Extended Abstract Submission for the 2019 PAA

ASSESSING GENETIC CONFOUNDING IN THE EDCUATION-HEALTH ASSOCIATION

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Introduction

Social and behavioral scientists have a long history of studying the social determinants of health, while biomedical scientists have traditionally focused on more biologically proximate causes (Harris 2010). While in more recent years, collaboration between biomedical and social scientists has been more common, many social scientists have continued to promote theories identifying social conditions as fundamental causes of health while criticizing biomedical scientists for failing to consider these explanations (Link and Phelan 1995; Phelan, Link, and Tehranifar 2010). One of the most widely studied of these social determinants has perhaps been education (Ross and Wu 1995). Education has been shown to be related to a variety of health outcomes, including but not limited to self-rated health, body mass index (BMI), and depression. (Hermann et al. 2011; Miech and Shanahan 2000; Mirowsky and Ross 2008).

Is Education Causal?

In order to provide evidence for the argument that education is a social determinant of health, researchers have had to move beyond demonstrating associations between education and various health outcomes. They have usually done this either by attempting to control for possible selection or confounding factors or by designing studies in a natural experiment framework that allows for the estimation of a causal effect of education (Amin, Behrman, and Kohler 2015; Boardman and Fletcher 2015; Davies et al. 2018; Fletcher 2015; Zheng 2017). Most of the studies that use exogenous variation in education to estimate a causal effect rely on the raising of the school leaving age in the 20th century (Lleras-Muney 2005). This means they are estimating the effect of an additional year of high school education in most cases. Effects from receiving a high school diploma or from additional years of college education cannot be estimated, and past research suggests that these effects may differ from those of additional years of high school education (Montez, Hummer, and Hayward 2012). Researchers who are interested in the effect of a college degree oftentimes must attempt to control for possible confounding factors (Zheng 2017). Genetic confounding has often been considered but has seldom been tested, primarily due to a lack of available data (Gaydosh et al. 2018; Wedow et al. 2018). Below, I explain why and when genetics could be an important confounder in the education-health association.

Genetic Correlation (rG*)*

Education and all three health outcomes of interest to this study, self-rated health, BMI, and depression, have been shown to be heritable using both twin models and molecular genetic methods (Boardman, Domingue, and Daw 2015; Haberstick et al. 2010; Johnson et al. 2002; Leinonen et al. 2005)

There is also evidence that education and each of the above health outcomes have common genetic influences, as indicated by genetic correlation (rG). Genetic correlation is a measure of the average correlation of the effect sizes of individual genetic variants across two different traits (Bulik-Sullivan et al. 2015). In an early attempt to use molecular genetic data to explore the possibility for genetic confounding in the education-health association, Boardman et al. (2015) test for the possibility of genetic confounding in the three education-health relationships I examine here by estimating rG between education and each measure of health in the Health and Retirement Study genetic data. Using genome-wide complex train analysis

(GCTA), they estimate a positive rG between education and self-rated health and a negative rG between education and depression, but find no evidence for rG between education and BMI (Boardman et al. 2015).

The disadvantage to estimating rG using GCTA is that it requires very large sample sizes to produce precise estimates, but also requires individual genetic data. Amassing this amount of individual genetic data is difficult because of privacy concerns. The recent development of cross-trait LD score regression has made rG estimation possible using summary statistics from GWAS rather than individual genetic data (Bulik-Sullivan et al. 2015). This allows for more precision in the estimation of rG because researchers can exploit the summary statistics from very large GWAS. Using this method, researchers have since estimated a positive rG between education and self-rated health, and an inverse rG between both education and BMI, and education and depression (Harris et al. 2017; Okbay et al. 2016; Wray et al. 2018). The positive rG between education and self-rated health indicates that genetic variants that have a positive effect on education also tend to have a positive effect on self-rated health on average. The negative rG between education and BMI indicates that genetics variants that have a posive effect on education tend to have a negative effect on BMI on average.

Pleiotropy

These estimates of rG between education and each health outcome provide suggestive evidence for the presence of pleiotropy, which occurs when one or more genetic variants influence two or more separate traits or phenotypes (Solovieff et al. 2013). Wedow et al. outline a clear distinction between two different types of pleiotropy which I adopt here because of its utility for explaining when rG could result in genetic confounding (Wedow et al. 2018). One possibility is that the genetic variants associated with both education and the health outcome have an indirect effect on the health outcome that is mediated through education. This is defined as mediated pleiotropy. If measured education completely mediates the relationship between the pleiotropic variants and the health outcome of interest, rG between education and that health outcome would not contribute to genetic confounding of the education-health association.

