The Genetic Lottery

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Essays on Genetics, Income and Inequality

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Vrije Universiteit Amsterdam

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THE GENETIC LOTTERY

Essays on Genetics, Income and Inequality

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Casper Adrianus Pieter Burik

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To Mayra

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Chapter 1

Introduction

"The disposition to admire, and almost to worship, the rich and the powerful, and to despise, or, at least, to neglect persons of poor and mean condition is the great and most universal cause of the corruption of our moral sentiments."

Adam Smith (1759), The Theory of Moral Sentiments

1.1 Why integrate genetics into economics?

Economics is a social science that studies production, consumption and trades of goods and services. Usually, economics is split into two parts. Macroeconomics focusses on aggregate markets, studying the factors that affect production and consumption levels, as well as savings and investments. Microeconomics analyses individual economic agents: firms, households or individuals, and how they interact on markets. They are traditionally modelled as rational agents, who optimize their choices to maximize their profits or utility. Simple or complex models can be made to describe their behaviour.

So why should economists care about genetics? At the end of the day, these economic agents are people making choices based on their personal preferences. While these choices and preferences may be put into consumption and utility functions, they remain a description of human behaviour and human traits. Moreover, half a century of twin studies have shown that every single human trait is heritable to a degree (Polderman et al., 2015). This observation, that all human traits are heritable, has also been coined "the first law of behaviour genetics" (Turkheimer, 2000). Of course, the researched traits includes economically relevant outcomes and descriptors like income (Benjamin, Cesarini, Chabris, et al., 2012; Hill et al., 2019; Taubman, 1976), educational attainment (de Vlaming et al., 2017; Lee et al., 2018; Okbay et al., 2016; Rietveld et al., 2013) and risk preferences (Karlsson Linnér et al., 2019).

Many potential uses of genetic data in economics and other social sciences have been described in the literature (Beauchamp et al., 2011; Benjamin et al., 2012; Freese, 2018; Harden & Koellinger, 2020). I will summarise several of them below. Following this summary, I will describe the tools and methods available to include genetic data in social sciences. Next, I will describe the contributions this thesis makes to the literature, based on the research conducted in the following chapters. I will end with a statement of my personal contributions to each chapter.

First, genetic research in economics provides an opportunity to measure otherwise unobserved differences between individuals. As genetic factors may be descriptive of differences between people, they provide economists a chance to measure heterogeneity in economic agents. Economists may describe people as economic agents optimizing their utility based on how they value outcomes and costs. The differences in choices individual agents make, may be attributed to differences in individual preferences. However, measures of these preferences remain elusive as self-reported preferences are often mistrusted. The preferred option is to rely on revealed preferences (Samuelson, 1948). Genetic heterogeneity in economic agents may give alternative measures for individual preferences. For example, one could use the results of a recently published genome-wide association study (GWAS) of risk tolerance and risky behaviours (Karlsson Linnér et al., 2019) to create measures of individual risk preferences. While such GWAS-based measures are noisy and currently cannot be used for individual level predictions, they may be useful for analyses on the group level.

Furthermore, as genetic factors may be descriptive of individual differences, they can serve as a measure to study the influences of policy measures in practice. Through gene–by–environment studies (i.e., considering interaction effects between genetic factors and environment), we can start to account for potential heterogeneity in the effects of policy measures. Such efforts may shine a light on who is benefiting most from certain policy measures, and who is benefitting least. For example, in a recent study, Barcellos, Carvalho and Turley (2018) analysed the effects of an increase in compulsory schooling on health and found that increased education leads to better health outcomes and those effects were stronger among people with a high genetic risk for obesity, thus mitigating (in part) the genetic risk factors. The uses of gene–by–environment studies are not limited to studying policy measures; such studies can also be used to investigate interactions between other environmental measures and genetic factors, as I show in Chapter 2.

Second, measures of genetic factors may be used as control variables. One could simply include these variables to reduce variance in statistical models (Benjamin, Cesarini, Chabris, et al., 2012). More importantly though, when studying a relation between explanatory variable and outcome in non-experimental data, confounding is always a serious concern. When genetic factors between explanatory variables and outcome are shared or correlated, not controlling for it would lead to biased estimation results. For example, a labour economist, interested in estimating the returns to schooling while controlling for confounding factors such as cognitive ability, may create a proxy for ability using the results from a genetic study on cognitive performance (Davies et al., 2018) or educational attainment

(Lee et al., 2018). In Chapter 2, I extensively explore such research designs using genetic factors as control variables.

Third, as genotypes can be seen as random draws from parental genotypes, they are a good candidate for instrumental variable regression. The use of genotypes as instruments is called Mendelian Randomisation (MR; Davey Smith & Ebrahim, 2004). While MR is a promising concept and it could be used for medical outcomes that are only affected by a handful of genes, the use for social sciences is severely limited by several factors. First, socioeconomic outcomes and behavioural traits are generally genetically complex, meaning that they are affected by a large number of genes that individually have small effects (Chabris et al., 2015). Such genetic complexity could lead to the well-known problem of weak instruments (Hahn & Hausman, 2003), although the large increases in sample sizes of genotyped individuals in the last decade may abate this issue to some degree. Second, there is the possibility of genes affecting multiple outcomes, a phenomenon known as pleiotropy. As a result of pleiotropy, the genes that are used as instruments may affect both the explanatory variable and the outcome (Chen et al., 2016), violating the basic assumptions of instrumental variable regression. Third, while genotypes are random draws of parental genotypes, the possibility exists that parental genotypes indirectly influence the outcomes of their offspring (Kong et al., 2018). This possibility might be especially true for socioeconomic outcomes. There are multiple promising augmentations of MR to address some of these issues (Bowden, Davey Smith, & Burgess, 2015; Verbanck, Chen, Neale, & Do, 2018; Zhu et al., 2018). However, these approaches are all dependent on varying sets of assumptions that may fail to hold in practice.

Finally, the wealth of data and methods that genetics brings to economics not only helps us to re-examine the answers to old questions, but also enables us to answer questions that we could not answer at all before. For example, in Chapters 5–7 we estimate the effects of genetic factors on inequality in income, education and health. We show, using random genetic differences between siblings, that these effects are partially causal. This result raises new questions about the underlying mechanisms that cause disparities in such important life outcomes. Moreover, the same result also raises questions about fairness, as these disparities are not caused by people themselves, but rather through a genetic lottery at conception. However, nothing in our research implies that the effects of genetic factors on socioeconomic outcomes are biologically predetermined. The channels through which genetic factors operate could be purely environmental. As mentioned above Barcellos, Carvalho and Turley (2018) show that the genetic risk factors for obesity can (in part) be mitigated through additional education. Similarly, the genetic factors driving part of inequalities in income may be mitigated with policy changes.

1.2 Methods in social-science genetics

Twin studies have been a central tool in genetics since the 70s. A large meta-analysis of 2,748 publications on twin studies has shown that all studied traits are heritable to some degree (Polderman et al., 2015). In twin studies, one compares the correlation of phenotypes between monozygotic (MZ) twins, also known as identical twins, with the correlation between dizygotic (DZ) twins, also known as fraternal twins. MZ twins share all of their DNA and DZ twins share the same amount of DNA as regular siblings. By studying differences in correlations between MZ twin pairs and DZ twin pairs, you can estimate the heritability of a trait (the proportion of phenotypic variance that may be attributed to genetic effects). Twin models can be extended to estimate more than just heritability. However, using only twin models constrains the range of possible studies that can be done as the underlying genetic markers are not measured in classical twin models and the models typically need constraining assumptions on the environments of twins.

Fortunately, technological advances made way for many new opportunities to study genetics. Two decades ago, the International Human Genome Project published sequences of the human genome (Lander et al., 2001; Venter et al., 2001). The human genome consists of 23 pairs of chromosomes, each chromosome is a sequence of DNA molecules. They can be denoted by a chain of four letters, ‘G’, ‘C’, ‘T’ and ‘A’, representing the four different possible nucleobases of the nucleotides forming the sequence (guanine, cytosine, thymine and adenine). Most of the sequence is identical for all human beings (The 1000 Genomes Project Consortium, 2015). However, since there are approximately 3 billion nucleotide pairs in the human DNA sequence, there is still a plethora of variation to study. The most common variation comes in the form of single nucleotide polymorphisms (SNPs), these are variations in a single base-pairs creating two possible alleles. Where one person may have a ‘C’ in the sequence, another may have a ‘T’. As one inherits one copy of each chromosome from each parent (excluding the sex chromosomes), this can be summarized in simple count variables where one individual can have 0, 1, or 2 of the reference alleles.

Since the International Human Genome Project, many more advances have been made and with cheap commercial genotyping arrays (chips that allow measurement of hundreds of thousands of markers at the same time) now available, the cost of genotyping has gone down substantially. This decrease in costs made it possible to genotype individuals on an increasingly larger scale and led to the creation of large scale Biobanks, like the UK Biobank which contains the genotypes of approximately half a million Brits (Fry et al., 2017; Sudlow et al., 2015).

The availability of all this data has made it possible for researchers to test the associations of SNPs with various human traits on a much larger scale than ever before. The standard approach is to do hypothesis-free testing in the form of genome-wide association studies (GWAS). In a GWAS all available SNPs are tested in separate regression models on their association with the phenotype. Here, the statistical significance thresholds are set very stringent to account for the testing of millions of SNPs. GWAS are typically done in samples of individuals with similar ancestries and the leading principal components from the genetic data are added as control variables to account for population structure (Price et al., 2006), which limits the possibility of spurious findings due to unobserved variable bias where environments are correlated to individual markers due to ancestry being correlated to both environments and individual markers. Finally, GWAS studies often include replication in a sample that is independent from their discovery sample to further reduce the possibility of spurious findings.

The results of GWAS studies allow for many follow-up analyses. For instance, bioinformatics tools allowed Lee et al. (2018) to find that the genes that lie close to the SNPs most strongly associated with educational attainment are overwhelmingly expressed in tissues related to the brain and central nervous system. Furthermore, by analysing the results of GWAS for multiple phenotypes, it is possible to calculate genetic correlations directly from the GWAS results (Bulik-Sullivan et al., 2015a; Bulik-Sullivan et al., 2015b), which can lead to new insights on how phenotypes are related to each other as well as aid in the discovery of the channels through which SNPs affect the studied phenotypes. This is even possible when two phenotypes have never been measured in the same sample. The creation of LD Hub (Zheng et al., 2017), an online repository to calculate genetic correlations, has made it especially convenient to include this in follow-up analyses to GWAS.

Finally, one of the most valuable tools for economists and social-scientists, who want to do genetically informed analyses, is the use of polygenic indices (PGI)[1]. The results of various GWAS of social-science outcomes show that those traits are usually genetically complex (Chabris et al., 2015), meaning that the effects of individual SNPs are very small, yet all SNPs combined can explain a substantial amount of variance. Of course, it's impractical or impossible to include thousands or potentially millions of markers into a single regression model. A convenient work-around is to create a single index for every individual, wherein the effects of the individual SNPs are summed up. This can be as simple as a weighted sum of all genotypes, where the weights are the estimated GWAS effect sizes. However, more elegant solutions are advised to account for the correlation structure between SNPs (Vilhjálmsson et al., 2015). These PGI have proven to be very valuable in social-science genetics and play a crucial role throughout this thesis. The use of PGI to study within-sibling differences may be especially powerful as it provides the opportunity to control for family-specific environments while studying the effects of genetic factors on your outcome of interest.

1.3 Contributions of this thesis

The contributions of this thesis can be divided in two main categories. The first is providing fellow scientists with new tools to do research with. These tools come in the form of new statistical methods and the production of new variables and data made available for others to use (i.e., PGI and GWAS summary statistics). The second category of contributions is the applications of these new methods together with existing methods in answering both old and new questions related to genetics, income and inequality. The rest of this section will summarize the findings and contributions of each chapter.

In **Chapter 2** we develop a new method to support identification of causal effects in nonexperimental data. While some experiments may be done in economics and other social sciences, often ethical and legal considerations constrain them. Therefore, many analyses will be done using nonexperimental data, which often limits the causal interpretation of the findings.

An often-used technique to circumvent this problem is using instrumental variable methods. One of the methods suggested by the literature is Mendelian Randomisation, discussed earlier in this chapter. Yet its

[1] Here I use the relatively new term PGI instead of the commonly used polygenic score (PGS) or polygenic risk score (PRS), which was suggested by members of the scientific community to make it less likely to be wrongly interpreted as a value judgement.

usefulness is limited due to SNPs possibly affecting multiple outcomes (pleiotropy). As socio-economic outcomes are often biologically distal and genetically complex, the channels through which SNPs operate are often unknown. This prohibits their use as instruments as they may violate the exclusion restriction for instrumental variables. Moreover, the SNPs themselves may cause bias due to pleiotropy by possibly confounding relations when they are not controlled for.

In this chapter we develop Genetic Instrumental Variables regression (GIV) to deal with the possible biases due to pleiotropic effects between an exposure and outcome. Naïvely using PGI as control variables is not sufficient in this case, because PGI are only noisy estimates of the underlying genetic architecture. This creates a problem equivalent to the classic econometric problem of errors-in-variables. This problem can be solved using instrumental variable methods if a suitable instrument can be found.

We make use of the fact that multiple PGI can be constructed using GWAS results from independent samples. If the estimation error in both PGI is independent from each other, then one can be used as an instrument for the other. We use this idea to design two estimators (GIV-C and GIV-U), which provide upper and lower bounds for the effect of the exposure on the outcome. We test our method using simulations for a wide array of scenarios. Our estimator works in most scenarios, except when there is a strong environmental bias. In an empirical example we use GIV to show how the estimated effects of body height on education are biased due to pleiotropic effects.

Additionally, during the development of this method, we found that two PGI from independent GWAS samples for the same trait can be used to estimate heritability. Using PGI for educational attainment we show that our estimates are close to the heritability estimates obtained using an established and widely-used method, Genome-based restricted maximum likelihood (GREML; Yang et al., 2010).

We further explored this method for estimating heritability in **Chapter 3**. While the project was shelved before a manuscript was written, a summary of the results is included in this thesis. In this project, we compare heritability estimates of our GIV method to GREML. While GIV requires the availability of two independent samples for GWAS, it does not require the same assumptions as GREML on trait architecture, because in this regard it is completely agnostic. Thus, GIV potentially provides better heritability estimates when the GREML assumptions on trait architecture are not met. We test both our method and GREML in various scenarios, where some scenarios violate the GREML assumptions. However, the GREML estimator proved surprisingly resilient to these violations and was proven to be a more efficient estimator in all our simulation scenarios. Yet, there may still be applications for which GIV can be used. It may be possible, with some tweaking, to disentangle genetic nurture and heritability estimates using within-family GWAS. However, since large scale within-family GWASs are not yet available, we shelved further development of this method for the time being.

Chapter 4 aims to remove several barriers for researchers wanting to use PGI in their study. First, creating PGI is a time-consuming process and requires knowledge of the specific software tools used. Second, to create the most accurate PGI possible one needs to use summary statistics from the largest GWAS sample possible. However, GWAS summary statistics are not always publicly available, adding additional hurdles. Third, publicly available GWAS summary statistics often includes the dataset in which the researcher wants to do their analyses. Such sample overlap may cause biases due to overfitting. Fourth, comparison of results between studies is often difficult due to different methodologies used by different researchers.

To address the first hurdle, we construct a broad array of PGI covering a wide range of phenotypes for a number of datasets used by social scientists. These PGI will be made available for download through the providers of the datasets. For the second problem, the PGI are constructed from GWAS results from a meta-analysis for the largest GWAS sample size possible. These meta-analyses include novel GWAS results and GWAS summary statistics available to us that are not easily obtainable for most researchers. The third problem is solved by making sure that for each dataset, the provided PGI are constructed from summary statistics that exclude that dataset. Finally, the PGI are constructed using a uniform methodology across all phenotypes and datasets, so that results across studies are comparable.

Furthermore, in this chapter a theoretical framework is introduced for interpreting associations with PGIs. Here, PGIs are shown to be noisy, but unbiased estimators of the *additive SNP factor*, a term that is introduced to describe the best linear predictor of the phenotype from the measured genetic variants. Within this theoretical framework we derive an estimator that corrects for the errors–in–variables bias that is encountered when using noisy variables in an ordinary least squares framework. This estimator tackles the same problem described in Chapter 2, but using a different methodology. In Chapter 2, an instrumental variables approach using multiple PGIs is introduced to derive a consistent estimator. Here, the errors–in–variables bias is corrected for using a newly derived estimator based on parameters that can be estimated in the sample where the estimator is implemented.

The last three chapters are about the effects of genetic factors on income and inequalities in income, education and health. It has long been recognized that parental socioeconomic status is a strong predictor for children's health, educational attainment and income. As these traits are all heritable to some degree (Benjamin et al., 2012; De Vlaming et al., 2017; Polderman et al., 2015; Taubman, 1976), parents provide both the environment in which their children grow up as well as pass on their genes. In a way, one has already participated in two lotteries at birth: a social lottery that determines who your parents are and which environment you grow up in and a genetic lottery that determines which part of your parent's genome you have inherited. The results of these two lotteries potentially provide inequal opportunities in life, through which they may affect disparities in education, income and health. Moreover, the results of these two lotteries could be correlated, which further exacerbates the resulting inequalities. Moreover, it provides a major challenge to distinguish different channels through which economic prosperity is passed on through generations. A better understanding of these channels would provide an important contribution to the study of causes of socioeconomic disparities and the mechanisms through which they affect health.

In **Chapter 5,** we conduct the first large scale GWAS on personal income, using data from the UK Biobank. We find that approximately 10% of the variation in occupational wages is captured by common genetic variants. Our findings are validated in two US samples using PGI constructed from our GWAS results. These PGI capture approximately 1 percent of the variation in these US samples and approximately 3 percent using a holdout sample in the UK Biobank. A one–standard–deviation increase in the PGI is associated with a 6 to 8 percent increase in self-reported hourly wages. Using within-sibling differences in PGI in the UK Biobank we show that part of the covariance between the PGI and income is causal. Furthermore, we find that a higher PGI is linked to higher education and better health. The relation between the genetic endowment and health is in part mediated by education. Finally, we show using GIV regression, that even after controlling for genetic confounding the returns–to–schooling is strong, suggesting that education may alleviate the inequalities caused by genetic endowments.

