uses DNA methylation-based measurements to index a similar profile of aging to that of the aforementioned Pace of Aging, but which utilizes only measures of DNA methylation taken at one point in time rather than clinical biomarkers taken

repeatedly over time. Both these measures are unique as they index trajectories independent of variation in early–life health status, and have an added advantage in that they are valid in younger-aged individuals, indexing trajectories of health decline long before the actual manifestation of its consequences.

The specific aims are to:

- Assess whether PoA is associated with educational attainment (measured as highest academic level achieved) and educational attainment PGS. Our specific goal is to answer the question: does an individual's genotype render them impervious to the positive effects of education?
- Assess whether this association is generalizable across time and geographical location.
- Assess whether this association is accounted for by lifestyle factors known to be associated with both educational attainment and health, using tobacco smoking as a test case.
- Assess whether any observed associations are accounted for by early life factors known to be associated with both educational attainment and health, using SES background as a test case.

We will initially test our hypotheses in the Dunedin Study. We will then aim to replicate our findings in a number of different cohorts: a) the E-Risk study, b) the Netherlands Twin Register, c) the Health and Retirement Study and, d) the UK Household Longitudinal Study (Understanding Society). We have identified these particular cohorts for replication attempts because 1) they represent individuals born in different periods of time, which will help identify generation-related cohort effects, 2) they represent individuals born and raised in different countries, which will help identify effects arising from geographical variation in attitudes or access to education, and 3) they are sufficiently powered to test these hypotheses and they contain the needed measurements: genome-wide SNP data, DNA methylation data, and educational attainment.

Data analysis methods:

To address our aims, we plan to conduct the following analyses:

1. **Does an individuals' genotype render them impervious to the positive effects of education?**

To address this question, we will test the association between Pace of Aging of Dunedin Study participants at age 45 and a) educational attainment (measured as highest academic level achieved) and b) educational attainment PGS.

2. **Is the Pace of Aging associated with educational attainment and education PGS in cohorts from different countries and of different ages?**

Here we will test whether associations we see in the Dunedin Study are generalizable across geographical space and time (rather than specific to the educational climate in NZ for children entering the schooling system in the late 1970's). To achieve this, we will test the same models

described in aim 1 in three additional cohorts; a) the E-Risk study, b) the Netherlands Twin Register, c) the Health and Retirement Study, and d) the UK Household Longitudinal Study (Understanding Society). These cohorts span three additional geographical regions (UK, Netherlands, USA), and a wide range of ages (18 to 99). In these four cohorts, we will substitute DunedinPoAm as the outcome variable, and where appropriate, add an additional control for participant age at assessment (N.B. we will use both DunedinPoAm trained on pace of aging at age 38 as described in[7], and DunedinPoAm4x, a novel and currently unpublished algorithm trained on Dunedin Pace of Aging at age 45, currently under development by our team).

3. **Are associations uncovered in aims 1 and 2 accounted for by a lifestyle factor known to be associated with both educational attainment and health? Using tobacco smoking as a case in point.**

Here we will test whether any associations we see between education and Pace of Aging are accounted for by tobacco smoking. Tobacco smoking negatively impacts health [8] and is inversely related to level of education [9,10], so we will explicitly test whether increased tobacco smoking constrains the relationship between education and Pace of Aging (if observed in aim 1 and 2).

4. **Are associations uncovered in aims 1 and 2 accounted for by early life factors known to be associated with both educational attainment and health? Using SES background as a case in point.**

Here we will test whether any associations we see between education and Pace of Aging are accounted for by early life Social Economic Status (SES). Lower childhood SES predicts later poor health [11] and subsequent lower educational attainment [12-14], so we will explicitly test whether lower childhood SES constrains the relationship between education and Pace of Aging (if observed in aim 1 and 2).

Variables needed at which ages:

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Dunedin Study
POA45s: Pace of Aging, ages 26 to 45
HiEduc45: highest education attainment through BA, age 45
EA3PGS: Educational Attainment PGS, based on Lee *et al*, 2018
PackYrLifTm45: Smoking pack years by age 45
SESchildhd: family SES averaged from birth to age 15
Sex:

E-Risk Study
DunedinPoAm: methylation Pace of Aging, age 18

DunedinPoAm4x: methylation Pace of Aging (trained on age 45 pace of aging) , age 18
educachve18: highest educational achievement (based on QCF), age 18
EA3PGS: Educational Attainment PGS, based on Lee et al, 2018
SMKPKYRE18: Smoking pack years, age 12-18
Seswq35: Social Class Composite ages 3-5 (or other appropriate measure)
Zygosity:
Sampsex: sex

Replication cohorts: the Netherlands Twin Register, the Health and Retirement Study and the UK Household Longitudinal Study (Understanding Society, if applicable)

The following list is for initial reference purposes; instructions and scripts for calculating derived variables will be distributed upon concept paper approval, as well as tables to be filled in to create parallel results across the cohorts. We leave the choice of covariates to the discretion of study investigators.

mPoA: to be calculated from whole-epigenome BeadChip data; script containing methods for calculation will be provided. NOTE: mPoA must be assessed from DNA methylation data **after** educational attainment.

Educational achievement: measure of highest level of educational achievement. Preference for categorical variable with four levels (no qualifications, school certificate or equivalent, high school diploma or equivalent, BA/BS degree or higher), or number of years of education.

EA PGS: Educational Attainment PGS, based on Lee *et al*, 2018. PGS should be residualized for genetic PCs to control for ethnic stratification.

Smoking behavior: indication of smoking behavior, preferably a quantitative variable such as pack years though other variable types are acceptable.

SES: measure of childhood Social Economic Status

Age: age of participant (where cohort is not comprised of same-age individuals)

Sex

Other appropriate variables deemed necessary on a cohort-by-cohort basis (e.g. zygosity, genetic relationship identifiers etc.)

Significance of the Study (for theory, research methods or clinical practice):

This study will expand our understanding of the routes via which education leads to better health outcomes. If our hypotheses are supported, and that education in itself is a major vehicle by which better health is achieved, then this would suggest that increased education benefits all, regardless of genetic liability. If our hypotheses are not supported, this would suggest that funneling resources into improving educational standards for population health improvements would be a futile exercise for those not in possession of the genetic propensity to higher education. Regardless

of which of these situations we find ourselves in, there will be far-reaching implications for health, education, and social policy makers.

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