The other possibility is that the genetic variants associated with both education and the health outcome have an effect on a trait that is proximate to the genetic variants, such as cognitive ability. That trait would then have a direct effect on both education and the health outcome. This is defined as biological pleiotropy. In the case of biological pleiotropy, because the effect of the genetic variants is not mediated through education, rG is likely to confound the education-health association.

Polygenic Scores (PGSs)

An ideal measure to test for genetic confounding would capture all common genetic causes of education and each health outcome. Because there are no available methods that are capable of doing this, I rely primarily on a polygenic score (PGS) for education. A PGS is an additive measure of the effects of individual variants across the genome on a phenotype. It can be conceptualized as an additive whole-genome measure of predisposition towards some outcome (Belsky and Israel 2014; Dudbridge 2013). I focus my tests of genetic confounding on the PGS for education for two reasons. The first is that the predictive power of a PGS is partly a function of the sample size of the GWAS used to calculate it (Dudbridge 2013). The current PGS

for education is calculated from a GWAS with a sample size of over 1 million individuals (Lee et al. 2018). The sample size of the GWAS used to calculate polygenic scores for depression and BMI are smaller, so they have less power to detect causal SNPs. Therefore, if we are interested in common genetic effects on education and a given health outcome, the PGS for education is likely to capture more of those effects than a PGS calculated from a GWAS with less power.

The second reason I focus primarily on the PGS for education is because I can use it to identify mechanisms to test that are examples of both mediated and biological pleiotropy which will in turn provide suggestive evidence for whether genetics are an important confounder in these associations. In my discussion of mediated pleiotropy above, I describe the motivation for testing for it using the PGS for education.

In order to test for biological pleiotropy, I identify two separate traits that could act as mechanisms in a biological pleiotropic relationship as described above. The first is cognitive ability and the second is self-efficacy. Self-efficacy is defined as "peoples' beliefs in their capabilities to produce desired efforts by their actions" (Bandura 1997). Cognitive ability and self-control have been shown to mediate the relationship between a PGS for education and later educational success (Belsky et al. 2016). Research has also shown that self-control and self-efficacy are highly similar personality traits to the extent that a single latent variable can be used to represent them (Ajzen 2002). As one might expect from the definition, self-efficacy has been shown to be associated with better health outcomes measured by BMI, self-rated health, and depression (Annesi and Gorjala 2010; Grembowski et al. 1993). There are also demonstrated associations between cognitive ability and the three health outcomes of interest (Batty et al. 2006; Belsky et al. 2013; Zammit et al. 2004).

I also include PGSs for BMI and depression in models that include BMI and depression as dependent variables to ensure that as many common genetic effects are controlled for as possible. Because a similarly high-powered GWAS is not available, I include the PGS for BMI in all models that include self-rated health as a dependent variable.

Aims

Aim 1 of this study is to assess how much of the association between education and measures of health (BMI, self-rated health, and depression) is confounded by PGSs for education and relevant health outcomes. Researchers relying on observational data without access to genome-wide data and who are interested in the effect of education on health outcomes must implicitly assume that genetic factors contributing to both education and health outcomes are mediated through either education or another variable that has been controlled. If genetic factors associated with education affect health outcomes at least partially through pathways other than education or controlled variables, genotype would be an important omitted variable and failure to control for it would result in biased estimates of the effect of education.

Aim 2 of the study is to determine whether the level of genetic confounding varies with respect to childhood socioeconomic status (SES). Given the evidence that genetic effects operate differently in different environments, it would be erroneous to assume that the level of genetic confounding in the relationship between education and health would be the same for all individuals without testing this. For example, there is evidence to suggest that the genetic effects on educational attainment are stronger for individuals from high SES backgrounds in Add Health (Belsky et al. 2018). If that is the case, then genetic confounding in the relationship between education and health could differ by childhood SES.

Aim 3 of this study is to determine whether the PGS for education predicts health outcomes early in the life course, before individuals have completed their education. If genetic factors confound the association between education and health later in the life-course, this suggests that the PGS for education does not only affect health outcomes through the mediating factor of education itself. If this is the case, it is possible that the PGS for education could predict health outcomes earlier in life before the individual has completed their education.