In **Chapter 6** we build upon the results of Chapter 5 and further investigate the genetic and environmental factors underlying socioeconomic and health inequality. Here, we estimate a lower bound for the relevance of genetic factors and early-childhood environment for differences in education, income and body mass index in a sample of 38,698 siblings in the UK Biobank. Our estimates are based on models that combine family-fixed effects with gene-by-environment interactions. We find that the random differences between siblings in their genetic endowments clearly contribute towards inequalities in the outcomes we study. Our rough proxy of the environment people grew up in, which we derived from their place of birth, are also predictive of the studied outcomes, but not beyond the relevance of family environment. Overall, our estimates suggest that at least 13 to 17 percent of the inequalities in education, wages and BMI in the UK are due to inequalities in opportunity that arise from the outcomes of the social and the genetic lottery.

In **Chapter 7** we conduct the first large-scale GWAS meta-analysis on personal income. While this large project is still ongoing, this chapter presents the first phase of the project. The meta-analysis has a total sample size of 1,161,574 observations from approximately 756,000 individuals using four different measures of income: personal income, household income, occupational wages and parental income. In this chapter I present the first phase of the project by summarising the data collection process, the quality control protocol and presenting the first set of results of this project. The genetic variants underlying income capture between 4 and 7 percent of the variation in our measures of income. Combining the results of all four measures of income, we identify 160 independent genome–wide–significant SNPs that are associated with income. Furthermore, we find a very high genetic correlation with other socioeconomic variables like educational attainment. Finally, we find evidence of genetic heterogeneity between men and women.

1.4 Statement of contributions

Chapters 2–7 are all based on collaborative work with many colleagues, who all contributed in various ways. In this section I will state my personal contributions as well as possible and highlight the work of the main contributors to each chapter.

Chapter 2 was the first project I worked on and it was an extension of my master's thesis. All authors contributed to the development of the method. DiPrete extended the mathematical derivations to the final method. I conducted the simulations and the empirical analyses. All authors were involved in writing and editing the manuscript.

For **Chapter 3** De Vlaming, Koellinger and I designed the study. De Vlaming focussed on the theory and I focussed on the simulations. I wrote the manuscript, incorporating comments and notes from De Vlaming.

For **Chapter 4**, I was one of the analysts. The design and supervision of the study was done by Benjamin, Cesarini, Okbay and Turley. Okbay supervised the analyses and led the writing of the manuscript. Becker was responsible for the GWAS and MTAG analyses, quality control of the GWAS summary statistics and did the validation analyses for the PGI. I was involved in cleaning the genetic data and creating harmonized datasets, creating the UK Biobank phenotypes and constructing PGI and genetic principal components. Goldman conducted the illustrative application and wrote the Python code. Turley derived the measurement-error-correction estimator. Benjamin, Cesarini, Okbay and Turley wrote the manuscript.

For **Chapter 5**, I was one of the analysts. Koellinger designed, lead and oversaw the study. Kweon was the lead analyst. He developed the method for imputing income in the UK Biobank and conducted many of the analyses. I mainly conducted analyses in the Health and Retirement Study. I contributed to the writing and editing of the manuscript, but Koellinger and Kweon made especially major contributions to the writing and editing.

I was the lead analyst for **Chapter 6** and lead the writing of the manuscript. Koellinger, Kweon and I designed the project. I conducted the MTAG analyses, created the PGI and conducted the analyses presented in the chapter. Kweon conducted the GWAS in UK Biobank, linked the neighbourhood data and prepared the phenotypic data. Koellinger supervised the study.

Chapter 7 is the start of a very large collaborative study involving many researchers. I am the lead analyst for this project. Next to the many cohort analysts who conducted GWAS, Kweon and I conducted several GWAS. I was responsible for the quality control of the summary statistics. Kweon and I also implemented the imputation algorithm from chapter four to studies from other countries. I was specifically responsible for the implementation in Dutch datasets. I also conducted the meta-analyses and LDSC analyses. Karlsson Linnér created the Manhattan plots of the results. Koellinger lead and oversaw the study. I wrote the chapter presenting first phase of this project included in this thesis, incorporating previous texts from Koellinger and Kweon.

During my PhD I also contributed to the following publications not included in this thesis:

Bansal, V., Mitjans, M. *et al.* (2018) Genome-wide association study results for educational attainment aid in identifying genetic heterogeneity of schizophrenia. *Nature Communications*, *9*(1), 1-12. [3078].

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Chapter 2

Genetic instrumental variable regression: Explaining socioeconomic and health outcomes in nonexperimental data

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Abstract

Identifying causal effects in nonexperimental data is an enduring challenge. One proposed solution that recently gained popularity is the idea to use genes as instrumental variables [i.e., Mendelian randomization (MR)]. However, this approach is problematic because many variables of interest are genetically correlated, which implies the possibility that many genes could affect both the exposure and the outcome directly or via unobserved confounding factors. Thus, pleiotropic effects of genes are themselves a source of bias in nonexperimental data that would also undermine the ability of MR to correct for endogeneity bias from nongenetic sources. Here, we propose an alternative approach, genetic instrumental variable (GIV) regression, that provides estimates for the effect of an exposure on an outcome in the presence of pleiotropy. As a valuable by product, GIV regression also provides accurate estimates of the chip heritability of the outcome variable. GIV regression uses polygenic scores (PGSs) for the outcome of interest which can be constructed from genome-wide association study (GWAS) results. By splitting the GWAS sample for the outcome into nonoverlapping subsamples, we obtain multiple indicators of the outcome PGSs that can be used as instruments for each other and, in combination with other methods such as sibling fixed effects, can address endogeneity bias from both pleiotropy and the environment. In two empirical applications, we demonstrate that our approach produces reasonable estimates of the chip heritability of educational attainment (EA) and show that standard regression and MR provide upwardly biased estimates of the effect of body height on EA

2.1 Introduction

A major challenge in the social sciences and in epidemiology is the identification of causal effects in nonexperimental data. In these disciplines, ethical and legal considerations along with practical constraints often preclude the use of experiments to randomize the assignment of observations between treatment and control groups or to carry out such experiments in samples that represent the relevant population (McNeill, 1993). Instead, many important questions are studied in field data which make it difficult to discern between causal effects and (spurious) correlations that are induced by unobserved factors (Stigler, 2005). Obviously, confusing correlation with causation is not only a conceptual error; it can also lead to ineffective or even harmful recommendations, treatments, and policies, as well as a significant waste of resources (e.g., as in (Lawlor, Smith, & Ebrahim, 2004)).

One important source of bias in field data stems from genetic effects: Twin studies (Plomin, 1999) as well as methods based on molecular genetic data (Yang et al., 2010; Yang, Lee, Goddard, & Visscher, 2011) allow estimation of the proportion of variance in a trait that is due to linear genetic effects (so-called narrow-sense heritability). Using these and related methods, an overwhelming body of literature demonstrates that almost all important human characteristics, behaviors, and health outcomes are influenced both by genetic predisposition and by environmental factors (Turkheimer, Haley, Waldron, D'Onofrio, & Gottesman, 2003; Polderman et al., 2015; Conley, 2016). Most of these traits are "genetically complex", which means that the observed heritability is due to the accumulation of effects from a very large number of genes that each have a small, often statistically insignificant, influence (Chabris, Lee, Cesarini, Benjamin, & Laibson, 2015).

Furthermore, genes often influence several seemingly unrelated traits, a phenomenon called direct or vertical pleiotropy (Paaby & Rockman, 2013; Solovieff, Cotsapas, Lee, Purcell, & Smoller, 2013). For example, a mutation of a single gene that causes the disease phenylketonuria is responsible for mental retardation and also for abnormally light hair and skin color (Low, 2001). Pleiotropy is not restricted to diseases. All genes involved in healthy cell metabolism and cell division can be expected to directly influence a broad range of traits such as body height, cognitive ability, and longevity, even if the effect on each of these traits may be tiny. Similarly, any gene involved in neurodevelopment and brain function is likely to contribute to human behavior and mental health in some way (Boyle, Li, & Pritchard, 2017).

In addition to direct pleiotropic effects, genes can also have indirect or horizontal pleiotropic effects, where a genetic variant influences one trait, which in turn influences another trait (Paaby & Rockman, 2013). The similarity of the genetic architecture of two traits is estimated by their genetic correlation (i.e., the correlation of the "true" effect sizes of all genetic variants on both traits) (Okbay, Beauchamp, et al., 2016), which captures both direct and indirect pleiotropic effects (Lynch & Walsh, 1998; S. H. Lee, Yang, Goddard, Visscher, & Wray, 2012; B. Bulik-Sullivan et al., 2015). Genetic correlations exist between many traits and often exceed their phenotypic correlations (Zheng et al., 2017), giving rise to the concern that direct pleiotropy may substantially bias studies that do not control for genetic effects (D'Onofrio et al., 2010).

If an experimental design is not possible, the gold standard in the presence of genetic confounds is to compare outcomes for monozygotic (MZ) twins (Asbury, Dunn, Pike, & Plomin, 2003; Caspi et al., 2004), who are by definition genetically (almost) identical (Ehli et al., 2012). In addition, this approach also controls for effects that arise from shared parental environment. However, the practical challenge is that such studies require very large sample sizes of MZ twin pairs because differences within MZ twin pairs tend to be small or non-existent. Furthermore, unobserved environmental differences between the twins or reverse causation can still lead to wrong conclusions in this study design.

Another popular strategy to isolate causal effects in nonexperimental data is to use instrumental variables (IVs) (Wooldridge, 2002). Valid IVs are conceptually similar to natural experiments: They provide an exogenous "shock" on the exposure of interest to isolate the effect of that exposure on an outcome. Valid IVs need to satisfy two important conditions.[1] First, they need to be correlated with the exposure conditional on the other control variables in the regression (i.e., IVs need to be "relevant"). Second, they need to be independent of the error term of the regression conditional on the other control variables and produce their correlation with the outcome solely through their effect on the exposure (the so-called exclusion restriction). In practice, finding valid IVs that satisfy both requirements is difficult. In particular, satisfying the exclusion restriction is challenging.

Epidemiologists have proposed to use genetic information to construct IVs and termed this approach Mendelian randomization (MR) (Smith & Ebrahim, 2003; Davey Smith & Hemani, 2014; Pickrell, 2015; Davey Smith, 2015). The idea is in principle appealing because genotypes are randomized in the production of gametes by the process of meiosis. Thus, conditional on the genotype of the parents, the genotype of the offspring is the result of a random draw. So if it could be known which genes affect the exposure, it may be possible to use them as IVs to identify the causal influence of the exposure on some outcome of interest. However, there are four challenges to this idea. First, we need to know which genes affect the exposure and isolate true genetic effects from environmental confounds that are correlated with ancestry. Second, if the exposure is a genetically complex trait, any gene by itself will capture only a very small part of the variance in the trait, which leads to the well-known problem of weak instruments (Hahn & Hausman, 2003; Murray, 2006). Third, genotypes are randomly assigned only *conditional* on

[1] Two other conditions that valid IVs need to satisfy are monotonicity (everyone who is affected by the IV is affected in the same direction) and the stable unit treatment value assumption (SUTVA): the "treatment" of one unit does not affect the outcome variable for other units.

the genotype of the parents. Unless it is possible to control for the genotype of the parents, the genotype of the offspring is *not* random and correlates with everything that the genotypes of the parents correlate with (e.g., parental environment, personality, and habits) (Hamer & Sirota, 2000). Fourth, if direct pleiotropic effects of genes are the source of the confound, these genes could obviously not be used as IVs. One could try to isolate a subset of genes that influence only the exposure, but such attempts are still hindered by our limited knowledge of the function of most genes (Bowden, Davey Smith, & Burgess, 2015; Pickrell, 2015; Verbanck, Chen, Neale, & Do, 2017).

Recent advances in complex trait genetics make it possible to address the first two challenges of MR. Array-based genotyping technologies have made the collection of genetic data fast and cheap. As a result, very large datasets are now available to study the genetic architecture of many human traits and a plethora of robust, replicable genetic associations have recently been reported in large-scale genome-wide association studies (GWASs) (Welter et al., 2014). These results begin to shed light on the genetic architecture that is driving the heritability of traits such as body height (Wood et al., 2014), body mass index (BMI) (Locke et al., 2015), schizophrenia (Ripke et al., 2014), Alzheimer's disease (Lambert et al., 2013), depression (Okbay, Baselmans, et al., 2016), and educational attainment (EA) (Okbay, Beauchamp, et al., 2016).

High-quality GWASs use several strategies to control for genetic structure in the population, and empirical evidence suggests that the vast majority of the reported genetic associations for many traits is not confounded by ancestry (Price et al., 2006; Rietveld et al., 2014; B. K. Bulik-Sullivan et al., 2015; Loh et al., 2015). Polygenic scores (PGSs) have become the favored tool for summarizing the genetic predispositions for genetically complex traits (Purcell et al., 2009; Dudbridge, 2013; Okbay, Baselmans, et al., 2016; Okbay, Beauchamp, et al., 2016). PGSs are linear indexes that aggregate the estimated effects of all currently measured genetic variants (typically single nucleotide polymorphisms (SNPs)). The effects of each SNP on an outcome are estimated in large-scale GWASs that exclude the prediction sample. Recent studies demonstrate that this approach yields PGSs that begin to predict genetically complex outcomes such as height, BMI, schizophrenia, and EA (Rietveld et al., 2013; Wood et al., 2014; Locke et al., 2015; Ripke et al., 2014; Okbay, Baselmans, et al., 2016). Although PGSs still capture substantially less of the variation in traits than suggested by their heritability (Witte, Visscher, & Wray, 2014) (an issue we return to below), PGSs capture a much larger share of the variance of genetically complex traits than individual genetic markers. The third challenge to MR in the above list could in principle be addressed if the genotypes of the parents and the offspring are observed (e.g., in a large sample of parent–offspring trios) or by using large samples of siblings or dizygotic twins where the genetic differences between siblings are random draws from the parent's genotypes. However, the fourth challenge (i.e., pleiotropy) remains a serious obstacle despite recent efforts to relax the exogeneity assumptions in MR (Bowden, Davey Smith, & Burgess, 2015; van Kippersluis & Rietveld, 2017; Zhu et al., 2018).

Here, we address the implications of pleiotropy for modeling causal relationships using nonexperimental data. We demonstrate that pleiotropy is a serious source of bias in ordinary least-squares regression (OLS) and MR. We propose alternative estimation strategies that use PGSs for the outcome of interest to reduce bias arising from pleiotropy. In particular, we propose an approach that we call genetic instrumental variables (GIV) regression that can be implemented using widely available statistical software. GIV regression estimates practically useful upper and lower bounds for the causal effect of an exposure on an outcome even in the presence of substantial direct pleiotropy.

We begin by providing intuition and laying out the assumptions of our approach. We go on to show that GIV regression produces accurate estimates for the effect of the PGSs on the outcome variable when the other covariates in the model are exogenous, when the true PGS is uncorrelated with the error term net of the included covariates, and when the GWAS sample sizes are sufficiently large relative to the number of SNPs. We then turn to the more complex case of when a regressor of interest (T) is potentially correlated with unobserved variables in the error term because of pleiotropy, and we show with evidence from a comprehensive set of simulations that the bias under these assumptions with GIV regression is generally smaller than with OLS, MR, or what we term an enhanced version of MR (EMR).

Next, we demonstrate the practical usefulness of our approach in empirical applications using the publicly available Health and Retirement Study (HRS) (Sonnega et al., 2014). First, we demonstrate that a consistent estimate of the so-called chip heritability (Witte et al., 2014) of EA can be obtained with our method. Then, we estimate the effects of body height on EA. As a "negative control," we check whether our method finds a causal effect of EA on body height (it should not).[2]

Formal derivations and technical details are contained in *Supplementary Information (SI)*, sections S2.1–S2.5.

2.2 Theory

2.2.1 Intuition

To build intuition for our approach, we introduce the concept of the true PGS for y which would be constructed using the true effects of each SNP on y. In theory, the true SNP effects could be estimated in a GWAS on y in an infinitely large sample that is drawn from the same population as the prediction sample. The true PGS would capture the narrow-sense heritability of y. Of course, the true PGS is unknown. All one can practically obtain is a PGS from a finite GWAS sample that will capture a part, but not all, of the genetic influence on y because the effect of each SNP is estimated with noise. The attenuated predictive accuracy of practically available PGSs (Daetwyler, Villanueva, & Woolliams, 2008; Dudbridge, 2013; Witte et al., 2014) is conceptually similar to the well-known problem of measurement error in regression analysis. It has long been understood that multiple indicators can, under certain conditions, provide a strategy to correct regression estimates for attenuation from measurement error (Bielby, Hauser, & Featherman, 1977; Bollen, 2002; Angrist & Pischke, 2009). We show below that by splitting the GWAS sample into independent subsamples, one can obtain several PGSs (i.e., multiple indicators) in the prediction sample. Each will have even lower predictive accuracy than the original score due to the smaller GWAS subsamples used in their construction, but these multiple indicators can be used as instrumental variables for each other, and the instruments will satisfy the assumptions of IV regression to the extent that the measurement errors (the difference between the true and calculated PGSs) are uncorrelated. Standard two-stage least-squares (2SLS) regression (Wooldridge, 2002) (readily available in statistics software packages) using at least one valid IV for the PGS of y can then be used to back out an unbiased estimate of the heritability of y.

[2] Note that a clean experimental design which randomizes people into groups based on body height or EA is not possible. Thus, any attempt to study the causal relationship between the two variables must rely on observational data and naturally occurring experiments like the genetic endowment of individuals, which we exploit here.

Next, presume the matter of interest is not heritability, but the causal effect of some treatment T on y, where T is also heritable and some genes have direct pleiotropic effects on both. If these genes are not known and not controlled for, regressing y on T would result in omitted variable bias.[3] Suppose the effects of all genes that influence y through channels other than T could be known. Theoretically, one could estimate these effects in a GWAS on y that controls for T in an infinitely large sample. That information could be used to construct a "true conditional" PGS in a prediction sample. Adding the true conditional PGS to a regression of y on T in the prediction sample would effectively eliminate bias arising from direct pleiotropy. However, the true conditional PGS is also unknown and all we can practically obtain is a noisy proxy of it from a finite GWAS sample. While it is not guaranteed, the general conclusion of the literature is that the use of proxy variables is an improvement over omitting the variable being proxied (Wickens, 1972; Aigner, 1974). Furthermore, having a valid IV for the conditional score would potentially correct for its noise and get us closer to estimating the true causal effect of T on y. As before, a valid IV can be practically obtained by splitting the GWAS sample into independent parts and standard IV estimation techniques such as two-stage least squares can be used. We refer to this approach as conditional genetic IV regression (GIV-C).