Data and Measures

I draw on data collected by the National Longitudinal Study of Adolescent to Adult Health, hereafter referred to as Add Health. Add Health is a nationally representative longitudinal study of adolescents in the United States who were in grades 7-12 in 1994-1995 during Wave I. Data are available for four waves, and data for Wave V of the study are currently being collected. I will be using data from Waves I, III, and IV, and plan to add data from Wave V when it becomes available. For Waves III and IV, respondents were aged 18-26 and 24-32 respectively. Respondents are now aged 32-43 during the Wave V data collection. Genotyping was performed in Wave IV, and of the 15,701 participants in Wave IV, approximately 12,200 were genotyped using two Illumina platforms. Approximately 80% of the sample were genotyped using the Illumina Omni1-Quad BeadChip and 20% were genotyped with the Illumina Omni2.5 - Quad BeadChip. Genotyped data were available on 609,130 SNPs for 9,974 individuals after applying standard quality control procedures. More information on the genotyping procedures in Add Health can be found in the Quality Control Analysis of Add Health GWAS Data documentation (Highland et al. 2018). To account for population stratification, I restrict my analysis to individuals of European genetic ancestry, bringing the size of the analytical sample to 5,728 (Braudt and Harris 2018).

Add Health is an ideal data set to use for this question both because of the available measures in the data set and because the sample consists of a younger cohort that was representative of the United States population at the time of sampling. Add Health provides rich environmental and health measures over the first part of the life course, while also providing genetic data on a large portion of its respondents. In addition, it has an advantage over other larger datasets with genetic data like the UK Biobank in that it began with a nationally representative sample of adolescents. While there are other social science datasets with genetic data that are nationally representative like the Health and Retirement Study, Add Health provides the opportunity to look at a cohort who has more recently experienced their educational attainment. Given the evidence that genetic effects are conditional on the environmental context, it is important to assess genetic confounding for different cohorts who experience their educational environments in different periods.

It is important to note that while Add Health was designed to be nationally representative, it is not clear that my analytic sample is nationally representative due to the large amount of missing genetic data. Furthermore, given that my analysis is restricted to individuals with European genetic ancestry, the results cannot be generalized to populations with non-European genetic ancestry.

I will measure educational attainment in Wave IV in order to capture the highest level of education that respondents have attained at the age of 24-32. The question asks the respondent: "What is the highest level of education that you have achieved to date?" Respondents can choose one of the following: 8th grade or less, some high school, high school graduate, some

vocational/technical training (after high school), completed vocational/technical training (after high school), some college, completed college (bachelor's degree), some graduate school, completed a master's degree, some graduate training beyond a master's degree, completed a doctoral degree, some post baccalaureate professional education (e.g., law school, med school, nurse), completed post baccalaureate professional education (e.g., law school, med school, nurse). I will recode the categories of the education variable to create a binary variable indicating whether the respondent is a college graduate or not.

Because Wave V data on the full sample is not yet released, I will also measure the three health outcomes of interest at Wave IV. While it would be ideal for the measurement of education to occur at a time point before the health measurements, most of the respondents will not have finished their educations at Wave III. Body mass index was calculated using the height and weight of respondents measured in Wave IV, and I plan to treat it as a continuous variable. Anthropomorphic measures like height and weight and BMI calculated from those measures have been shown to be highly reliable in Add Health (Hussey et al. 2015). To measure self-rated health, respondents were asked "In general, how is your health?" and were able to choose between "excellent", "very good", "good", "fair", and "poor". I will treat self-rated health as an ordinal variable.

To measure depression, I plan to use a shortened version of the CES-D depression scale proposed and validated by Perreira et al. which, in line with measurement theory, is composed of only the effect indicators in the original scale while excluding any causal indicators or outcomes of depression. While the reliability of the shortened version may have a smaller Chronbach's alpha than the widely used 19-item version, Chronbach's alpha assumes that all indicators measure a single dimension and that all are effect indicators. Neither of these are true for the 19-item scale (Perreira et al. 2005). The scale ranges from 0 to 12, with higher values indicating more symptoms associated with depression. Respondents were asked, "How often was the following true during the past seven days?" and then given the following four prompts. "You could not shake off the blues, even with help from your family and your friends." "You felt depressed." "You felt happy." "You felt sad." Respondents were given a 0 if they chose "never or rarely", a 1 if they chose "sometimes" a 2 if they chose "a lot of the time", and a 3 if they chose "most of the time or all of the time". Scores for each item will then be summed and respondents will be assigned a value from 0 to 12 on the scale.