If conditional GWAS results are not available, one can still add the unconditional PGS for y as a control variable and use IV regression with multiple indicators for this score to correct for measurement error. We refer to this as unconditional GIV regression (GIV-U). GIV-U still corrects for bias arising from direct pleiotropy, but this strategy will overcontrol and result in estimates for T that are biased toward zero because the unconditional PGS also includes indirect pleiotropic effects of genes that affect y only because they affect T. However, extensive simulations show that the combination of GIV-C and GIV-U turns out to produce reasonable upper and lower bounds for the effect of T on y across a broad range of scenarios if the only sources of bias are pleiotropic genes.

The GIV strategy starts to break down when bias arises from unobserved nongenetic factors as well as from pleiotropic effects. We show below that both GIV and MR produce biased estimates in this case. However, we demonstrate that the combination of GIV-C and GIV-U still outperforms OLS and MR. Furthermore, the GIV approach has additional utility because it can be combined with other strategies to

[3] Unfortunately, that is the reality in most social scientific and epidemiological studies that use nonexperimental data

reduce the effects of environmental endogeneity (e.g., additional control variables or family fixed effects). We demonstrate that these combined strategies can potentially provide accurate information about the effects of an exposure in situations with both genetic and nongenetic sources of endogeneity. In contrast, the problems for MR that are produced by pleiotropy bias are not fixable in a similar manner.

2.2.2 Assumptions

GIV regression builds on the standard identifying assumptions of IV regression (Wooldridge, 2002). In the context of our approach, this implies six specific conditions:

i) Polygenicity: The outcome is a genetically complex trait that is influenced by many genetic variants, each with a very small effect.

ii) Complete genetic information: The available genetic data include all variants that influence the variable(s) of interest.

iii) Genetic effects are linear: All genetic variants influence the variable(s) of interest via additive linear effects. Thus, there are no genetic interactions (i.e., epistasis) or dominant alleles.

iv) Unbiased GWAS results: The available GWAS results are not systematically biased by omitted environmental variables. For example, failure to control for population structure can lead to spurious genetic associations (Hamer & Sirota, 2000).

v) Nonoverlapping samples: It is possible to divide GWAS samples into nonoverlapping subsamples drawn from the same population.

vi) The genetic effects on y are the same in the GWAS and the prediction samples; i.e., the genetic correlation between samples is one.

2.2.3 Estimating Narrow-Sense SNP Heritability from Polygenic Scores

Under these assumptions, consistent estimates of the chip heritability of a trait (i.e., the proportion of variance in a trait that is due to linear effects of currently measurable SNPs) can be obtained from polygenic scores (for full details, see *Supplementary Information,* section S2.2). If y is the outcome variable, X is a vector of exogenous control variables, and $S^*_{y|X}$ is a summary measure of genetic tendency for y in the presence of controls for X, then one can write

$$y = \alpha + X\beta + \gamma S^*_{y|X} + \epsilon \tag{2.1}$$

$$= \alpha + X\beta + \gamma(G\zeta_{y|X}) + \epsilon,$$

where G is an $n \times m$ matrix of genetic markers, and $\zeta_{y|X}$is the $m \times 1$ vector of SNP effect sizes, where the number of SNPs is typically in the millions. If the true effects of each SNP on the outcome were known, the entire genetic tendency for y would be captured by the true unconditional score $S_{y^*|X}$, and the marginal R^2 of $S^*_{y|X}$ in Eq. 2.1 would be the chip heritability of the trait. We refer to the estimate of the PGS from actually available GWAS data in the presence of controls for X as $S_{y|X}$, where

$$S_{y|X} = S^*_{y|X} + v_1 = G\zeta_{y|X} + Gu_{y|X} \tag{2.2}$$

and $u_{y|X}$ is the estimation error in $\zeta_{y|X}$and $S_{y|X}$is substituted for $S^*_{y|X}$in Eq. 2.1. The variance of a trait that is captured by its available PGS increases with the available GWAS sample size to estimate $\zeta_{y|X}$ and converges to the SNP-based narrow-sense heritability of the trait at the limit if all relevant genetic markers were included in the GWAS and if the GWAS sample size were sufficiently large (Daetwyler et al., 2008; Dudbridge, 2013; Witte et al., 2014).

Eq. 2.1 contains what is called in econometrics a "generated regressor" in that S^* is a function of a set of variables (G) and coefficients ($\zeta_{y|X}$) from another model. As previous work (Pagan, 1984; Murphy & Topel, 2002) has established, OLS will provide consistent estimates of the parameters of Eq. 2.1 (although corrections for standard errors are needed) if S is substituted for S^* under a set of reasonable assumptions that include convergence in probability of $\hat{\zeta}_{y|X}$ to $\zeta_{y|X}$ as the sample size grows larger. However, the practical utility of this mathematical result is questionable in the current context, when the number of variables in G is in the millions while the number of cases available to estimate S^* is far smaller than that. The imposed ratio of coefficients to cases requires nonconventional estimation methods that use a combination of statistical assumptions to obtain estimates of S. Empirical studies using PGSs for a variety of traits have consistently demonstrated substantial attenuation in the estimate of γ (Daetwyler et al., 2008; Dudbridge, 2013; Witte et al., 2014), and, while the bias diminishes with GWAS sample size, we are a long time away from having large enough sample sizes to bring this attenuation down to ignorable levels. This situation, therefore, calls for alternative strategies to address important questions with the datasets currently available.

The most straightforward solution to the problem of attenuation bias is to obtain multiple indicators of the PGS by splitting the GWAS discovery sample for y into two mutually exclusive subsamples with at least partially overlapping sets of SNPs. This produces noisier estimates of $S^*_{y|X}$, with lower predictive accuracy, but the multiple indicators can be used as IVs for each other. The 2SLS regression using $S_{y1|X}$ as an instrument for $S_{y2|X}$ will then recover a consistent estimate of γ in Eq. 2.1 under standard IV assumptions (Angrist & Pischke, 2009; Burgess, Small, & Thompson, 2015).

As discussed more technically in *SI*, section S2.1, an additional important assumption for $S_{y1|X}$ to be a valid instrument for $S_{y2|X}$ is that y be a complex trait, meaning that it is influenced by a large number of genetic markers, each of which has a very small effect. If y is primarily influenced by a relatively small number of markers, then the method proposed here would not work well. However, there would also be no need for the proposed method, because the markers with large effects could be easily identified and their effects estimated with reasonable precision using discovery sample sizes that are already obtainable.

Another required assumption is that the genetic markers are independent of each other. In general, genetic markers are correlated if they are located close to each other on the same chromosome. However, it is currently possible to isolate several hundred thousand markers from the total set of millions of SNPs that have sufficient spatial separation in the DNA to be essentially mutually independent, which means that this assumption can be satisfied to a sufficient level of accuracy.

Assuming that the variables in Eq. 2.1 are standardized to have mean zero and a SD of one, and further assuming that the variables contained in X control for population stratification or are not correlated with genotype G, a consistent estimate of the chip heritability of y can now be obtained from $\widehat{h_y^2} = \hat{\gamma}^2 \rho(S_{y1|X}, S_{y2|X})$, where ρ is the correlation coefficient. The heritability estimate $\widehat{h_y^2}$ is not equal to $\hat{\gamma}^2$ simply because we regressed on $S_{y|X} = S_{y|X}^* + v$ instead of $S_{y|X}^*$. Thus, we standardize with respect to the variance of $S_{y|X}$ instead of $S_{y|X}^*$, which leads to a bias equal to $1/Var(S_{y|X}^*)$. Multiplying $\hat{\gamma}^2$ with the correlation between $S_{y1|X}$ and $S_{y2|X}$ recovers a consistent estimate for $\hat{\gamma}^2$ (*SI*, section SI 2.2.1).[4]

[4] For an alternative approach to correcting attenuation bias based on the use of multiple indicators in a structural equation modeling framework, see ref. Tucker-Drob, 2017.

2.3 Reducing bias arising from genetic correlation between exposure and outcome

Polygenic scores also play a potentially important role in situations where the question of interest is not the chip heritability of y per se, but rather the effect of some nonrandomized exposure on y (e.g., a behavioral or environmental variable or a nonrandomized treatment due to policy or medical interventions). We can rewrite Eq. 2.1 by adding a treatment variable of interest T, such that

$$\begin{aligned} y &= \delta T + X\beta_y + \gamma\, S^*_{y|XT} + \epsilon_y \\ &= \delta T + X\beta_y + G\zeta_{y|XT} + \epsilon_y \end{aligned} \tag{2.3}$$

where

$$\begin{aligned} T &= \alpha\, S^*_{T|X} + X\beta_T + \epsilon_T \\ &= G\xi_{T|X} + X\beta_T + \epsilon_T, \end{aligned} \tag{2.4}$$

We assume that the disturbance term is uncorrelated with genetic variables.[5] We now use the true conditional score $S^*_{y|XT}$ rather than $S^*_{y|X}$ in the equation. Given that T is in the model, the effect of individual SNPs on y will generally involve a direct net effect of T (ζ) and an indirect effect stemming from the combination of their effect on T (ξ) and the effect of T on y. Having $S^*_{y|XT}$ in the equation would effectively control for pleiotropic effects on T and y.

In standard MR, a measure of genetic tendency ($S_{T|X}$) for a behavior of interest (T in Eq. 2.3) is used as an IV in an effort to purge $\hat{\delta}$ of bias that arises from correlation between T and unobservable variables in the disturbance term under the assumption that $S_{T|X}$ is exogenous (Burgess, Butterworth, Malarstig, & Thompson, 2012; Burgess et al., 2015). One such example would be the use of a PGS for height as an instrument for height in a regression of EA on height. The problem with this approach is that the PGS for height will fail to satisfy the exclusion restriction if (some of) the genes affecting height also have a direct effect on EA (e.g., via healthy cell growth and metabolism) or if they are correlated with unmeasured environmental factors that affect EA. (Classic MR typically does not use PGSs as

[5] We drop this assumption later. Also, we drop the subscript on the coefficients for the exogenous control variables X below when it would not lead to confusion.

instruments. Instead, the idea is to use single genetic variants that are known to affect the exposure via well-understood biological mechanisms that make it unlikely to violate the exclusion restriction. In practice, limited knowledge about the biological function of most genes makes it difficult to argue that direct pleiotropic effects of the gene on the exposure and the outcome of interest exist.)

If the true conditional (net of *T*) genetic propensity for y could be directly controlled in the regression, pleiotropy would not bias coefficient estimates. For example, fixed-effects regression where the same individual is observed multiple times would effectively control for pleiotropy (which does not vary over time), but this strategy is often not available (e.g., in a study of the effect of height on EA).[6] Direct control for the conditional genetic propensity for y is, of course, not possible, because $S^{*}_{y|XT}$ (more specifically, the coefficients $\zeta_{y|XT}$in Eq. 2.3) is not known. What is obtainable instead is a proxy $S^{*}_{y|XT}$, namely $S_{y|XT}$, which contains measurement error due to finite GWAS sample size and potential bias in the estimate of T in the GWAS.

We refer to the combined use of $S_{y|XT}$ as a control and $S_{T|X}$ as an IV for T as EMR. However, controlling for $S_{y|XT}$ as a proxy for $S^{*}_{y|XT}$ is not a perfect solution to pleiotropy because it leaves a component of $S^{*}_{y|XT}$ in the error term which is correlated with S_T due to pleiotropy. As a result, the EMR estimate for δ will be biased. The practical question, then, is whether alternative strategies that split the GWAS sample for Y to obtain multiple indicators of $S_{y|XT}$ that can be used as IVs for each other (e.g., $S_{y1|XT}$ and $S_{y2|XT}$) are sufficient to rescue S_T as a practically useful IV for T.[7] This is a practical question beyond the reach of formal mathematics and best answered by simulation analyses. Unfortunately, and as we show in *SI*, section S2.2, the pleiotropy-induced violation of the exclusion restriction when using genetic IVs for T is sufficient to produce serious bias in the estimated effect of T even if one attempts to control for pleiotropy using such strategies. The magnitude of bias clearly

[6] Fixed-effects estimation with panel data would also preclude MR-type strategies because the IV does not vary over time, and genetic indicators for *T* would generally have a weak relationship to changes in *T* over time. Fixed-effects regressions based on other strategies (e.g., sibling or neighborhood fixed-effects models) would not control for pleiotropy. We discuss these strategies at greater length below.

[7] An earlier version of our paper pursued this approach and called it GIV regression. However, we later found that controlling for *T* in a GWAS for y induces a correlation of $S_{y1|XT}$ with S_T that invalidates the latter as an IV. The version of GIV-U and GIV-C regression we describe below does not have this problem because it does not use a genetic instrument for *T* anymore. Instead, GIV-U and GIV-C both rely on a proxy-control strategy that uses only an instrument for $S_{y1|XT}$ or $S_{y1|X}$ to correct for measurement error in these proxies for $S^{*}_{y|XT}$ and $S^{*}_{y|XT}$.

depends on the quality of the proxies for $S^*_{y|XT}$. However, we find that pleiotropy leads to considerable bias in MR in virtually all scenarios we investigated (*SI* sections S2.2 – S2.4 and Tables S2.2–S2.15).

The problems posed by pleiotropy cannot be completely eliminated without knowledge of $S^*_{y|XT}$ (*SI*, section S2.2). However, this situation does not mean that the estimation problems introduced by pleiotropy are intractable. When endogeneity bias is driven by genetic correlation, the PGS for y can still be used to obtain more accurate estimates of the effect of T than can be obtained with MR or, for that matter, with OLS that lacks controls for the direct effect of genetic markers on y. To gain insight into the best strategy, we consider the reasons for the pleiotropy bias. Regardless of whether the estimation strategy is OLS or the second stage of IV regression involving OLS on predicted variables from the first stage, the coefficient bias comes from the extent to which the expected estimate of the OLS coefficients differs from the true coefficients;[8] namely,

$$E\big[\hat{\beta}\big|X\big] = \beta + E[(X'X)^{-1}X'\epsilon|X] \tag{2.5}$$

In other words, the coefficient bias from OLS is the expected regression coefficient of the error on the included variables in the regression. If is the sum of an omitted variable, z, which is correlated with the regressors, and additional variables that are uncorrelated with the regressors, then the bias for each coefficient β_k in Eq. 2.5 becomes the product of the regression coefficient for x_k in the regression of z on all of the omitted variables multiplied by the effect of z on the outcome. For simplicity, we assume that the only variables in the regression are T and a potential proxy for $S^*_{y|XT}$, which we call $\tilde{S}_{y|XT}$. For any given proxy$\tilde{S}_{y|XT}$, the bias in the estimate of $\hat{\delta}$ (the coefficient for T in Eq. 2.3) comes from the expected coefficient of T from a regression of $\gamma S^*_{y|XT} - \tilde{\gamma}\, \tilde{S}_{y|XT}$ on T and $\tilde{S}_{y|XT}$. We consider three alternative approaches for the proxy $\tilde{S}_{y|XT}$, which we call simple OLS, GIV-C, and GIV-U. First, we use $S_{y|XT}$ as a proxy for $S^*_{y|XT}$ in a simple OLS regression. Second, we observe that $S_{y|XT}$ is correlated with T; its inclusion in the error (by virtue of its being controlled) may affect the bias in $\hat{\delta}$. So we construct an estimate for $S_{y1|XT}$, namely $\hat{S}_{y1|XT}$, by using $S_{y2|X}$ (the unconditional PGS from the second GWAS sample) as its IV. We call this approach, where $\hat{S}_{y1|XT}$ is used as the regressor in the second stage, GIV-C.

[8] It is possible to have finite-sample bias that disappears asymptotically, in which case the estimator is consistent. We use the expectation formula instead because it is arguably more straightforward to understand.

We also use a third estimator that uses the same IV as in GIV-C (i.e., $S_{y2|X}$), but that substitutes the unconditional PGS for y (i.e., substitutes $S_{y1|X}$ for the conditional PGS $S_{y1|XT}$) in the structural model in Eq. 2.3. We then use $S_{y2|X}$ to predict $S_{y1|X}$, obtaining $\hat{S}_{y1|X}$ as the regressor in the second stage. We call this third approach GIV-U.

We generally expect the use of GIV-C to perform better than the use of the proxy $S_{y|XT}$ in simple OLS. If the true effect of T on y is positive and positive pleiotropy is present, the estimated effect of T on y will have positive bias. This follows from the positive correlation between $S_{y^*|XT}$ and T and from the positive effect of $S^*_{y|XT}$ on y. The presence of the proxy $S_{y|XT}$ in the first approach (simple OLS) adds a partially offsetting negative bias, because the correlation between $S_{y|XT}$ and T is positive and the effect $\tilde{\gamma}_{OLS}$ is also positive, but $\hat{\gamma}_{OLS}S_{y|XT}$ is being subtracted, which causes the offsetting bias to be negative. The net bias is expected to be positive, but we would expect it to be smaller with the inclusion of the proxy than with no proxy at all, both because the correlation between T and $S_{y|XT}$ would be lower than between T and $S_{y^*|XT}$ and because we expect $\hat{\gamma}_{OLS}$ to be attenuated relative to γ. When GIV-C is used instead, the term in the error becomes
$\gamma S^*_{y|XT} - \hat{\gamma}_{IVc}\hat{S}_{y1|XT}$. The presence in the first stage of GIV-C of T, which is correlated with $S^*_{y|XT}$, prevents the IV strategy from obtaining a consistent estimate of γ. Nonetheless, we would generally expect $\hat{\gamma}_{IVc} > \hat{\gamma}_{OLS}$, and therefore we expect the positive bias for the estimate of δ to be smaller when using GIV-C than when estimating δ using OLS and the proxy $S_{y1|X}$. We confirm this in the simulations in *SI*, Tables S2.2–S2.7.

With GIV-U, the problem term in the error is $\gamma S^*_{y|XT} - \hat{\gamma}_{IVu}\hat{S}_{y1|X}$. As before, the presence of the first term produces a positive bias in the estimate of δ, while the second term produces an offsetting negative bias. The offset will be stronger when the unconditional PGS for y is the regressor in the structural model, because the coefficients of the genetic markers in S_{y1} are $\hat{\delta}\hat{\xi} + \hat{\zeta}$, where ξ is the effect of the genetic marker on T. The presence of $\hat{\delta}(G\hat{\xi})$ in the second endogenous term in the error (i.e., the second term in $\gamma S^*_{y|XT} - \tilde{\gamma}\tilde{S}_{y|XT}$) produces a stronger downward bias. This downward bias is made still stronger by the use of $\hat{\gamma}_{IVu}$ instead of $\hat{\gamma}_{OLS}$ as the coefficient, because we expect the first-stage regression to reduce the downward bias of $\hat{\gamma}_{OLS}$. In other words, we expect these three proxies to behave differently in the simulations, and, as we will see, this expectation is met in practice. We establish via a comprehensive set of simulations that GIV-C and GIV-U provide upper and lower bounds for the effect of T across a range of plausible scenarios for pleiotropy and for heritability (*SI*, Tables S2–S7). We further establish through simulation analyses that GIV-C and GIV-U perform similarly in the case when endogeneity arises from pleiotropy and when it arises from pleiotropy in combination with genetic confounds for reasons other than pleiotropy (epistasis, effects from rare alleles, or genetic nurturing effects, where the environment of ego is shaped by genetically related individuals to ego (Kong et al., 2017)) (*SI*, section S2.3 and Tables S2.8–S2.10).

2.4 Simulations

We explored the performance of GIV regression in finite sample sizes using three sets of simulation scenarios (*SI*, sections S2.2–S2.4). The simulations generated genetic and phenotypic data at the individual level from a set of known models in a training sample and a holdout sample using parameters that are realistic for genetically complex traits. We then estimated genetic effects on T and y using GWAS in the training sample and constructed polygenic scores with the estimated parameters for each SNP in the holdout sample. Thus, the polygenic scores in our simulations have the realistic property that their predictive accuracy increases with the size of the training (i.e., GWAS) sample and the average effect size of each SNP (Daetwyler et al., 2008; Dudbridge, 2013). Finally, we analyzed the extent to which various estimation strategies recover the effect of the PGS for y on y and the effect of T on y in the holdout sample. We produced these estimates using OLS, MR, EMR, proxy OLS, GIV-C, and GIV-U regression, and we compared these results with the true answer across a range of parameter values. We ran 20 simulations with different random seeds for each set of parameters to obtain a distribution of estimated effects.[9]

The simulations specify that the true PGS scores for y and T covary as a result of genetic correlation. We made the conservative assumption that the entire genetic correlation between y and T is due to direct pleiotropy; i.e., all genes that are associated with both phenotypes have direct effects on both. In practice, this is unlikely to be the case, but it is equally unlikely that one can put a credible upper bound on (or completely rule out) direct pleiotropy.

[9] The computer code for these simulations is available at https://github.com/cburik/GIVsim.

In the first set of simulations, we assumed that the entire endogeneity problem arises from genetic confounds (*SI*, section S2.2).

In the second set of simulations, we allowed endogeneity to arise from sources that are both correlated with genes and that cause the disturbance term in the structural equation for y to be correlated with the disturbance term in the structural model for T even if the true conditional PGS for y were included in the structural equation (*SI*, section S2.3). This situation would occur if rare alleles were missing from the true PGS for T and the true conditional PGS for y based on known SNPs and if the effect of these alleles was correlated with the true PGS scores for T and y. It would also occur under conditions of epistasis where nonlinear effects of genes were in the error and were correlated with the linear effects of genes in the PGS for T and the conditional PGS for y. Third, this situation would occur if the genetic factors that affect T are correlated with the environmental factors in the disturbance term for y that are caused or selected by parental genes, which are correlated with the genes of sample members and therefore also with variables (like T) that are affected by the genes of sample members, i.e., by genetic nurturing (Kong et al., 2017).

In the third set of simulations, we specified the presence of a correlation between the error terms in the models for y and T that was not itself correlated with genetic variables (*SI*, section S2.4). This would occur in a situation where some environmental or behavioral factor that is unrelated to genetics produces both an effect on T and an effect on y.

A summary of these results is in Table 2.1 for the case where the effect of T is set to 1.0 (see *SI*, Table S2.16 for details on the standardized effect size). Scenarios A–D in Table 2.1 refer to situations where pleiotropy is the only source of bias, scenario E contains pleiotropy plus other sources of genetic confounds, while scenarios F and G also include endogeneity from nongenetic (i.e., environmental) sources. The results provide considerable reason to be skeptical of estimates from MR. When pleiotropy is present, the MR strategy is undermined by the violation of the exclusion restriction for genetic IVs. Our results find that MR performs poorly even when nongenetic endogeneity is present along with pleiotropy. In contrast, GIV regression provides reasonable upper and lower bounds of the true effect of T on y if the source of endogeneity is only from pleiotropy or other genetic confounds (i.e., unobserved genetic variants, epistasis, or genetic nurturing) and the heritability of T and y is not extreme. GIV-C generally overestimates the effect of T but the overestimation is modest at low to moderate levels of pleiotropy and heritability and is more accurate than OLS without proxies, MR, or EMR. GIV-U generally underestimates the effect of T on y but provides an estimate that is reasonably close to the true answer under conditions of low to moderate levels of pleiotropy and heritability. Even at higher levels of pleiotropy and heritability, the combination of GIV-C and GIVU provides useful information about whether T actually has a causal effect on y and what the upper bound of this effect is likely to be.

In the case where the true value of T is zero (i.e., where the true model is Eq. 2.1), we expect that GIV-U will produce an estimate that is close to zero as long as the endogeneity comes either from pleiotropy or from other genetic confounds (see *SI*, sections SI 2.2–2.4, for details). The simulations in SI section S2.2 show that when the endogeneity is only from genetic sources, GIV-U estimates the effect of T to be close to zero regardless of the level of pleiotropy or inheritance that is specified in the simulations.

When the source of endogeneity is nongenetic in origin, we find that neither MR nor proxy controls for pleiotropy provide a satisfactory method for determining the effect of T on y. In this scenario, the pleiotropy creates endogeneity bias for genetic IVs that defeats the ability of MR to solve the problem of nongenetic endogeneity via an IV strategy. Nongenetic endogeneity can cause even GIV-U to overpredict the effect of T on y, although in our simulations it is clearly the most accurate of all of the estimators that we have surveyed when the effect of T is zero. Indeed, GIV-U always provides the most conservative estimate across the entire range of scenarios that we have surveyed, both for the case where an effect of T on y exists and when the effect of T is zero.

Inference with the GIV can be further strengthened in cases where nongenetic endogeneity can be controlled either through observable variables or through strategies such as family fixed effects that reduce or eliminate the impact of nongenetic forms of environmental endogeneity. Indeed, environmental endogeneity is a concern in most applied-research questions that use nonexperimental data. Reassuringly, our simulations show that GIV regression is a good estimation strategy in the presence of both direct pleiotropy and environmental endogeneity if control variables are available that manage to absorb a substantial share of the nongenetic confounds (*SI*, Tables S2.13– S2.15). Therefore, we recommend using GIV regression always in combination with control variables the capture possible environmental confounds, ideally in datasets that allow controlling for family fixed effects (e.g., using siblings or dizygotic twins). In SI, section S2.6, we provide additional practical guidelines for GIV regression.

The simulations described in this paper certainly do not cover all conceivable data-generating processes, but they are nonetheless of considerable utility.

2.5 Empirical Applications

We illustrate the practical use of GIV regression in two empirical applications using data from the Health and Retirement Survey (HRS) for 2,751 unrelated individuals of northwest European descent who were born between 1935 and 1945 (*SI*, section S2.5).

2.5.1 The Narrow-Sense SNP Heritability of EA

First, we demonstrate that GIV regression can recover the unbiased genomic– relatedness-matrix restricted maximum-likelihood (GREML) estimate of the chip heritability of EA. Specifically, we follow the common practice in GREML estimates of heritability and analyse the residual of EA from a regression of EA on birth year, birth year squared, gender, and the first 20 principal components from the genetic data (de Vlaming et al., 2017). Next, we standardize the residual and regress it on a standardized PGS for EA using OLS or GIV. The results are displayed in Table 2.2. The OLS estimate of the PGS accounts for 6.8% of the variance in EA ($\beta^2 = \Delta R^2 = 6.8\%$), which is substantially lower than the 17.3% (95% CI ± 4%) estimate of chip heritability reported by ref. 64 in the same data using GREML.[10] Instead, the GIV regression results in columns 2 and 3 of Table 2.2 imply a chip heritability of 13.4% (CI ± 3.9%) and 13.8% (±4.0%), respectively. Thus, the 95% CIs of the GREML mate and the two GIV estimates overlap, demonstrating that GIV regression can recover the chip heritability of EA from polygenic scores.

2.5.2 The Relationship Between Body Height and Educational Attainment

Previous studies using both OLS and sibling or twin fixed-effects methods have found that taller people generally have higher levels of EA (Silventoinen, Kaprio, & Lahelma, 2000; Case, Paxson, & Islam, 2009; Anne Case & Christina Paxson, 2008). They are also more likely to perform well in various other life

[10] GREML yields unbiased estimates of SNP based heritability that are not affected by attenuation (Yang et al., 2015).

domains, including earnings, higher marriage rates for men (although with higher probabilities of divorce), and higher fertility (Heineck, 2005, 2009; Schick & Steckel, 2015; Weitzman & Conley, 2014; Kanazawa, 2005; Cinnirella, Piopiunik, & Winter, 2011). The question is what drives these results. Can they be attributed to genetic effects that jointly influence these outcomes? Are there social mechanisms that systematically favor taller or penalize shorter individuals? Or are there nongenetic factors (e.g., the uterine and postbirth environments especially related to nutrition or disease) that affect both height and these life-course outcomes? The literature on the relationship between height and EA has found evidence that the association arises largely through the relationship between height and cognitive ability, which may suggest that the height–EA association is driven largely by genetic association between height and cognitive ability. We use GIV regression with individual-level data from the HRS to clarify the influence of height on EA, and we compare these results with those obtained from OLS and from MR. In addition, we conduct a negative control experiment that estimates the causal effect of EA on body height (which should be zero). A complete description of the materials and methods is available in *SI*, section 2.5.

GWAS summary statistics for height were obtained from the Genetic Investigation of Anthropometric Traits (GIANT) consortium (Wood et al., 2014) and by running a GWAS on height (conditional on EA and unconditional on EA) in the UKB (Marchini et al., 2015). The UKB was not part of the GIANT sample. GWAS summary statistics for EA were obtained from the Social Science Genetic Association Consortium (SSGAC) for the unconditional PGSs. The most recent study of the SSGAC on EA used a meta-analysis of 64 cohorts for genetic discovery (Okbay, Beauchamp, et al., 2016). We obtained meta-analysis results from this study with the HRS, UKB, and 23andMe cohorts excluded and we refer to the PGS constructed from these results as EA SSGAC. Furthermore, we obtained GWAS estimates for EA in the full UKB release ($N = 442{,}183$) from Lee et al. (2018). We refer to this PGS as PGS EA unc. UKB. We also created a PGS for EA conditional on height by running a GWAS on EA in the same UKB sample (PGS EA cond. UKB). There is sample overlap between Height GIANT and EA SSGAC. Therefore, whenever one of the two was used as regressor, we excluded the other as instrument and used a PGS from UK Biobank data instead to ensure independence of measurement errors in the PGS.

In Table 2.3 we report the estimated standardized effect of height on EA. The OLS results show that height appears to have a strong positive effect on EA, with 2.5 additional centimeters in height generating one additional month of schooling. MR appears to confirm the causal interpretation of the OLS result; indeed, the point estimate from MR is even slightly larger than from OLS. As discussed above, MR suffers from probable violations of the exclusion restriction due to pleiotropy. These violations could stem from the possibility that some genes have direct effects on both height and EA.[11] They could also stem from the possibility that the PGS for height by itself is correlated with the genetic tendency for parents to have higher EA and income, which enables higher parental investments into their children who may therefore be more likely to reach their full cognitive potential and have higher EA. Controlling for the PGS is an imperfect strategy for eliminating this source of endogeneity because the bias in the estimated effect of the PGS score also biases the estimated effect of height.

If all of the bias in EA came from positive pleiotropy, then we would expect GIV-C and GIV-U to provide upper and lower bounds for the true effect of height on EA, respectively. Thus, if the only source of endogeneity is pleiotropy, the results in Table 2.3 would suggest that the true standardized effect is between 0.11 (from GIV-U) and 0.17 (from GIV-C).

However, the negative control regression results in Table 2.4 provide substantial evidence of endogeneity bias from environmental sources. Given that the true effect of EA on height should be zero, then GIV-U would accurately estimate this effect to be zero in the absence of environmental endogeneity. Instead, GIV-U reports a significant positive effect of EA on height. MR also reports a positive and statistically significant effect of EA on height. This upward bias in the MR estimate is strong evidence of pleiotropy bias that invalidates the IV in MR. The guidance from the simulations points to a true estimate of the effect of height on EA that is as small or smaller than the GIV-U estimate, which is 25% smaller than the estimate from MR. The extent of upward bias in the GIV-U estimate depends on the strength of environmental variables that simultaneously affected the height of HRS respondents and also affected their EA.

These results also point toward a productive strategy for learning more about the true effect of height on EA. The demonstration that pleiotropy as well as environmental bias is affecting the estimates in Table 2.3 implies that there is no effective fix for MR; its genetic instruments are contaminated by pleiotropy and therefore cannot be used to adjust for environmental endogeneity. Comparisons between

[11] Results from B. Bulik-Sullivan et al. (2015) and Okbay, Beauchamp, et al. (2016) suggest a genetic correlation between height and EA of about 0.15.

monozygotic twins would effectively control for pleiotropy, but unobserved environmental factors affecting height and EA could still bias the results from MZ twin data. The most productive strategy is arguably to use GIV-U and GIV-C as proxy strategies to address bias from pleiotropy while also correcting for environmental confounds either by controlling for the relevant environmental factors directly or by using data on siblings that allow controlling for shared environmental variables via family fixed-effects. With such data, the estimates from GIV-C and GIV-U would provide approximate bounds as long as the GIV-U estimate of the effect of EA on height was close to zero. If the negative control regression suggests bias from environmental sources, the GIV-U estimate will be more conservative than all of the other estimators considered in this paper, and it will underpredict the true effect unless positive bias from both pleiotropy and genetic-unrelated endogeneity is quite strong.

These results do not provide as clean and neat a conclusion as might be desired, although uncertainty is inevitable in the absence of experimental data or a valid IV. At the same time, the empirical example provides considerable insight into the implications of the available estimates. Our results strongly imply that OLS provides an upwardly biased estimate of the effect of height on EA. They also strongly imply that the MR estimate suffers from pleiotropy bias and that MR is not an effective strategy for determining whether and to what extent height affects EA. Other studies suggest that pleiotropy between EA and height is not extremely high (B. Bulik-Sullivan et al., 2015). Our simulation results therefore suggest that GIV-U either is a plausible estimate for the effect of height on EA if genetic-unrelated endogeneity is relatively strong or underpredicts this effect if the endogeneity is weaker. If the estimate of GIV-U continued to be positive and statistically significant in a sibling fixed-effects analysis, we would be rather confident that the effect is real and not an artifact of bias either from pleiotropy or from genetic-unrelated endogeneity. In other words, these results represent progress toward the goal of understanding how large the social advantage provided by height is in the process of EA given the existence of genetic confounds.[12]

2.6 Conclusion

Accurate estimation of causal relationships with observational data is one of the biggest and most important challenges in epidemiology and the social sciences—two fields of inquiry where many

[12] Obviously, none of the estimation strategies we discussed here address possible bias from nonrandom selection into samples.

questions of interest cannot be adequately addressed with properly designed experiments due to practical or ethical constraints. One important confound in nonexperimental data comes from direct pleiotropic effects of genes on the exposure and the outcome of interest. Both OLS and MR yield biased results in this case. We proposed GIV regression as an empirical strategy that controls for such pleiotropic effects using polygenic scores. GIV regression uses standard IV estimation algorithms such as two-stage least squares that are widely available in existing statistical software packages. Our approach provides reasonable upper and lower bounds of causal effects in situations when pleiotropic effects of genes are the only source of bias. We showed that OLS, MR, and GIV regression yield biased estimates if both genetic and environmental sources of endogeneity are present. However, GIV regression still outperforms OLS and MR in this scenario. Furthermore, GIV regression can (and should) be combined with additional strategies that allow controlling for bias from purely environmental or behavioral factors, such as using covariates or family-fixed effects. Together, these approaches can provide reasonable estimates of causal effects across a broad range of scenarios.

GIV regression is called for whenever an experimental design, a valid IV strategy, or a large-enough sample of MZ twins is not available and when pleiotropy is a potential problem—a situation that is frequently encountered in practice. The main requirements for GIV regression are a prediction sample that has been comprehensively genotyped and large-scale GWAS results for the outcome of interest from two nonoverlapping samples. Due to rapidly falling genotyping costs that enable a growing availability of genetic data and large GWAS samples for many traits, these requirements have become increasingly feasible for many applications. Indeed, the combination of new estimation tools and continued rapid advancements in genetics should provide a significant improvement in our understanding of the effects of behavioral and environmental variables on important socioeconomic and medical outcomes.