Because I am interested in measuring genetic confounding that would not be captured by variables that researchers usually have access to in observational studies, I plan to include a wide range of variables from Wave I In-Home Student and Parent Questionnaire that could have a direct effect on both educational attainment and the health outcomes I am interested in. I will include the resident parent's level of education completed and a measure of reported family income from the family to control for the respondent's socioeconomic status at adolescence. Respondents are also asked to report who lives with them and their relationship with each household member, so I can control for family structure using the family structure constructed variable in Add Health (Harris 1999). I will also control for parent response to the question "How important is religion to you?" in order to control for the religious environment in the home. The respondent's parent reports on whether the respondent has health insurance, so I can also control for whether the respondent had health insurance in Wave I.

However, because I am also interested in whether genotype is an important omitted variable for studies that do not have access to genetic data, I will use a second set of controls in order to test for possible mediating variables between the PGSs and health outcomes. The Add

Health Picture Vocabulary Test is a shortened version of the Peabody Picture Vocabulary Test, which is commonly used as a measure of verbal ability and scholastic aptitude and can be used as a rough measure of cognitive ability. For assessing non-cognitive skills, Wave I has a section made up of four questions meant to assess the self-efficacy of the respondent. Self-efficacy could potentially be an important mediating factor in the relationship between the PGSs and health outcomes. While three out of the four questions are related to sexual health, it is useful for my purposes that the questions are related to health and not only self-efficacy in general. The four questions are: "If you wanted to use birth control, how sure are you that you could stop yourself and use birth control once you were highly aroused or turned on?" "How sure are you that you could plan ahead to have some form of birth control available?" "How sure are you that you could resist sexual intercourse if your partner did not want to use some form of birth control?" "Compared with other people your age, how intelligent are you?" I plan to create a scale from these items ranging from 4 to 24 where higher values indicate greater self-efficacy.

Methods

Analyses in this study are based on a combination of polygenic scores (PGSs) used to measure the additive genetic effects on education and the health outcomes. Here I will describe how the PGSs used in this study are calculated and how they are used to examine genetic confounding in the relationship between education and health.

Polygenic Score calculation

To measure genetic contributions to the outcomes of interest in this study, I will rely on three publicly available PGSs from Add Health for educational attainment, BMI, and major depressive disorder. Each polygenic score represents the cumulative additive genetic influence on the phenotype of interest (Belsky and Israel 2014). The PGS for an individual i is calculated as:

$$PGS_i = \sum_{j=1}^{k} \beta_j SNP_{ij}$$

where, SNP_{ij} is the number of alleles of the j^{th} SNP for the i^{th} individual and β_j is the estimated association between SNP j and the phenotype as reported in the summary statistics for a GWAS of that phenotype based on an independent sample. The PGSs are then standardized to have a mean of 0 and a standard deviation of 1. For more information on the calculation of the PGSs used in this study, see Braudt and Harris (Braudt and Harris 2018).

Assessing Genetic Confounding

It is important to remember that the goal of this paper is to show how much of the association between education and health can be accounted for by genetic factors. Furthermore, it is important to assess whether genetics are still an important confounder after controlling for available environmental confounders. If environmental controls capture all common genetic effects, researchers interested in this relationship do not need to worry when they do not have access to genetic data. However, if controlling for genetic heterogeneity substantially reduces the

estimate for the effect of education after traditional controls have been added, the effect of education may be overestimated in research without a strong causal design or genetic data.

For brevity, I refrain from discussing each health outcome separately in this section, as the structure of the models I will estimate will be identical for each outcome. BMI and depressive symptoms are measured using continuous variables, so all models predicting BMI and depressive symptoms will use linear regression. Because, self-rated health is measured as an ordinal variable, I estimate all models predicting self-rated health using ordinal probit regression. In order to achieve a similar interpretation to the linear regression models, I will report marginal effects of a college degree standardized by the estimated standard deviation of the latent variable underlying the categories of self-rated health (Long and Freese 2006). While not explicitly discussed below, all models control for sex and birth year.

To assess the confounding effect of genetics I will calculate the proportional reduction in effect size observed after adding the PGSs as covariates. To estimate the simple association between having a college degree and each health outcome, I regress the health outcome on college degree, where the coefficient on college degree will represent the effect of having a college degree on health compared to those without a college degree (**Model 1**). Then, I will regress each health outcome on years of education while controlling for both the PGS for educational attainment and the PGS associated with the health outcome of interest if available[2] (**Model 2**). The coefficient in this second model will represent the same effect after controlling for genetic variation. The proportion by which the effect size decreases can be interpreted as the upper bound of genetic confounding in the relationship between education and the measure of health.

The next two models that I will estimate will control for the measures of cognitive functioning and self-efficacy that I described above. This is to test whether any remaining direct effect of the PGSs is mediated by either cognitive functioning or self-efficacy. **Model 4** adds the measure of cognitive ability (vocabulary test) as a covariate, and mediation can be assessed by comparing to **Model 3. Model 6** adds the measure of self-efficacy and mediation can be assessed by comparing to **Model 5.** If these two variables were to somehow mediate the entire effect of the PGSs on the health outcomes, this would provide evidence for their ability to act as proxies for PGSs in some cases when genetic data is not available.

While the comparison between the simple association between education and health outcomes and the association controlling for genetic variation is interesting in and of itself because it shows the proportion of the association between education and health that can be explained by genetic variation, most researchers who study this relationship are not only controlling for sex and birth year. In fact, many of the covariates that researchers commonly control for in their analyses could inadvertently capture a large proportion of the genetic variation between individuals. However, it is unlikely that the common controls capture all of the genetic variation. In order to estimate the proportion of the effect of education that can be explained by genetic variation after controlling for environmental confounders, I will first regress each health outcome on education, controlling for the environmental confounders listed above (**Model 7**). I will then estimate the same model, adding PGSs for educational attainment and the health outcome of interest as controls (**Model 8**). A comparison of the coefficients on years of education between the two models will tell us whether genetic variation is an important omitted variable in analyses considering the relationship between education and health, and to

[2] For all models where self-rated health is a dependent variable, the PGS for BMI will be included as a covariate.

what extent the effect of education is overestimated when genetic factors are omitted from the model.

As can be ascertained from how I describe my methods for assessing genetic confounding above, I expect the inclusion of PGSs to weaken the relationship between education and health. This expectation is based on past research where other confounders in the education-health association weakened the effect of education (Zheng 2017). I have no reason to think that including genetic controls will increase the effect of education, but cannot rule out that possibility before running the analyses. It is also important to note that the predictive power of PGSs is limited by the sample size of the GWAS used to calculate the PGSs. While the upper limit of genetic confounding that I will estimate is the upper limit conditional on the PGSs that I have access to, it is possible that the level of genetic confounding could be greater with more predictive scores.

Genetic Confounding by Childhood SES

The second aim of this paper is to estimate whether the extent of genetic confounding differs by adolescent socioeconomic status. Returning to **Model 1** above, I will estimate the same model, but I will the resident parent's education as a covariate, in addition to interaction terms between parent's education and each PGS and between parents' education and respondent's education (**Model 9**). This will allow me to assess whether the effect of both education and the PGSs vary according to adolescent SES. I can then compare the effect of education for each level of parental education to the effect of education in **Model 1** to determine whether the proportion of the effect of education explained by genetic variation differs by parent education level.

Again, while this is interesting in and of itself, it is also important to assess whether genetic variation is an important omitted variable for researchers who are interested in how the effect of education on health may differ by SES. To answer this question, I will add interaction terms between parents' and each PGS and between parents' education and respondent's education to Model 3 (**Model 10**). I can then compare the effect of education for each SES group to the effect of education in Model 3 to determine whether the proportion of the effect of education explained by genetic variation after controlling for environmental confounders differs by SES.

Does the PGS for educational attainment predict health outcomes early in the life course?

The final aim of this paper is to test whether the PGS for educational attainment predicts health outcomes early in the life course before individuals have gone on to complete their education. If the PGS for educational attainment still has a significant effect on health outcomes even controlling for educational attainment itself in the above models, this suggests that the PGS for education is measuring something like cognitive ability, or a non-cognitive skill like self-efficacy, that contributes to increased educational attainment but also results in better health outcomes through a path other than education. Therefore, we might expect that the PGS for education could predict health outcomes before the individual has completed their education. I use health outcomes from Wave I here because all individuals are still enrolled in school, meaning that none of them could have completed their education.