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2.8 Tables

Table 2.1 Illustrative results from simulations, estimated coefficient for T

Model	Parameter	OLS	MR	GIV-C	GIV-U
A	Pleiotropy only	1.1004	1.5040	1.0131	0.9419
	$h_y^2 = h_T^2 = 0.2$	(0.0001)	(0.0012)	(0.0001)	(0.0001)
B	Pleiotropy only	1.2011	1.5024	1.0604	0.8575
	$h_y^2 = h_T^2 = 0.4$	(0.0001)	(0.0004)	(0.0001)	(0.0001)
C	Pleiotropy only	1.3016	1.5020	1.1573	0.7263
	$h_y^2 = h_T^2 = 0.6$	(0.0001)	(0.0002)	(0.0001)	(0.0002)
D	Pleiotropy only	1.5004	3.4922	1.0776	0.8689
	$h_y^2 = 0.8, h_T^2 = 0.2$	(0.0005)	(0.0093)	(0.0002)	(0.0002)
E	Genetic Confounds	1.3106	1.4609	1.1922	0.6422
	$h_y^2 = h_T^2 = 0.5,$	(0.0001)	(0.0002)	(0.0001)	(0.0002)
	$\rho_{vy} = \rho_{vT} = 0.5$				
F	Nongenetic confounds	1.4520	1.5032	1.4259	1.1193
	$h_y^2 = h_T^2 = 0.5,$	(0.0001)	(0.0002)	(0.0001)	(0.0001)
	$\rho_e = 0.4$				
G	Non genetic confounds	1.3643	1.5064	1.3346	0.9587
	with control	(0.0001)	(0.0002)	(0.0001)	(0.0001)
	$h_y^2 = h_T^2 = 0.5,$				
	$\rho_e = 0.4, s = 0.5$				

Shown are mean estimated coefficient for *T* and SE within parentheses of 20 simulations using different estimation methods for several models. For all models the genetic correlation (ρ) was 0.5 and the coefficient for $T(\delta)$ was 1. $h^2{}_y$ and $h^2{}_T$ are the heritability parameters of *y* and *T*. ρ_{vy} is the correlation between *y* and the genetic confound for *y*. ρ_{vT} is the correlation between *T* and the genetic confound for *T*. ρ_e= 0.4 is the correlation between the nongenetic confound and *y*. *s* is the share of the confound that is controlled for in terms of variance of the confound. These results are a selection from *SI*, Tables S2.2–S2.4, S2.7, S2.9, S2.11, and S2.14; see *SI*, sections S2.2–S2.4 for all results. A, Table S2.2; B, Table S2.3; C, Table S2.4; D, Table S2.7; E, Table S2.9; F, Table S2.11; and G, Table S2.14. See row 2 of each table. See *SI*, Table S2.6 for more details on the parameters, variance, and standardized effect size.

Table 2.2 Effects of the polygenic score for educational attainment (PGS EA) on (residualized) educational attainment in the Health and Retirement Study (HRS)

	(1)	(2)	(3)
Variables	OLS	IV1	IV2
PGS EA Unc. UKB	0.259 ***	0.523 ***	
	(0.0183)	(0.0385)	
PGS EA SSGAC			0.530 ***
			(0.0389)
$\widehat{h^2}$	n.a.	0.134	0.138
	n.a.	(0.0197)	(0.0202)
N	2,751	2,751	2,751

**P*< 0.05, ***P*< 0.01, ****P*< 0.001. We regress the residual of EA on the different PGSs and calculate the implied heritability estimates. SEs are in parentheses. All variables have been standardized. EA is measured in years of schooling needed to obtain the highest achieved educational degree according to International Standard Classification of Education (ISCED) classifications. We use the residual of EA after a regression on birth year, birth year squared, gender, and the first 20 principal components in the genetic data. PGS EA SSGAC: PGS for EA using meta-analysis from Okbay, Beauchamp, et al. (2016), excluding data from 23andMe, UK Biobank (UKB), and HRS; PGS EA UKB, PGS for EA using UKB data. IV1 uses PGS EA SSGAC as instrument and IV2 uses PGS EA UKB as instrument. NA, not applicable.

Table 2.3 Estimates of the effect of height on educational attainment (EA)

Variables	OLS	MR	GIV-C	GIV-U
Height	0.136***	0.160***	0.168***	0.110***
	(0.0262)	(0.0481)	(0.0264)	(0.0262)
PGS EA cond. UKB			0.396***	
			(0.0367)	
PGS EA uncond. UKB				0.384***
				(0.0354)
N	2,751	2,751	2,751	2,751

**P*< 0.05, ***P*< 0.01, ****P*< 0.001. Standardized effect sizes and SEs are in parentheses. Birth year, birth year squared, gender, EA mother, EA father, and the first 20 principal components are included as control variables. For MR, a PGS for height from UK Biobank (UKB) data was used as instrument for height. For GIV-C and GIV-U PGS EA SSGAC was used as an instrument.

Table 2.4 Estimates of the effect of height on educational attainment (EA)

Variables	OLS	MR	GIV-C	GIV-U
EA	0.072*** (0.0138)	0.179** (0.0543)	0.050*** (0.0119)	0.040*** (0.0120)
PGS height cond. UKB			0.448*** (0.0174)	
PGS height uncond. UKB				0.446*** (0.0175)
N	2,751	2,751	2,751	2,751

*$P< 0.05$, **$P< 0.01$, ***$P< 0.001$. Standardized effect sizes and SEs are in parentheses. Birth year, birth year squared, gender, EA mother, EA father, and the first 20 principal components are included as control variables. For MR, a PGS for EA from UK Biobank (UKB) data was used as an instrument for EA. For GIV-C and GIV-U PGS height GIANT was used as an instrument.

Chapter 2

Supplementary Information

The Supporting Information (SI) for this article consists of six sections. In section 1, we provide technical details of the method for estimating narrow-sense SNP heritability from polygenic scores. In section 2, we discuss the details of GIV regression and why it provides more accurate estimates than OLS or MR for the case where measured SNPs have direct pleiotropic effects on the exposure and the outcome. In section 3, we discuss estimating the effects of an exposure in the presence of pleiotropy combined with other sources of endogeneity that are related to the observed genotypes (e.g. unobserved genetic variants, epistasis, genetic nurturing). Section 4 extends the possible sources of endogeneity further to cases that are unrelated to genetics (e.g. purely environmental unobserved confounds).

For each of these sections, we provide evidence from detailed simulations under a varying set of assumptions that cover a range of empirically-likely situations. Each of these simulations is generated at the level of individual SNPs. The SNP level simulations are used to generate data for the exposure and outcome variable in both the simulated GWAS samples and the replication sample and the simulated data are then used to estimate the parameters of interest using alternative methods.

Section 5 describes the data and methods used for our empirical examples, and we provide additional information about the empirical examples described in the article. The last section of the SI provides some practical guidelines for the usage of GIV regression.

S2.1 Estimating narrow-sense SNP heritability from polygenic scores

S2.1.1 Technical details

We begin by showing that consistent estimates of the chip heritability of a trait (i.e. the proportion of variance in a trait that is due to linear effects of currently measurable SNPs) can be obtained from polygenic scores. If y is the outcome variable, X is a vector of control variables including a constant, and $S^*_{y|X}$ is a summary measure of genetic tendency for y in the presence of controls for X, then one can write

$$y = X\beta + \gamma S^*_{y|X} + \epsilon \tag{S2.1}$$

where, for example, y is educational attainment. Typical variables in X would be age, gender, and the first twenty principal components in the genetic data as controls for population structure. If the heritability of y is caused by a large number of genetic loci, each with a very small effect (Chabris, Lee, Cesarini, Benjamin, & Laibson, 2015), we call y a "genetically complex trait." In this situation, the genetic liability for y cannot be adequately represented by just one gene. Rather, it is preferable to approximate the genetic liability with a polygenic score (PGS). The weights of each SNP that are summed up in the PGS are obtained from a GWAS on y in an independent sample (Dudbridge, 2013; McCarthy et al., 2008). In a GWAS, y is regressed on each SNP separately, typically including a set of control variables such age, sex, and the first few principal components of the genetic data to control for population structure (Price et al., 2006). Thus, the obtained estimates for each SNP do not account for correlation between SNPs (a.k.a. linkage disequilibrium LD), which may bias the PGS. In practice, several solutions are available to deal with this challenge, including pruning SNPs for LD prior to constructing the score (Abdellaoui & Al., 2013) or using a method that explicitly takes the LD structure between SNPs into account (e.g. LDpred, see (Vilhjælmsson et al., 2015)). The scores themselves ($S_{y|X}$) are linear combination of the elements in G weighted by the estimated coefficients, $\zeta_{y|X}$ obtained from

$$y = X\beta + G\hat{\zeta}_{y|X} + \epsilon \tag{S2.2}$$

where G is an $n\times m$ matrix of genetic markers, and $\hat{\zeta}_{y|X}$ is the $m\times 1$ vector of LD-adjusted estimated effect sizes, where the number of SNPs (the size of m in equation S2.2) is typically in the millions. If the true effects of each SNP on the outcome were known, the true genetic tendency ($S^*_{y|X}$) would be expressed by the PGS for y, and the marginal R^2 of $S^*_{y|X}$ in equation S2.1 would be the chip heritability of the trait. In practice, GWAS results are obtained from finite sample sizes that only yield noisy estimates of the true effects of each SNP. Thus, a PGS constructed from GWAS results typically captures far less of the variation in y than suggested by the chip heritability of the trait (Dudbridge, 2013; Daetwyler, Villanueva, & Woolliams, 2008; Witte, Visscher, & Wray, 2014). We refer to the estimate of the PGS from available GWAS data as $S_{y|X}$, and substitute $S_{y|X}$ for $S^*_{y|X}$ in equation S2.1. The variance of a trait that is captured by its available PGS increases with the available GWAS sample size to estimate ζ and converges to the true narrow-sense heritability of the trait at the limit if all relevant genetic markers were included in the GWAS and if the GWAS sample size were sufficiently large (Witte et al., 2014).

As reported in Dudbridge (2013) and Rietveld et al. (2013), the explained variance in a regression of a phenotype on its PGS can be expressed as

$$R^2_{y,S_y} = \frac{\left(\frac{n}{m}\right)h^4}{\left(\frac{n}{m}\right)h^2 + 1} \tag{S2.3}$$

where y is standardized, σ_g^2 is the genetic variance of y (i.e., the proportion of the variance in y explained by G), n is the sample size, and m is the number of genetic markers. For example, a PGS for EA based on a GWAS sample of 100,000 individuals would be expected to explain about 4% of the variance of EA in a hold-out sample (assuming there are 70,000 effective loci, all of them included in the GWAS, and a chip heritability of 20% (Rietveld et al., 2013)), even though the estimated total heritability of EA in family studies is roughly 40% (Branigan, McCallum, & Freese, 2013).

It has long been understood that multiple indicators can, under certain conditions, provide a strategy to correct regression estimates for attenuation from measurement error (Bielby, Hauser, & Featherman, 1977; Bollen, 2002). Instrumental variables (IV) regression using estimation strategies such as two stage least squares (2SLS) and limited information maximum likelihood (LIML) will provide a consistent estimate for the regression coefficient of a variable that is measured with error if certain assumptions are satisfied (Angrist & Pischke, 2009; Burgess, Small, & Thompson, 2015): (1) The IV is correlated with the problem regressor, and (2) conditional on the variables included in the regression, the IV does not directly cause the outcome variable, and it is not correlated with any of the unobserved variables that cause the outcome variable [13]. In general, these assumptions are difficult to satisfy. In the present case, however, GWAS summary statistics can be used in a way that comes close enough to meeting these conditions to measurably improve results obtainable from standard OLS regression and from standard Mendelian Randomization (MR) (Davey Smith & Hemani, 2014).

Multiple indicators of the PGS provide a theoretical solution to the problem of attenuation bias, and, we argue, a practical solution as well. The most straightforward solution to the problem is to split the GWAS discovery sample for y into two mutually exclusive subsamples. This produces noisier estimates of $S^*_{y|X}$, with lower predictive accuracy. However, it also produces an IV for $S^*_{y|X}$ that has desirable properties. Formally, we let $\hat{\zeta}_{y_1|X}$ be the estimated coefficient vector for $\zeta_{y|X}$ in equation S2.2 from the first training sample, and $\hat{\zeta}_{y_2|X}$ be the coefficient vector estimated from the second training sample. It follows then that

$$\hat{\zeta}_{y_{1j}|X} = \zeta_{y_j|X} + u_{y_{1j}|X}$$
$$\hat{\zeta}_{y_{2j}|X} = \zeta_{y_j|X} + u_{y_{2j}|X}$$

for the j-th genetic marker, where $u_{y_1|X}$ and $u_{y_2|X}$ are asymptotically normally distributed errors with $E\left(u_{y_{1j}|X}\right) = E\left(u_{y_{2j}|X}\right)$ and $V\left(u_{y_{1j}|X}\right) = V\left(u_{y_{2j}|X}\right) = \sigma_\epsilon^2 n^{-1}/var(x_j)$, and where x_j is the observed number of reference alleles for location j. In practice, the SNPs in $\hat{\zeta}_{y_1|X}$ and $\hat{\zeta}_{y_2|X}$ do not need to be exactly identical. Our derivations and results hold if the SNPs in both scores capture a sufficiently large amount of the SNP heritability of y, even if they are not the same SNPs. This is feasible because SNPs that are close to each on the same chromosome are often correlated with each other (a phenomenon referred to as linkage disequilibrium or LD), but the coefficient vectors $\hat{\zeta}_{y_1|X}$ and $\hat{\zeta}_{y_2|X}$ typically come from GWAS analyses that regress the outcome on one SNP at a time, ignoring the correlation structure between SNPs. Thus, neighboring SNPs that are correlated typically carry similar information about their contribution to y via $\hat{\zeta}_{y_1|X}$ and $\hat{\zeta}_{y_2|X}$ and can therefore we substituted with each other in the construction of the PGS.

Because the two discovery samples are non-overlapping, $u_{y_1|X}$ and $u_{y_2|X}$ would be independent of each other if the PGS model is correctly specified (we return to this point below). By applying the two vectors of estimated coefficients, we obtain two PGS,

$$S_{y_1|X} = S^*_y + v_1 = G\zeta_{y|X} + Gu_{y_1|X} = S^*_y + Gu_{y_1|X} \tag{S2.4}$$
$$S_{y_2|X} = S^*_y + v_2 = G\zeta_{y|X} + Gu_{y_2|X} = S^*_y + Gu_{y_2|X}$$

where G is the matrix of genetic markers for the analytical sample. We then rewrite equation S2.1 in terms of the observed first PGS as

$$\begin{aligned} y &= X\beta + \gamma S^*_{y|X} + \epsilon \\ &= X\beta + \gamma\left(S_{y_1|X} \ - Gu_{y_1|X}\right) + \epsilon \\ &= X\beta + \gamma S_{y_1|X} \ + (\epsilon - Gu_{y_1|X}) \end{aligned} \tag{S2.5}$$

As can be seen from equation S2.5, the PGS $S_{y_1|X}$ is correlated with the error term via its correlation with $Gu_{y_1|X}$ from equation S2.4. However, under the assumptions that equation S2.5 accurately describes the relationship between G and y and that the genetic architecture of the trait is identical across GWAS and prediction samples, then $S_{y_2|X}$ would meet the two requirements to be a valid instrument for $S_{y_1|X}$, if it is correlated with $S_{y_1|X}$ (through their mutual dependence on $S^*_{y|X}$) and if it is uncorrelated with the disturbance term. Clearly, the first requirement is met. Also, clearly $S^*_{y|X}(= G\zeta_{y|X})$ is not correlated with $Gu_{y_1|X}$. The remaining question, then is whether $Gu_{y_2|X}$ is correlated with $Gu_{y_1|X}$. The covariance of $Gu_{y_1|X}$ and $Gu_{y_2|X}$ is

$$\begin{aligned} Cov\left(Gu_{y_1|X}, Gu_{y_2|X}\right) &= E\left(\left[Gu_{y_1|X}\right]\left[Gu_{y_2|X}\right]\right) - \left(E\left[Gu_{y_1|X}\right]\right)\left(E\left[Gu_{y_2|X}\right]\right) \\ &= \ E\left(\left[Gu_{y_1|X}\right]\left[Gu_{y_2|X}\right]\right) \end{aligned}$$

This follows because each term of $Gu_{y_1|X}$ has the form $g_j u_j$ and the expectation of each of these terms is zero by virtue of the properties of OLS regression, namely that the residual has mean zero and is orthogonal to the regressors. Now,

$$\begin{aligned} E\left(\left[Gu_{y1|X}\right]\left[Gu_{y2|X}\right)\right. &= E\left\{\sum_{j=1}^{m} g_j^2 u_{y1j|X} u_{y2j|X} + \sum_{j=1}^{m}\sum_{k\neq j}^{m} g_j g_k u_{y1j|X} u_{y2j|X}\right\} \\ &= \sum_{j=1}^{m} E\left(g_j^2\right)E\left(u_{y1j|X}u_{y2j|X}\right) + \sum_{j=1}^{m}\sum_{k\neq j}^{m} E\left(g_j g_k\right)E\left(u_{y1j|X}u_{y2j|X}\right) \\ &= \sum_{j=1}^{m} E\left(g_j^2\right)E\left(u_{y1j|X}\right)E\left(u_{y2j|X}\right) \end{aligned} \tag{S2.6}$$

$$
\begin{aligned}
&+\sum_{j=1}^{m}\sum_{k\neq j}^{m} E\left(g_j g_k\right)E\left(u_{y1j|X}\right)E\left(u_{y2j|X}\right)\\
&=0
\end{aligned}
$$

where the third row follows because the coefficient errors for any given genetic marker from one sample will be independent of their value in a second independent sample. Now IV regression will be valid if the IV $S_{y_2|X}$ is uncorrelated with the error term in equation S2.5,

i.e., if

$$
\begin{aligned}
&plim\frac{1}{n}\sum_i \left(S_{y2|X}\right)_i (\epsilon_i - \left(Gu_{y1|X}\right)_i = plim\frac{1}{n}\sum_i \left(S^*_{y|X} + Gu_{y_2|X}\right)_i (\epsilon_i - \left(Gu_{y1|X}\right)_i \qquad \text{(S2.7)}\\
&= plim\frac{1}{n}\sum_i [\left(S^*_{y|X}\right)_i \epsilon_i + \left(S^*_{y|X}\right)_i \left(Gu_{y_1|X}\right)_i + \left(Gu_{y_2|X}\right)_i \epsilon_i + \left(Gu_{y_1|X}\right)_i \left(Gu_{y_2|X}\right)_i]\\
&= plim\frac{1}{n}\sum_i \left(Gu_{y_1|X}\right)_i \left(Gu_{y_2|X}\right)_i = 0
\end{aligned}
$$

A complexity in the present situation is that the condition in equation S2.7 does not automatically follow from equation S2.6, because the correlation in the sample is computed on the given coefficient errors that were generated via the regressions in the two GWAS samples. This is readily appreciated if the number of markers was very small. If this number m equaled one, for example, then clearly the sample average of the square of each person's genetic marker multiplied by two given coefficient errors would not be zero even though the coefficient errors themselves were independent random draws from a distribution with mean zero.