In order to test whether the PGS for education can predict health outcomes in Wave I, I regress each health outcome from Wave 1 on the PGS for education conditional on year in

school so that any effect of additional years of education is controlled for. However, the question of which environmental confounders should be controlled for is important. Because of gene-environment correlation, many of the environmental confounders used as covariates in previous models may be correlated with the PGS for education. For example, individuals with high PGSs are more likely to be raised in high SES environments, so it is not clear whether an individual characteristic like is the effect of environmental inputs or genotype. It is most likely a combination of both. Therefore, I will regress health outcomes on the PGS for education, controlling for all environmental confounders used in the models above to get a conservative estimate of the effect of the PGS for education (**Model 9**). If we see a positive effect of the PGS for education on measures of health in Wave I controlling for family characteristics, it is evidence that the PGS for education is at least to a certain extent operating through some other mechanism than education to affect health outcomes.

If the PGS for education is predictive of health outcomes at Wave I, I will estimate a final model (**Model 10**), adding controls for cognitive ability and self-efficacy. This will allow us to see whether either or both of these characteristics mediate the effect of the PGS for education. If an effect of the PGS remains, it would call for further research into other mechanisms that might mediate the relationship between the PGS for education and health outcomes.

As is standard practice, I will adjust all analyses for the first ten principal components of the genetic data in order to adjust for population stratification, or the non-random patterning of alleles across populations based on geography or other environmental variation. Population stratification can result in spurious associations between genetic variants and phenotypes that are unrelated to real effects of the genetic variants on a phenotype of interest (Campbell et al. 2005; Price et al. 2006).

Preliminary results from models predicting BMI, future directions, and importance

So far, I have run the initial models assessing the extent of genetic confounding in the association between education and results suggest minor confounding. In **Table 1** below, **Model 1** shows that having a college degree is associated with a lower BMI of approximately 2.28. After adding the PGSs in **Model 2**, the absolute value of this effect decreases to approximately 1.88, which is a proportional reduction of about 18%. This reduction is modest but is not negligible. Because of missing data on both the vocabulary test to measure cognitive ability and self-efficacy, **Model 3** and **Model 5** are re-estimations of **Model 2** to match the samples from **Model 4** and **Model 6**. Results from these models suggest that self-efficacy and cognitive ability do not mediate the remaining direct effect of the PGS for BMI on measured BMI. My future analysis plan to be completed well before PAA will follow the design outlined above in the methods section and is already well underway.

Results from this study will provide guidance to researchers interested in whether omitting genetic factors will affect estimates of the effect of education on health in observational data. Including measures of genetic predisposition to educational attainment and health outcomes to traditional models will extend previous theory on why those with higher levels of educational attainment tend to be healthier by modeling genetic and environmental influences and testing how the genetic influences might operate differently in diverse environments.

References

Ajzen, Icek. 2002. “Perceived Behavioral Control, Self-Efficacy, Locus of Control, and the Theory of Planned Behavior1.” *Journal of applied social psychology* 32(4):665–683.

Amin, Vikesh, Jere R. Behrman, and Hans-Peter Kohler. 2015. “Schooling Has Smaller or Insignificant Effects on Adult Health in the US Than Suggested by Cross-sectional Associations: New Estimates Using Relatively Large Samples of Identical Twins.” *Social Science & Medicine* 127:181–189.

Annesi, James J., and Srinivasa Gorjala. 2010. “Relations of Self-regulation and Self-efficacy for Exercise and Eating and BMI Change: A Field Investigation.” *BioPsychoSocial medicine* 4:10.

Bandura, Albert. 1997. *Self-efficacy: The Exercise of Control*. New York: W.H. Freeman.

Batty, G. David, Geoff Der, Sally Macintyre, and Ian J. Deary. 2006. “Does IQ Explain Socioeconomic Inequalities in Health? Evidence from a Population Based Cohort Study in the West of Scotland.” *BMJ (Clinical Research Ed.)* 332(7541):580–584.

Belsky, Daniel W. et al. 2013. “Is Obesity Associated with a Decline in Intelligence Quotient During the First Half of the Life Course?” *American Journal of Epidemiology* 178(9):1461–1468.

Belsky, Daniel W. et al. 2016. “The Genetics of Success: How Single-Nucleotide Polymorphisms Associated With Educational Attainment Relate to Life-Course Development.” *Psychological Science* 27(7):957–972.

Belsky, Daniel W. et al. 2018. “Genetic Analysis of Social-class Mobility in Five Longitudinal Studies.” *Proceedings of the National Academy of Sciences of the United States of America* 115(31):E7275–E7284.

Belsky, Daniel W., and Salomon Israel. 2014. “Integrating Genetics and Social Science: Genetic Risk Scores.” *Biodemography and social biology* 60(2):137–155.

Boardman, Jason D., Benjamin W. Domingue, and Jonathan Daw. 2015. “What Can Genes Tell Us About the Relationship Between Education and Health?” *Social Science & Medicine* 127:171–180.

Boardman, Jason D., and Jason M. Fletcher. 2015. “To Cause or Not to Cause? That Is the Question, but Identical Twins Might Not Have All of the Answers.” *Social Science & Medicine* 127:198–200.

Braudt, David B., and Kathleen M. Harris. 2018. *Polygenic Scores (PGSs) in the National Longitudinal Study' ' of Adolescent to Adult Health (Add Health) – Release 1*. Chapel Hill, NC: Carolina Population Center, University of North Carolina at Chapel Hill. Retrieved August 14, 2018 (http://www.cpc.unc.edu/projects/addhealth/documentation/restricteduse/datasets/WaveIVPolygenicScoresPGS.zip).

Bulik-Sullivan, Brendan et al. 2015. “An Atlas of Genetic Correlations Across Human Diseases and Traits.” *Nature Genetics* 47(11):1236–1241.

Campbell, Catarina D. et al. 2005. “Demonstrating Stratification in a European American Population.” *Nature Genetics* 37(8):868–872.

Davies, Neil M., Matt Dickson, George Davey Smith, Gerard J. van den Berg, and Frank Windmeijer. 2018. "The Causal Effects of Education on Health Outcomes in the UK Biobank." *Nature human behaviour*.

Dudbridge, Frank. 2013. "Power and Predictive Accuracy of Polygenic Risk Scores." *PLoS Genetics* 9(3):e1003348.

Fletcher, Jason M. 2015. "New Evidence of the Effects of Education on Health in the US: Compulsory Schooling Laws Revisited." *Social Science & Medicine* 127:101–107.

Gaydosh, Lauren, Daniel W. Belsky, Benjamin W. Domingue, Jason D. Boardman, and Kathleen Mullan Harris. 2018. "Father Absence and Accelerated Reproductive Development in Non-Hispanic White Women in the United States." *Demography* 55(4):1245–1267.

Grembowski, D. et al. 1993. "Self-efficacy and Health Behavior Among Older Adults." *Journal of Health and Social Behavior* 34(2):89–104.

Haberstick, Brett C. et al. 2010. "Stable Genes and Changing Environments: Body Mass Index Across Adolescence and Young Adulthood." *Behavior Genetics* 40(4):495–504.

Harris, K. M. 1999. "The Health Status and Risk Behaviors of Adolescents in Immigrant Families." *Children of immigrants: Health, adjustment, and public assistance* 286–347.

Harris, Kathleen Mullan. 2010. "An Integrative Approach to Health." *Demography* 47(1):1–22.

Harris, Sarah E. et al. 2017. "Molecular Genetic Contributions to Self-rated Health." *International Journal of Epidemiology* 46(3):994–1009.

Hermann, Silke et al. 2011. "The Association of Education with Body Mass Index and Waist Circumference in the EPIC-PANACEA Study." *BMC Public Health* 11:169.

Highland, Heather M., Christy L. Avery, Qing Duan, Yun Li, and Kathleen Mullan Harris. 2018. *Quality Control Analysis of' ' Add Health GWAS Data*. Chapel Hill, NC: Carolina Population Center. Retrieved August 15, 2018 (http://www.cpc.unc.edu/projects/addhealth/documentation/guides/copy_of_AH_GWAS_QC.pdf).

Hussey, Jon M. et al. 2015. "The Reliability of In-home Measures of Height and Weight in Large Cohort Studies: Evidence from Add Health." *Demographic Research* 32:1081–1098.

Johnson, W., M. McGue, D. Gaist, J. W. Vaupel, and K. Christensen. 2002. "Frequency and Heritability of Depression Symptomatology in the Second Half of Life: Evidence from Danish Twins over 45." *Psychological Medicine* 32(7):1175–1185.

Lee, James J. et al. 2018. "Gene Discovery and Polygenic Prediction from a Genome-wide Association Study of Educational Attainment in 1.1 Million Individuals." *Nature Genetics* 50(8):1112–1121.

Leinonen, Raija et al. 2005. "Genetic Influences Underlying Self-rated Health in Older Female Twins." *Journal of the American Geriatrics Society* 53(6):1002–1007.

Link, B. G., and J. Phelan. 1995. "Social Conditions as Fundamental Causes of Disease." *Journal of Health and Social Behavior* Spec No:80–94.