However, as we show through SNP-level simulations below, this condition will generally hold for genetically complex traits that have been investigated in large-scale GWAS. In particular, assuming that all measured SNPs are causal and independent and their effect sizes are drawn from a normal distribution, we find that even when the GWAS sample is smaller than is the number of SNPs, IV estimation with $S_{y2|X}$ as the instrument for $S_{y1|X}$ does a very good job of recovering the true coefficient for S_y^* across a range of scenarios. In practice, SNPs are not independent because of linkage disequilibrium. However, there are more than 1,000,000 approximately independent loci (i.e. groups of SNPs that vary together) in 1000 Genomes imputed data that might potentially affect traits (Auton et al., 2015).. And even after stringent quality control and filtering of GWAS summary statistics, typically at least 200,000 LD-independent loci remain (Bansal et al., 2017). If only independent loci are used in the construction of the PGS, it is reasonable to assume that the independence assumption holds so long as the polygenic score is not dominated by a relatively small number of loci. If we then assume that genetic effects on y stem from both correlated and uncorrelated markers, the situation becomes only slightly more complicated. As mentioned above, the practical challenge is that the coefficient vector $\zeta_{y|X}$ typically comes from GWAS analyses that regress the outcome on one SNP at a time, ignoring the correlation structure between SNPs. The statistical dependence among SNPs in the construction of PGS is then dealt with in one of various ways. One obviously suboptimal solution is to ignore LD structure entirely and to construct the PGS using all available SNPs and their univariate coefficients. In practice, this naive solution often performs relatively well, although not as good as more sophisticated approaches. A second solution is to use LD-pruning. In this approach, only the most strongly associated SNP in each independent locus is used to construct the score, and the score consists of tens or even hundreds of thousands of approximately independent SNPs (Wray et al., 2014). Finally, there are algorithm such as LDpred (Vilhjælmsson et al., 2015) that infer the LD-corrected, multivariate coefficients of each SNP from the original GWAS results taking all SNPs and their actual correlation structure into account. LDpred is the current best practice solution to construct PGS because it yields slightly better predictive performance than ignoring LD-structure or LD-pruning.

Our formal derivations until now assumed that the true coefficients of the genetic markers in G do not vary in the population. More generally, we might assume that the population consists of a finite number of (possibly latent) groups, $k = 1,...,K$ with the kth group having the polygenic score $S_{yk|X}^*$. Absent information about the specific number of groups and the group memberships of individuals in any specific population, the polygenic score that would be estimated from a sufficiently large sample from that population would be a weighted average of the scores for each group, with the weights dependent on the proportion each group is of the total population (Angrist & Pischke, 2009). Any population P therefore can be characterized in terms of its group composition, p_1,p_2,...,p_K. The above results apply straightforwardly when the PGS are estimated and analyzed using samples from a single group. When they are instead estimated on a population that is a mixture of groups, the situation is more complicated. The true PGS for any individual who is in group k can be expressed as

$$S^*_{yk|X} = \bar{S}^*_{yP|X} + \Delta_{yk|X}$$

where P = {p_1,p_2,...,p_K} is the group composition that defines population P and $\Delta_{yk|X}$ is the deviation between the group k specific PGS for trait y and the population average (for population P). Under this elaboration, equation S2.5 can be written as

$$\begin{aligned} y_{ik} &= X_i\beta + \gamma S^*_{yik|X} + \epsilon_i \\ &= X_i\beta + \gamma\left(\bar{S}^*_{yP|X} + \Delta_{yk|X}\right) + \epsilon_i \\ &= X_i\beta + \gamma\bar{S}_{y1iP|X} + \left(\epsilon_i + \gamma\Delta_{yk|X} - \gamma v_{1i}\right) \end{aligned}$$

Where the $S^*_{yik|X}$ is the true PGS for trait y for individual i in group k, and where $\bar{S}_{y1iP|X}$ is the first

the first polygenic score estimated using coefficients from the GWAS sample drawn from population P. Variation in true PGS by group creates the possibility that the exclusion restriction will be violated. If $\bar{S}_{y2P|X}$ is the IV, then $\bar{S}_{y2P|X}$ is correlated with $\Delta_{yk|X}$ to the extent that the true PGS differs by group and to the extent that the weighted average deviation of the true PGS estimated from each individual's group and the true PGS estimated from the other groups correlates with the PGS for the population P. If the two PGS scores were estimated on one pure group and the analysis sample was for a second pure group, then the deviation between the two PGS would of course correlate with the PGS for one of the groups, and the exclusion restriction would be violated unless the SNP coefficients of the PGS for the one group were the same as the beta coefficients of the PGS for the other group. If the analysis sample and the GWAS samples are drawn from the same population (i.e., the same mixture of groups), we would expect the correlation between the deviations for analysis sample members (drawn from each of the groups in the same proportion as the GWAS sample) and the true PGS for the GWAS sample to be very small. If the population consists only of a single group or, equivalently, if all groups have the same SNP coefficients in their PGS for trait y, then the issue of group-specific heterogeneity in PGS disappears.[1]

When PGS for y are used that were constructed with a different set of control variables than are used in the regression, the above results need to be modified. Let us assume that variables χ were controlled in the GWAS and variables X are controlled in the regression model. Then

$$\begin{aligned} y &= X\beta + \gamma S^*_{y|\chi} + \{S^*_{y|X} - S^*_{y|\chi} + \epsilon\} \\ &= X\beta + \gamma S^*_{y|\chi} + \{Gd_{yX\chi} + \epsilon\} \end{aligned}$$

where $d_{yX\chi}$ is the vector of differences in the effects of genetic markers on y when X is controlled and when χ is controlled. If a finite sample PGS of y is constructed using χ as controls, i.e., $S_{y1|\chi}$, and this finite sample PGS is used in place of $S_{y1|X}$ as a proxy for $S^*_{y|X}$ in model 1, one obtains

$$y = X\beta + \gamma S_{y1|\chi} + \left(Gd_{yX\chi} - Gu_{y1|\chi} + \epsilon\right)$$

where

$$S_{y1|\chi} = S^*_{y|\chi} + Gd_{yX\chi} + Gu_{y1|\chi}$$

The problem now is that using $S_{y2|\chi}$ as an IV would violate the exclusion restriction to the extent that $d_{yX\chi}$ differs from zero, because $Gd_{yX\chi}$ is both in $SS_{y2|\chi}$ and in the error, and because $S^*_{y|\chi}$ would generally be correlated with $Gd_{yX\chi}$. The extent of bias would depend on the extent to which the effects of the genetic markers on y differ when X and when χ are controlled.

Once a consistent estimate for $\hat{\gamma}$ has been obtained, it is possible to derive an estimate of the narrow-sense SNP (or chip) heritability of y. In a univariate linear regression model with standardized variables,

[1] This issue is similar to the attenuation of predictive accuracy of a PGS that results from an imperfect genetic correlation between the GWAS summary statistics in the hold-out sample and the GWAS summary statistics in the discovery sample (de Vlaming et al., 2017).

the squared regression coefficient is equal to R^2 . This follows directly from the definition of R^2 as the variance of y explained by X as a fraction of total variance of y. Thus, γ^2 in 1 can be thought of as the narrow-sense chip heritability of y if both y and $S^*_{y|X}$ are standardized variables with mean zero and a standard deviation of one (assuming the controls included in X are not correlated with genotype G). In practice, however, the estimate $\hat{\gamma}^2$ originates from a regression on a PGS that contain measurement error ($S_{y1|X}$ or $S_{y2|X}$) rather than on the true PGS $S^*_{y|X}$. In particular, the obtained regression coefficient $\hat{\gamma}$ will be standardized using the variance of $S_{y1|X}$ or $S_{y2|X}$ instead of the variance of $S^*_{y|X}$. [2] It turns out that this implies that the heritability estimate $\hat{\gamma}^2$ is biased by a factor equal to $var(S_{y|X})/var(S^*_{y|X})$, which simplifies to $1/var(S^*_{y|X})$ if the observed score was standardized.[2] However, it is possible to derive a simple error correction because one can estimate the variance of $S^*_{y|X}$ by estimating the covariance of $S_{y1|X}$ and $S_{y2|X}$:

$$cov\left(S_{y1|X}, S_{y2|X}\right) = cov\left(S^*_{y|X} + e_{y1}, S^*_{y|X} + e_{y2}\right) = \rho\left(S_{y1|X}, S_{y2|X}\right) = var\left(S^*_{y|X}\right).$$

With an estimate of $var\left(S^*_{y|X}\right)$. at hand, we can back out an unbiased heritability estimate:

$$h^2_y = \hat{\gamma}^2 var(S^*_{y|X})/var(y).$$

When y is standardized, $var(y) = 1$, the error correction simplifies to

$$h^2_y = \hat{\gamma}^2 \rho\left(S_{y1|X}, S_{y2|X}\right).$$

An estimate of the standard error of $h^2{}_y$ can be obtained using the Delta method (Davidson & MacKinnon, 2004).[3]

S2.1.2 Simulations

Our first set of simulations are based on the following model for y:

$$y = \gamma_1 + \gamma_2 S^*(y) + \epsilon$$

[2] We thank Elliot Tucker-Drob for pointing this out to us.

[3] See Tucker-Drob (2017) for an alternative correction method.

We generate S^* using varying numbers of independently drawn genetic markers from 1,000 to 300,000 – up to the memory limits of our processor nodes (512 GB) – with a minor allele frequency of 0.5 and coefficients for these genetic markers.[4] The constant γ_1 is set to zero and the coefficients for the genetic markers are drawn from a normal distribution. We also draw from a normal distribution. The variance of the distributions for and the coefficients of the genetic markers are set such that the heritability is correct and the variance of y is equal to 1 (i.e. y is standardized). We use this data generating process to produce two independent samples, which together constitute the GWAS sample. We specify varying sizes of the total GWAS sample from 50,000 to 500,000 observations. We generate these data under three different assumptions about the SNP heritability of y, namely that h^2 is alternately set to 0.1, 0.3, and 0.5. We then use the two independent GWAS samples to estimate the effect of each marker twice, using bivariate regressions of y on each of the individual markers. In a third independent sample (N = $10{,}000$) we construct the PGS for y, which we designate as $S(y_1)$ and $S(y_2)$, using the two GWAS estimates.

We then estimate the effect $\hat{\gamma}_2$ of the PGS for y on y. We do this using an IV regression with $S(y_2)$ as the IV for $S(y_1)$. In other words, we use OLS to estimate the second stage model

$$y = \gamma_1 + \gamma_2 \hat{S}(y_1) + \epsilon$$

where the predicted value of $S(y_1)$ is obtained via estimates from a first stage regression of

$S(y_1)$ on $S(y_2)$, i.e.,

$$\hat{S}(y_1) = \hat{\beta}_1 + \hat{\beta}_2 S(y_2)$$

The standardized coefficient estimate $\hat{\gamma}_2$ from the second stage regression is used to obtain an estimate for h^2 via the equation

$$h^2 = \hat{\gamma}_2^2 \left(corr\big(S(y_1), S(y_2)\big)\right).$$

[4] Assuming a MAF of 0.5 for all markers is unlikely to affect our results beyond statistical power.

Table S2.1 shows the results of these simulations where we do 20 simulations for each condition and report average results in the table. Panel (a) presents simulations where the SNP heritability is set to 0.1. As can be seen in panel (a), the estimated heritability is very close to the true heritability so long as the GWAS sample size is as large or larger than the number of SNPs that are included in the computation of the PGS. Also, for all simulations where the GWAS sample exceeds the number of SNPs, the standard errors are small relative to the estimate. In panel (b), we simulate using a heritability of 0.3 and we obtain an accurate estimate with a relatively small standard error when the GWAS sample is as large or larger than the number of SNPs. The same result is obtained when the data are generated with a heritability of 0.5. Generally speaking, we observe that the sample size needed for an accurate estimate of heritability has an inverse relationship with the size of the heritability. Thus, 50,000 cases is not sufficient to estimate heritability precisely when the true SNP heritability is 0.1 and the number of SNPs is 100,000, and 100,000 cases produces an accurate estimate but a fairly large standard error. The precision of the estimates increases considerably for both of these cases, however, when the true SNP heritability is 0.3, and even 50,000 cases is sufficient to produce a precise and accurate estimate of heritability when the true SNP heritability is 0.5 and the number of SNPs is 100,000 or fewer. As mentioned above, most practical applications will be based on more than 100,000 independent SNPs, although many of them may actually have a true effect of zero. Hence, the remaining causal loci for y will tend to have slightly larger true effects than we simulated here under the assumption that all SNPs are causal. Slightly larger SNP effects imply better statistical power in GWAS analyses and a more favorable ratio of estimated effect sizes to their standard errors. Thus, our simulation results are likely to be conservative lower bounds for the accuracy that our method can achieve for estimating heritability in real data.

S2.2 Reducing bias due to direct pleiotropic effects on exposure and outcome

We next address situations where the question of interest is not the SNP heritability of y per se, but rather the influence of some non-randomized exposure T on y (e.g. a behavioral or environmental variable, or a non-randomized treatment due to policy or medical interventions). We rewrite equation S2.1 such that

$$\begin{aligned} y &= \delta T + X\beta_y + \gamma S^*_{y|XT} + \epsilon_y \\ &= \delta T + X\beta_y + G\zeta_{y|XT} + \epsilon_y \end{aligned} \tag{S2.8}$$

Where

$$\begin{aligned} T &= \alpha S^*_{T|X} + X\beta_T + \epsilon_T \\ &= G\xi_{T|X} + X\beta_T + \epsilon_T \end{aligned} \tag{S2.9}$$

where, for example, y could be educational attainment and T could be body height and where we assume that the disturbance term is uncorrelated with genetic variables. We drop the subscript on the coefficients on the exogenous control variables X below when it would not lead to confusion. In each case, it is presumed that the outcome variable is to some extent caused by genetic factors, and the concern is that the genetic propensity for the outcome variable is also correlated with the treatment represented by T in equation S2.8. We now use $S^*_{y|XT}$ rather than $S^*_{y|X}$ in the equation, where$S^*_{y|XT}$ is the linear combination of the effects of SNPs on y when T is controlled. Given that T is in the model, the effect of individual SNPs on y will generally involve a direct effect net of T (ζ) and an indirect effect stemming from the combination of their effect on T (ξ) and the effect of T on y.

Adding the true conditional score $(S^*_{T|X})$ as a control variable to a regression of Y on T would eliminate bias arising from direct pleiotropy. Pleiotropy leads to omitted variable bias from the failure to control for the (possibly tens of thousands of) individual SNPs in the structural model that influence both Y and T directly. So imagine a model that contained tens of thousands of variables for the SNPs and a sample large enough and computers capable enough of estimating the coefficients of this model using OLS. Aside from the enormous number of regressors, this is a standard regression problem. Under standard conditions and if uncontrolled pleiotropy is the only source of bias, then the the coefficients of the SNPs converge in probability to the true coefficients while the coefficient on T converges in probability to its true value. In other words, the sum of the SNPs multiplied by their coefficients converges in probability to the true conditional PGS $S^*_{y|XT}$. Thus, controlling for tens of thousands of SNP variables in the structural model becomes closer and closer to controlling for the true conditional PGS in sufficiently large samples. Of course, in sample sizes that are currently available or that might be available in the foreseeable future, we are very far from being able to use direct controls for the individual SNPs in order to address the pleiotropy problem. However, proxies for $S^*_{y|XT}$ are already available.

If the true $S^*_{y|XT}$ is not observed and cannot be explicitly controlled in equation S2.8, it is part of the disturbance term. If so-called Type 1 pleiotropy is present (Davey Smith & Hemani, 2014), then *T* itself is a function of the same genetic markers that have other effects on y that do not operate through T, and the coefficients of these markers on T (ξ), which represent the indirect effects of the markers on y that operate through T, are correlated with the direct effects of the markers on y (ζ) when *T* is controlled in equation S2.8. Because of the correlation between *T* and $S^*_{y|XT}$ (which along with ϵ_y is in the disturbance term in equation S2.8), $\hat{\delta}$ will be a biased estimate of the effects of *T.*

While the true $S^*_{y|XT}$ is unknown, we may be able to obtain a proxy $S_{y|XT}$ for it from GWAS in finite sample sizes. While it is not guaranteed, the general conclusion of the literature is that the use of proxy variables such as $S_{y|XT}$ is an improvement over omitting the variable being proxied (Wickens, 1972; Aigner, 1974). However, if the proxy is measured with error, some bias will remain. More specifically, if $S_{y|XT}$ is used instead of $S^*_{y|XT}$ in equation S2.8, we get

$$S_{y|XT} = S^*_{y|XT} + Gu_{y|XT} = S^*_{y|XT} + v$$

which yields

$$y = \delta T + X\beta + \gamma S_{y|XT} + (\epsilon_y - \gamma v) \tag{10}$$

The problem now is that $S_{y|XT}$ is constructed from a large number of regressions of one genetic marker at a time along with the control variable *T.* The presence of *T* in the GWAS regressions for y produces estimated coefficients for the markers, G, that are functions of T. The error in the conditional PGS for y is a function of the coefficient estimates for the individual genetic markers and therefore is correlated with T. The estimation error plus pleiotropy produces a correlation between T and v, which still induces bias in OLS estimates of δ. Thus, while the use of a proxy control such as $S_{y|XT}$ will generally reduce bias in the estimated effect of δ, some bias will remain as long as $S_{y|XT}$ is measured with error.

Because of its relevance later on, we also note that the problem cannot be solved by constructing a PGS for y that is unconditional on T, i.e., $S_{y|X}$. The use of $S_{y|X}$ instead of $S_{y|XT}$ produces an over-control, where an estimate of the total effect of each genetic marker is controlled instead of just the direct effect. This over-control would produce a severe downward bias in the estimate of δ. To see this, imagine that there are only two genetic markers, g_1 and g_2, where

$$T = \xi_1 g_1 + \xi_2 g_2 + e_T$$

and therefore, where

$$\begin{aligned} y &= \delta(\xi_1 g_1 + \xi_2 g_2 + e_T) + \zeta_1 g_1 + \zeta_2 g_2 + e_y \\ &= (\delta\xi_1 + \zeta_1) g_1 + (\delta\xi_2 + \zeta_2) g_2 + \delta e_T + e_y \\ &= (0S_T^* + \delta e_T) + \gamma S_y^* + e_y \end{aligned} \tag{S2.11}$$

Note that the effects $\delta\xi_k + \zeta_k$ represent the total effect of g_k on y and provide the reduced form for the structural model in equation S2.8 if T is omitted from the model. As can be seen in equation S2.11, a control for the true unconditional PGS for y S_y^*) would be expected to produce an estimated effect of T that biased towards zero. Substituting the proxy S_y for S_y^* would not eliminate the downward bias entirely.