Lleras-Muney, A. 2005. "The Relationship Between Education and Adult Mortality in the United States." *The Review of economic studies* 72:189–221.

Long, J. Scott, and Jeremy Freese. 2006. *Regression Models for Categorical Dependent Variables Using Stata*. Stata press.

Miech, Richard Allen, and Michael J. Shanahan. 2000. "Socioeconomic Status and Depression over the Life Course." *Journal of Health and Social Behavior* 41(2):162.

Mirowsky, John, and Catherine E. Ross. 2008. “Education and Self-Rated Health.” *Research on aging* 30(1):93–122.

Montez, Jennifer Karas, Robert A. Hummer, and Mark D. Hayward. 2012. “Educational Attainment and Adult Mortality in the United States: a Systematic Analysis of Functional Form.” *Demography* 49(1):315–336.

Okbay, Aysu et al. 2016. “Genome-wide Association Study Identifies 74 Loci Associated with Educational Attainment.” *Nature* 533(7604):539–542.

Perreira, Krista M., Natalia Deeb-Sossa, Kathleen Mullan Harris, and Kenneth Bollen. 2005. “What Are We Measuring? An Evaluation of the CES-D Across Race/Ethnicity and Immigrant Generation*.” *Social Forces* 83(4):1567–1601.

Phelan, Jo C., Bruce G. Link, and Parisa Tehranifar. 2010. “Social Conditions as Fundamental Causes of Health Inequalities: Theory, Evidence, and Policy Implications.” *Journal of Health and Social Behavior* 51 Suppl:S28–40.

Price, Alkes L. et al. 2006. “Principal Components Analysis Corrects for Stratification in Genome-wide Association Studies.” *Nature Genetics* 38(8):904–909.

Ross, Catherine E., and Chia-ling Wu. 1995. “The Links Between Education and Health.” *American sociological review* 60(5):719.

Solovieff, Nadia, Chris Cotsapas, Phil H. Lee, Shaun M. Purcell, and Jordan W. Smoller. 2013. “Pleiotropy in Complex Traits: Challenges and Strategies.” *Nature Reviews. Genetics* 14(7):483–495.

Wedow, Robbee et al. 2018. “Education, Smoking, and Cohort Change: Forwarding a Multidimensional Theory of the Environmental Moderation of Genetic Effects.” *American sociological review* 83(4):802–832.

Wray, Naomi R. et al. 2018. “Genome-wide Association Analyses Identify 44 Risk Variants and Refine the Genetic Architecture of Major Depression.” *Nature Genetics* 50(5):668–681.

Zammit, Stanley et al. 2004. “A Longitudinal Study of Premorbid IQ Score and Risk of Developing Schizophrenia, Bipolar Disorder, Severe Depression, and Other Nonaffective Psychoses.” *Archives of General Psychiatry* 61(4):354–360.

Zheng, Hui. 2017. “Why Does College Education Matter? Unveiling the Contributions of Selection Factors.” *Social science research* 68:59–73.

Table 1. Linear Regression Models Predicting BMI at Wave 4

Variables	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
College Degree	-2.275***	-1.876***	-1.839***	-1.870***	-1.686***	-1.696***
	(0.207)	(0.207)	(0.212)	(0.219)	(0.247)	(0.249)
Female	0.0196	-0.0772	-0.0777	-0.0678	0.0335	0.0263
	(0.192)	(0.186)	(0.191)	(0.191)	(0.221)	(0.222)
Birth Year	-0.144**	-0.123*	-0.120*	-0.121*	-0.242**	-0.240**
	(0.0548)	(0.0530)	(0.0546)	(0.0546)	(0.0915)	(0.0918)
Education PGS		-0.0166	-0.00955	-0.0195	-0.0688	-0.0698
		(0.0966)	(0.0992)	(0.101)	(0.115)	(0.115)
BMI PGS		1.824***	1.814***	1.814***	1.863***	1.863***
		(0.0944)	(0.0970)	(0.0970)	(0.112)	(0.112)
Vocabulary Test				0.00479		
				(0.00865)		
Self-efficacy scale						-0.0109
						(0.0385)
Constant	40.71***	39.00***	38.80***	38.34***	48.06***	47.99***
	(4.323)	(4.183)	(4.309)	(4.390)	(7.142)	(7.148)
N	5582	5582	5338	5338	3806	3806

Standard errors in parentheses; All models control for the first 10 principal components of the genetic data.
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$