In standard MR, a measure of genetic tendency ($S_{T|X}$) for a behavior of interest (T in equation S2.8) is used as an IV in an effort to purge $\hat{\delta}$ of bias that arises from correlation between T and unobservable variables in the disturbance term under the argument that the genetic tendency variable, e.g., the measured PGS $S_{T|X}$, is exogenous (Burgess et al., 2015; Burgess, Butterworth, Malarstig, & Thompson, 2012). This approach would generally be successful if the endogeneity in the error term is from nongenetic sources and, consequently, if the genetic information in the IV for T is uncorrelated with the error term. In the absence of pleiotropy and other forms of genetic endogeneity (e.g., genetic nurturing), MR should be an effective strategy if the IV is strong enough to provide reasonable precision in the estimator.

However, MR becomes problematic when genetic variables in the error term are affecting y net of T while at the same time are correlated with the genetic variables in the equation for T, in other words, when ξ is correlated with ζ in equations S2.8 and S2.9. An example of this situation would be the use of a PGS for height as an instrument for height in a regression of the effect of height on educational attainment. The second stage regression in MR, then, takes the form

$$y = \delta\hat{T} + X\beta + \{\epsilon_y + \gamma S^*_{y|XT} + \delta(T - \hat{T})\} \tag{S2.12}$$

The problem with this approach is that the PGS for height will typically fail to satisfy the exclusion restriction because of pleiotropy: the genetic variants that predispose individuals to be tall may also directly increase the predisposition for higher educational attainment (Bulik-Sullivan et al., 2015; Okbay, Beauchamp, et al., 2016) (e.g. via healthy cell growth and metabolism). Because ξ is correlated with ζ, $S^*_{T|X}$ is correlated with $S^*_{y|XT}$. This problem is not solved even if we could use the true PGS S^*_T as the IV, because the genetic effects in S^*_T are correlated with the genetic effects in

$S^*_{y|XT}$. Whether the endogeneity bias from pleiotropy is big enough to offset MR's potential advantages for addressing the endogeneity from non-genetic sources is an empirical question that depends on the specific situation. The problems that pleiotropy creates for MR could be solved if the true genetic propensity for y, net of T could be directly controlled in the regression.[5] Unfortunately, this is not possible because the best we can do is to use $S_{y|XT}$ as a proxy for $S^*_{y|XT}$.

Endogeneity bias that stems purely from non-genetic sources can sometimes be addressed through the use of non-genetic IVs that are available from randomized clinical trials (RCTs) or from natural experiments. It can also sometimes be addressed through the use of fixed effects strategies when data on siblings or dizygotic twins is available. It can also often be reduced by controlling for observable variables that affect both the "assignment" to T and also the outcome variable. However, in the absence of data from RCTs, endogeneity bias from genetic sources is a difficult problem, and certainly one that MR does not directly address. We therefore first discuss the cases where all the endogeneity bias is from genetic sources, whether pleiotropy alone or pleiotropy in combination with other genetic confounds. We subsequently address the implications of endogeneity bias that emerge from both genetic and non-genetic sources.

S2.2.1 Reducing bias from pleiotropy

First, we assume that the *only* source of endogeneity in equation S2.8 is pleiotropy, and we examine the performance of a set of estimators intended to reduce its impact. The first strategy is to reduce the correlation between the instrument S_T in MR and the error by controlling for a proxy of $S^*_{y|XT}$, namely $S_{y1|XT}$. We refer to the combined use of $S_{y|XT}$ as a control and $S_{T|X}$ as an IV as "enhanced Mendelian Randomization" (EMR). Controlling for $S_{y|XT}$ as a proxy for $S^*_{y|XT}$ is not fully adequate because the error in $S_{y|XT}$ (i.e., $S^*_{y|XT} - S_{y|XT}$) is correlated with $S_{T|X}$. As noted previously, the use of a proxy control should improve the quality of the estimate for δ. However, as we show below, the pleiotropy bias at levels that would be expected to occur for real-world applications creates serious problems for MR as an effective strategy for obtaining accurate estimates of δ even if $S_{y|XT}$ is included as a control variable.

[5] Note that this approach would not solve problems caused by other sources of genetic endogeneity such as environmental effects in the error term that were correlated with parental genes, which themselves are correlated with the genetic information in $S_{T|X}$.

The second set of strategies drop the use of S_T as an instrument because it is not a valid instrument in the presence of pleiotropy and is not of practical utility in this situation either, as we show below. Instead, we start with the well-known formula for endogeneity bias for a generic OLS with dependent variable y, included covariates X, and coefficients of these covariates contained in the vector β, namely

$$\begin{aligned}\hat{\beta} &= (X'X)^{-1}X'y \\ &= (X'X)^{-1}X'(X\beta + \epsilon) \\ &= \beta + (X'X)^{-1}X'\epsilon\end{aligned}$$

So

$$E\left[\hat{\beta}\middle|X\right] = \beta + E[(X'X)^{-1}X'e|X] \tag{S2.13}$$

In other words, the coefficient bias from OLS is the expected regression coefficient of the error on the included variables in the regression. If is the sum of an omitted variable that we can label as z, which is correlated with the regressors and additional variables that are uncorrelated with the regressors, then the bias for each coefficient β_k in the vector β in equation S2.13 becomes the product of the regression coefficient for x_k in the regression of z on all the omitted variables multiplied by the effect of z on the outcome.

For simplicity, we assume that the only variables in the regression are T and a potential proxy for $S^*_{y|XT}$, which we call $S_{y|XT}$. For any given proxy, $S_{y|XT}$, the bias in the estimate of δ (the coefficient for T in equation S2.8) comes from the expected coefficient on T in the regression of $\gamma S^*_{y|XT} - \tilde{\gamma} S_{y|XT}$ and T on $S_{y|XT}$. We consider three alternatives as proxies for $S^*_{y|XT}$. First, we use $S_{y|XT}$, i.e. the conditional PGS for y from the full GWAS sample, in a simple OLS regression.[6] Second, we attempt to adjust for measurement error in $S_{y|XT}$ by constructing the predicted conditional PGS for y, called $\hat{S}_{y1|XT}$,by using $S_{y2|X}$ (the unconditional PGS for y) as an IV for $S_{y1|XT}$ where GWAS coefficients for $\hat{S}_{y1|XT}$, and $S_{y2|X}$

[6] We also estimate versions of this model using only the first half of the GWAS sample to be able to compare results across methods while holding GWAS sample size constant. We call the resulting score $S_{y1|XT}$ and we present both sets of estimates in our simulation results.

are obtained from non-overlapping GWAS samples of the same population. We call this approach, where $\hat{S}_{y1|XT}$ (the predicted conditional PGS for y) is used as the regressor in the second stage, "conditional GIV regression" (GIV-C).

We generally expect the use of GIV-C to perform better than the use of the proxy $S_{y|XT}$ in simple OLS. Recall that where the true effect of T on y is positive and in the presence of positive pleiotropy, the estimated effect of T on y will have positive bias. This follows from the positive correlation between $S^*_{y|XT}$ and T and from the positive effect of $S^*_{y|XT}$ (which is a component of the error) on y. The presence of the proxy $S_{y|XT}$ with simple OLS adds a partially offsetting negative bias, because the correlation between $S_{y|XT}$ and T is positive and the effect $\tilde{\gamma}_{OLS}$ is also positive, but $\hat{\gamma}_{OLS}S_{y1|XT}$ is being subtracted, which causes the offsetting bias to be negative. The net bias is expected to be smaller with the inclusion of the proxy than with no proxy at all, but we still expect it to be positive both because the correlation between T and $S_{y|XT}$ would be lower than between T and $S^*_{y|XT}$, and because we expect $\hat{\gamma}_{OLS}$ to be attenuated relative to γ.

When GIV-C is used instead of simple OLS, the term in the error becomes

$$\gamma S^*_{y|XT} - \hat{\gamma}_{IVC}\hat{S}_{y1|XT} \qquad \text{(S2.14)}$$

The presence of T as a regressor in the first and second stages of GIV-C, which is correlated with $S^*_{y|XT}$, prevents the IV strategy from obtaining a consistent estimate of γ. Nonetheless, we would generally expect $\hat{\gamma}_{IVC} > \hat{\gamma}_{OLS}$ and therefore we expect the positive bias for the estimate of δ to be smaller when using GIV-C than when estimating δ using simple OLS with the proxy $S_{y|XT}$.

We also employ a third estimator that substitutes the unconditional PGS for y (i.e., substitutes $S_{y1|X}$ for the conditional PGS $S_{y1|XT}$) as the proxy control in the structural model in equation S2.8. We then use $S_{y2|X}$ (the same IV as with GIV-C) to predict $S_{y1|X}$, obtaining $\hat{S}_{y1|X}$ as the regressor in the second stage. We call this third approach "unconditional GIV regression" (GIV-U). With GIV-U, the problem term in the error is

$$\gamma S^*_{y|XT} - \hat{\gamma}_{IVU}\hat{S}_{y1|X} \qquad \text{(S2.15)}$$

As before, the presence of the first term produces a positive bias in the estimate of δ, while the second term produces an offsetting negative bias. The offset will be stronger when $S_{y1|X}$ is used as the covariate in the structural model than when $S_{y1|XT}$ is used because the coefficients of the genetic markers in $S_{y1|X}$ are $\hat{\delta}\hat{\xi} + \hat{\zeta}$, where ξ is the effect of the genetic marker on T. The presence of $\hat{\delta}G\hat{\xi}$ in the second term in the error produces a stronger downward bias. This downward bias is made still stronger by the use of $\hat{\gamma}_{IVU}$ instead of $\hat{\gamma}_{OLS}$ as the coefficient, because we expect the first stage regression to reduce the downward bias of $\hat{\gamma}_{OLS}$.

To summarize, we expect these three proxies to behave differently in the simulations, and, as we will see, this expectation is met in practice. It turns out to be the case that GIV-C and GIV-U provide upper and lower bounds for the effect of T across a range of plausible scenarios for pleiotropy and for heritability.

S2.2.2 Evidence from simulations

To address the utility of these estimators, we conducted a set of simulations. We first discuss simulations under various assumptions about endogeneity and heritability for the case where the data generation model includes an effect of T on y. After discussing each of the relevant scenarios, we will then revisit each of these scenarios and examine the performance of the alternative estimators using a data generation process in which there is no effect of T on y.

We simulated data for two independent GWAS samples and for an independent prediction sample. The data generating process for the pleiotropy analysis is as follows:

$$T = \alpha S_T^* + \epsilon_T, \quad \epsilon_T \sim N(0, \sigma_\eta^2)$$
$$y = \gamma S_{y|T}^* + \delta T + \epsilon_y, \quad \epsilon_y \sim N(0, \sigma_\epsilon^2)$$

$S_{y|T}^*$ and S_T^* were constructed from the simulation of 10,000 independent genetic markers and coefficients for these genetic markers. The coefficients for these markers are drawn from a joint multivariate normal distribution, where the correlation between the ζ_i for $S_{y|T}^*$ and the ξ_i for S_T^* (see equations S2.8 and S2.9) is varied in order to simulate varying degrees of pleiotropy (this genetic correlation is labelled as ρ in Tables S2.2- S2.14). Each simulation is based on a GWAS combined sample of 100,000 with 10,000 SNPs, a third independent prediction sample of 10,000 and twenty repetitions. We use these values because they are large enough to reveal the essential properties of the estimators under the alternative conditions considered in the tables.

T is standardized and has a mean of 0 and a variance of 1. The variance of the true polygenic scores ($S^*_{y|T}$ and S^*_T) are simulated to match the heritability of the two traits. Furthermore, y is standardized when T has no causal effect ($\delta = 0$) and in absence of pleiotropy. When δ is 1 and in the absence of pleiotropy, the variance of y is equal to 2. When pleiotropy increases, the scale of the coefficients of the markers is kept constant to minimize the parameter changes across simulations and thus the variance of y increases. See table S2.16 for a list of parameters with the matching variance and heritability of y, and the standardized effect size of T. We do not include any X variables in the simulations, because they are not needed in order to analyze the essential issues.

In these simulations, we vary the amount of genetic correlation as well as the heritability for both y and T.[7] In the tables below, we report average coefficient estimates and standard errors across 20 repetitions for each model. We also limit the simulations below to the case of positive pleiotropy. In practice, this corresponds to a state of knowledge where the analyst either knows the sign of the pleiotropy correlation, or knows that it is weak but is uncertain whether it is weak positive or weak negative.

Tables S2.2, S2.3, S2.4, and S2.5 show the results of this set of simulations where we vary both the extent of heritability (h^2) for T and for y and the strength of the genetic correlation (ρ) between the effects of SNPs on T and their effect on y, net of T (i.e., between ζ and ξ). Each of these columns has four panels across the columns:

[7] There is a logical relationship between the level of heritability for T and y, the strength of the correlation between the effects of genetic markers on T and on y, the size of the effect of T on y in the structural model for y, and the error variance in the equations for T and y. These logical relationships make some combinations of heritability and genetic correlation impossible, but we explore a wide range of the possible values in the simulations below.

- The first panel reports the OLS estimates of y on T with no additional controls.
- The second panel reports estimates that are based on MR, i.e., that use S_T as an instrument for T. The column labelled MR only includes T as the regressor and uses S_T as the as the IV. Column EMR-1 is a version of enhanced MR that uses S_T as an IV along with a control for S_{y1} in an effort to reduce pleiotropy. Column EMR-2 uses $S_{y1|T}$ as the control and uses two IVs, namely S_T and S_{y2}.
- The third panel, which is labelled "Conditional Proxy PGS", uses versions of the conditional PGS for y as a proxy control for $S^*_{y|T}$. The column labelled as "OLS S(*y/T*)" uses the conditional PGS for y from the entire GWAS sample as the proxy control. The column labelled as "OLS S(y_1| *T*)" uses the conditional PGS for y from the first half of the split GWAS sample as the proxy control. The column labelled as GIV-C uses the conditional PGS for y from the first GWAS sample as the proxy control but it uses S_{y2} as the IV. S_T is not used as an IV in any of these models.
- The fourth panel, which is labelled "Unconditional Proxy PGS," uses versions of the unconditional PGS for y as a proxy control. The first column (OLS S(*y*)) uses the unconditional PGS from the full GWAS sample (S_y) as the proxy control. The second column, which is labelled as "OLS S(y_1)" uses the unconditional PGS for y from the first half of the split GWAS sample (S_{y1}) as the proxy control. The column labelled as GIV-U uses the unconditional PGS for y from the first GWAS sample (S_{y1}) as the proxy control but it uses S_{y2} as its IV. S_T is not used as an IV in any of these models.

Each of the tables has six sets of rows. The first three panels down the rows present simulations where the true effect of T on y is 1.0. These rows show the ability of the various estimators to recover an accurate estimate of T when T actually has an effect on y. The second three panels present simulations where T is specified to have no effect on y. It is worth pointing out that T can be correlated with y (e.g., via a pleiotropic correlation between ξ and ζ) without it necessarily being the case that T has a causal effect on

y. It could be the case that T and y are correlated (partly) because y is a cause of T. It could also be the case that T and y are correlated with neither variable causing the other. These rows show the extent to which an estimator will erroneously report that T affects y when in reality it has no effect.

Table S2.2 shows the results under the conditions of modest heritability for both y and T, where we vary the genetic correlation (ρ) between ζ and ξ (i.e., between the effect of SNPs on T and on y, net of T) between 0.2 and 0.8. As can be seen in the first three row panels for Table S2.2, the MR estimate for T is upwardly biased, and the bias gets worse as the pleiotropy gets stronger. Indeed, MR seriously underperforms simple OLS (i.e., with no proxy control) in obtaining an accurate estimate for the effect of T on y when T is specified to have an actual effect. In the presence of positive pleiotropy, OLS of course overestimates the effect of T; it attributes the direct effect of SNPs on y to the indirect effect through T. The amount of over-estimation also, as expected, grows with the size of the genetic correlation between the effect of markers on T and their effect on y, net of T. GIV-C, in contrast, provides highly accurate estimates of the effect of T on y even in the case of very strong pleiotropy. Interestingly, GIV-U also produces rather accurate estimates of the effect of T on y, though at a heritability of 0.2, GIV-U underestimates the size of δ. We note that GIV-C and GIV-U are together providing bounds for the true answer at these specifications for the simulation. The use of an unconditional or a conditional proxy in OLS also performs well; it is only slightly less accurate than GIV-C, but sometimes it underestimates and sometimes it overestimates the true answer.

The bottom panels of Table S2.2 show the performance of the estimators when T has no true effect. MR erroneously finds that T has a significant effect on y and the size of this estimated effect grows with the strength of the pleiotropy. Simple OLS is more accurate, and both GIV-C and GIV-U are more accurate still. They both estimate a very small effect of T on y. This makes sense, because if the true effect of T on y is zero, this means that T should have a very weak relationship in a finite sample with the coefficient errors for the genetic markers in the unconditional PGS for y (i..e, $G(\zeta - \hat{\zeta}_1) = v_1$) hence with the PGS error that is part of the error term in 10. Similarly, S_{y2} will also have a very weak correlation with v_1. Therefore, T and S_{y2} are valid instruments for the case where δ =0 and where there is no non-genetic endogeneity, and the GIV-U estimates are very close to the true answer in this case.

Table S2.3 has the same layout as Table S2.2, but in Table S2.3 the heritability for both T and for y is increased from 0.2 to 0.4. Higher heritability slightly increases the positive bias of GIV-C, and it also increases the negative bias of GIV-U. Even though GIV-C has positive bias, it is always more accurate than MR and also more accurate than simple OLS. Greater heritability increases the positive bias of GIV-C when there is no true effect of T, and the over-prediction is larger when the pleiotropy is stronger. Nevertheless, GIV-C is clearly more accurate than either simple OLS or MR-based estimators. When the true effect of T on y is zero, GIV-U provides clear evidence of this fact. As before, GIV-C and GIV-U are bounding the true answer when it is specified to be 1.0. When the true answer is zero, GIV-U is very close to the true answer.

Table S2.4 has the same layout as Tables S2.2 and S2.3, but in Table S2.4, the heritability for both T and for y is increased to 0.6. Higher heritability slightly increases the positive bias of GIV-C when T is specified to have an actual effect on y, and it also increases the negative bias of GIV-U. Even though GIV-C has positive bias, it is always more accurate than MR and also more accurate than simple OLS. GIV-U continues to under-predict the true answer, and GIV-C and GIV-U together continue to provide bounds on the correct answer, though these bounds become gradually wider as we increase the amount of heritability of T and y in the simulations. When the true effect of T on y is zero, GIV-U provides clear evidence of this fact.

Table S2.5 shows simulations where the heritability of T and y is specified to be 0.8. Higher heritability further increases the positive bias of GIV-C though it remains more accurate than simple OLS or MR. Very high heritability also increases the negative bias of GIV-U and further widens the gap between GIV-C and GIV-U, though they continue to bound the true answer. When the true effect of T on y is zero, GIV-C is positively biased though not as much as simple OLS or MR. GIV-U remains very accurate in estimating the true effect of T on y when this effect is actually zero.

Next we consider in Table S2.6 the case where T has a high heritability of 0.8 while y has a low heritability of 0.2 (this is empirically possible because y has other causes than T and these other causes can be largely non-genetic). The pattern of estimates in Table S2.6 resembles those of Table S2.4 where heritability is 0.6 for both T and for y.

Table S2.7, then shows the case where T has a low heritability of 0.2 while y has a high heritability of 0.8. In this case, GIV-C and GIV-U are giving more accurate answers, and GIV-C is giving a much better answer than simple OLS or MR when the true answer is zero. By comparing Table S2.6 and Table S2.7, we see that the size of the upward bias of GIV-C depends on how strong is the relative heritability of T and y as well as on how strong is the pleiotropy. But in all of these cases, GIV-C and GIV-U are bracketing the true effect of T when the true effect is non-zero, and GIV-U gives accurate answers relative to all other methods when the true effect is zero.

2.3 Estimating exposure effects in the presence of both pleiotropy and genetic related endogeneity

Pleiotropy, of course, is not the only potential problem that challenges efforts to estimate the effect of T on y with accuracy, and, indeed, it was not the problem that MR was developed to solve. So now we elaborate the structural model to be as follows:

$$y = \delta T + X\beta_y + \gamma S^*_{y|T} + v_y + \epsilon_y \tag{S2.16}$$

$$T = \alpha S^*_T + X\beta_T + v_T + \epsilon_T \tag{S2.17}$$

Now the disturbance for both equations has two terms, v and ϵ. We assume that ϵ_T and ϵ_y are uncorrelated, but that v_T and v_y are correlated with each other (with correlation ρ_v), which produces endogeneity in the structural model. We also assume that v_T and v_y are correlated with the genetic markers in S^*_T and $S^*_{y|T}$ (ρ_{vT} and ρ_{vy}, respectively). There are three principal substantive conditions that could alone or in combination produce this correlation. The first condition is epistasis, meaning that SNPs have nonlinear or interactive effects that are correlated with the linear effects in the PGS. The second condition is when rare alleles have effects on y and on T and when these alleles are correlated with observed alleles. The third condition is "genetic nurturing." Genetic nurturing (Kong et al., 2017) is the condition where the environment of ego is shaped by genetically related individuals to ego. For example, children live in an environment that is partly created and selected by their parents. If environmental characteristics are related to parents' genes, which of course are correlated with ego's genes, and if the environment affects y while also being correlated with T, then the environment is endogenous to T while also being correlated with ego's genes. The model for height on educational attainment provides a useful example. Taller children could be taller partly for genetic reasons, but also because they grew up in an environment that provided better nutrition. Children who grew up in a better nutritional environment would also be expected to go further in school. Parents who provide a better nutritional environment for their children may have done so in part based on genetic advantages, or on behavioral consequences of genetic advantages (e.g., when a taller parent is rewarded for being tall in school or the workplace and therefore has more money to spend on their children).

While recognizing that the substantive reasons for this form of endogeneity can vary, we will refer to it below as genetic nurturing for ease of exposition.

In order to evaluate alternative estimation strategies in the presence of both pleiotropy and genetic nurturing, we elaborated the simulations to include the additional error terms v_T and v_y, assuming both to have a variance of 0.1 and assuming correlations of 0.4 between v_T and v_y (ρ_v = 0.4). We assumed varying genetic correlations between S_{T^*} and ν_T ($\rho_{\nu T}$), and between $S^*_{y|T}$ and ν_y ($\rho_{\nu y}$). We further assumed that the correlation between ν_T and $S^*_{y|T}$ is 0.4 as large as is the correlations set between S^*_T and ν_T, and that the correlation between ν_y and S^*_T is 0.4 as large as is the correlation between $S^*_{y|T}$ and ν_y for that particular set of simulations.

Table S2.8 shows the results from a set of simulations where the correlation between y and ν_y and also between T and ν_T (i.e., $\rho_{\nu y}$ and $\rho_{\nu T}$) is set at 0.2 and where the heritability for both y and T is set at 0.5. As for the simpler simulations that only included pleiotropy, we find that GIV-C consistently outperforms both OLS and MR. In all these cases, GIV-C is positively biased in its estimate of δ, and these biases are comparable to those that we found for the case of pleiotropy alone when the heritability of y and T was of comparable magnitude. As with the simpler case of pleiotropy without genetic nurturing, we find that GIV-U consistently underestimates the effect of T on y, and that GIV-C and GIV-U bracket the correct answer. The pattern of results for the case of a zero effect are also similar to what we saw in the case of moderate heritability without the additional genetic confounding; GIV-C over-predicts but not as much as for OLS and MR, and GIV-U provides a very accurate answer. This pattern is actually similar to what we find when we increase the extent of genetic confounding (i.e., increase ρ_{vy} and ρ_{vT}), as shown in Table S2.9, where $\rho_{vy} = \rho_{vT} = 0.5$, and in Table S2.10, where $\rho_{vy} = \rho_{vT} = 0.8$. If the reasons for the additional endogeneity do arise from genetic nurturing, and if these genetic nurturing effects are the same for siblings or for dizygotic twins, then the inclusion of family fixed effects are a good strategy that can be used in combination with GIV-C and GIV-U, because in these cases the fixed effects estimator will control for the unobserved but common family effect. Note that a fixed effects model among siblings or dizygotic twins does not solve the problem of endogeneity due to pleiotropy, and GIV-C and GIV-U can be used in combination to address that issue. At the same time, we note that family fixed effects models usually are only possible with smaller samples and they use up many degrees of freedom. Given the simulation results in Tables S2.8- S2.10, it may be that the greater statistical power available in using GIV-C and GIV-U alone offsets any additional advantage from the fixed effects estimator.

S2.4 Estimating exposure effects in the presence of both pleiotropy and genetic-unrelated endogeneity

Next we use simulated data to estimate the effects of T in the presence of both pleiotropy and genetic-unrelated endogeneity. Table S2.11 shows simulations where the heritability is 0.5 for both y and T and where there is also pleiotropy but where the error terms in equations S2.8 and S2.9 have a 0.4 correlation (ρ_e) with each other and are uncorrelated with the genetic variables $S_{T|XT}$ and $S_{y|XT}$. As Table S2.11 shows, this is the most challenging of all the simulation results obtained so far. Neither OLS or MR provide accurate answers at any level of genetic correlation, and the results for GIV-C are not an improvement. Moreover, GIV-U in this case also has a positive bias, and so GIV-C and GIV-U no longer provide bounds for the true answer. The table has a simple message: when the endogeneity problem stems from non-genetic sources, genetic information will not by itself provide a solution to the estimation strategy. Of course, the validity of this message depends on the extent of the endogeneity problem, as can readily be seen in Table S2.12. The simulations in Table S2.12 differ from those in Table

S2.11 only in that the non-genetic endogeneity is much weaker; instead of a 0.4 correlation between the errors in equations S2.8 and S2.9, we assume a -0.1 correlation. The consequence of weakening the non-genetic endogeneity is that GIV-C produces very accurate estimates of the effect of T, estimates which are more accurate than those of either OLS or MR. Finally, and consistent with the earlier simulations, the use of $S_{y1|T}$ as a proxy control in OLS provides an estimate that is more sensitive to the extent of pleiotropy than is GIV-C, being smaller at low levels of genetic correlation and larger at higher levels. However, it is not as consistent in the sign of its bias and therefore is less useful for the purpose of establishing bounds.

While we do not wish to minimize the challenges posed by non-genetic endogeneity, we also note that this situation provides grounds for optimism. Non-genetic sources of endogeneity can often be measured and included in the model as control variables. Once this is done, the endogeneity problem is reduced in severity. We show this illustratively in Tables S2.13, S2.14, and S2.15. In the simulations reported in these tables, the non-genetic endogeneity correlation (ρ_e) is again 0.4, but we specify it explicitly as the consequence of two unmeasured variables. We then assume that one of these environmental confounds can be measured, and so we include it explicitly in the regression and re-estimate the models. In Table S2.13, we assume that the measurable environmental variable accounts for 20% of the variance of the original error term, such that the remaining correlation between the error terms is 0.27. In Table S2.14, we assume instead that the measurable environmental variable accounts for 50%, implying a remaining correlation of 0.20. In Table S2.15, we assume that it accounts for 80% of the non-genetic endogeneity, implying a remaining correlation of 0.13. Perhaps not surprisingly, the performance of both GIV-C and GIV-U improve and the level of improvement depends upon the amount of the environmental confounding variables that can be controlled. It's notable that even if 80% of the confounding effects of nongenetic environmental variables were controlled, GIV-C still shows considerable upward bias, though generally not as much as MR. GIV-U, on the other hand, performs reasonably well when most of the environmental confounds are controlled.

We also note that GIV-U does not consistently under-predict the effect of T on y when there are positive-biasing environmental confounds as well as pleiotropy. On the other hand, it does reliably give the most conservative answer of all the estimators we have considered. If the pleiotropy is not extreme and if the amount of uncontrolled environmental endogeneity is not too large, then estimates from GIV-U are in the neighborhood of the true answer.

Another strategy for addressing the environmental confounds problem is to use fixed effects models where the clustered cases (e.g., siblings) have similar values on the environmental variables that are producing the non-genetic environmental endogeneity. In general, we conclude that non-genetic endogeneity causes potentially large problems for estimating causal effects when pleiotropy is moderate to large in size. Fixed effects models with monozygotic twins will solve pleiotropy problems but it is difficult to obtain monozygotic twin data at sufficient scale to address most problems of interest in the social and behavioral sciences. Well-designed experiments using randomized assignment to treatment would address all the problems considered here, though experiments are frequently infeasible to conduct for well-known reasons. Valid non-genetic environmental IVs would similarly address both the problems of environmental endogeneity and pleiotropy, though these variables are often unavailable. In such cases, the strategy of addressing as much non-genetic endogeneity as possible either with explicit control variables or with fixed-effects models and then calculating both the GIV-C and the GIV-U estimates provides more information about the true effect of T than any of the other strategies considered here.

SI 2.5 Empirical application

We used data from the Health and Retirement Survey (HRS) for our empirical example [28]. The HRS is a longitudinal survey on health, retirement and aging which is presentative for the US population aged 50 years or older. The survey consists of eleven waves from 1992 to 2012. We used phenotypic data that has been cleaned and harmonized by the RAND cooperation.[8]

[8] RAND HRS Data, Version O. Produced by the RAND Center for the Study of Aging, with funding from the National Institute on Aging and the Social Security Administration. Santa Monica, CA (August 2016). See http://www.rand.org/labor/aging/dataprod/hrs-data.html for additional information.

Since 2006, data collection has expanded to include biomarkers and a subset of the participants has been genotyped.[9] Autosomal SNPs were imputed using the worldwide reference panel from phase I of the 1000 Genomes project (v3, released March 2012) (The 1000 Genomes Project Consortium, 2012). If the uncertainty about the genotype of an individual was greater than 10 percent, the SNP was removed. Furthermore, SNPs were removed from the entire sample if the imputation quality was below 70 percent, if the minor allele frequency was smaller than 1 percent, or if the SNP was missing in over 5 percent of the sample. Our analyses were restricted to unrelated participants of European descent according to the standard HRS protocol. Specifically, HRS filtered out parent-offspring pairs, siblings and half-siblings. Selection on European descent was done based on self-reported race and principal component analysis (Weir, 2012). The PGS for educational attainment is negatively correlated with birth year (r = -0.06; p < 0.0001) and educational attainment has been shown to affect longevity (van Kippersluis, O'Donnell, & van Doorslaer, 2011; Cutler & Lleras-Muney, 2008). Thus, age-related sample selection is likely to be correlated with educational attainment and its PGS, which could potentially bias our results. Since the HRS is a sample of an older population spanning across many birth years, we further restricted our analysis sample to a a relatively younger group of people born between 1935 and 1945. This subsample is still large enough to for our analyses (N = 2,839), yet less likely to be affected by age-related sample selection.

We constructed polygenic scores starting with a set of 2,224,079 SNPs that were either directly genotyped in HRS or present in the HapMap3 reference panel (The International HapMap Consortium, 2010) providing us with a high-resolution coverage of common genetic variants. To control for linkage disequilibrium (LD) between SNPs, we constructed all polygenic scores using LDpred (Vilhjælmsson et al., 2015) with the default LD window (total number of SNPs divided by 3000) and assuming that all of the SNPs are causal.

The first unconditional polygenic score for educational attainment was constructed by using GWAS results provided by the Social Science Genetic Association Consortium (SSGAC) (Okbay, Beauchamp,

[9] See https://hrs.isr.umich.edu/data-products/genetic-data

et al. 2016), excluding HRS, UK Biobank and the *23andMe* cohort from the meta-analysis. The remaining SSGAC sample consists of several cohorts from around the world ($n = 207{,}605$, see Supplementary Table S2.18). We included all SNPs that overlapped with our initial set in LDpred. After LDpred filtered out ambiguous SNPs and SNPs with minor allele frequency smaller than 0.01; 1,849,602 autosomal SNPs remained.

The second unconditional polygenic score for educational attainment was constructed by using results from a GWAS in the UK Biobank, also provided by the SSGAC (Lee et al., 2018) ($n = 442{,}183$; 1,870,853 SNPs).

The first unconditional polygenic score for height was constructed using the publicly available GWAS summary results from the GIANT consortium ($n = 253{,}288$) (Wood et al., 2014),[10] which are based on ≈ 2.5 million autosomal SNPs that were imputed using the HapMap 2 CEU reference panel (The International HapMap Consortium, 2007) (See Supplementary Table S2.19). Merging this set with the directly genotyped and HapMap 3 SNPs resulted in 1,264,571 SNPs that were included in the score by LDpred.

We conducted three GWASs in the UK Biobank (UKB) to obtain the other required polygenic scores. The UKB is a publicly available population-based prospective study of individuals aged 40-69 years during recruitment in 2006-2010 (Sudlow et al., 2015). We restricted the analysis to unrelated Brits of European descent (Marchini et al., 2015) that were available in the full release of the genetic data ($n = 441{,}298$). Autosomal SNPs were imputed using the UK10K reference panel. Details on genotyping, pre-imputation quality control, and imputation have been documented extensively elsewhere (Marchini et al., 2015).

To obtain a second unconditional polygenic score for height, the GWAS analysis included as control variables dummies for genotyping batches and sex. We also included a third order polynomial of age and it's interaction terms with sex. Furthermore, the first 20 principal components of the genetic data were

[10] http://portals.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files #GWAS_Anthropometric_2014_Height

also included to control for subtle population structure. The obtained GWAS results underwent quality control following an extended version of the EasyQC protocol (Winkler et al., 2014) described in detail elsewhere (Okbay, Baselmans, et al., 2016). Two loci had SNPs with p-values that were numerically equal to 0, these could not be entered into LDpred. From each of the two loci one SNP was included into the score after LDpred was done. This yielded a score consisting of 1,861,847 autosomal SNPs.

For the conditional polygenic score for educational attainment, we included as control variables height, genotyping batches, sex, age, age and height squared and cubed, the interaction terms between the terms for age and height, as well as their interaction terms with sex. Furthermore, the first 20 principal components of the genetic data were included as controls for population stratification and the GWAS results underwent quality control, yielding 1,861,878 autosomal SNPs.

For the conditional polygenic score for height, an identical GWAS analysis was conducted where we controlled for educational attainment instead (including squared, cubic and interaction terms). This yielded a score based on 1,861,847 autosomal SNPs (including the same two SNPs that were manually added, as described above).

There is an overlap in the cohorts used by the GIANT consortium in the GWAS on height and by the SSGAC GWAS on educational attainment (Okbay, Beauchamp, et al., 2016). To ensure independence of measurement errors in the PGS, whenever the GIANT height PGS was used, we excluded the other as an instrument and used a PGS constructed from the UK Biobank GWAS results instead.

Using these data, we demonstrate the value of the GIV regression approach in several important empirical applications. First, we estimated the chip heritability of educational attainment (EA) in the HRS data from a PGS for EA. We use the residual of EA after regressing it on control variables. The results are shown in Table 2.1 of the main text. All reported coefficients are standardized. Since the squared standardized coefficient in OLS equals R^2, our OLS result in column 1 of Table 2.1 implies that the PGS for EA currently captures 6.8% of the variance in EA.

Using the GIV regression results reported in columns 2 and 3 of Table 2.1 and the error correction described above 1.1, we obtain chip heritability estimates of 13.4% (95% CI +/3.9%) and 13.8% (+/-4.0%), respectively.

Second, we estimated the (causal) effect of body height on EA. Earlier studies have reported a positive relationship between these variables (Silventoinen, Kaprio, & Lahelma, 2000; Case, Paxson, & Islam, 2009; Anne Case & Christina Paxson, 2008). Third, we present results from a negative control that estimates the (causal) effect of EA on body height (which should be zero). We estimated these effects using OLS, MR, GIV-C, and GIVU regression. In each regression, we included birth year, birth year squared, educational attainment of both parents and (in pooled models) sex as control variables. We included PGS of EA or height depending on the method. All variables have been standardized. The results are shown and discussed in main text (see Tables 2.3 and 2.4).

SI 2.6 Practical recommendations

We discussed two main sources of bias in this paper – direct pleiotropy and unobserved environmental confounds that may or may not covary with genetic effects. These sources of bias are relevant in almost all research questions in the social sciences and epidemiology when experimental data is not available.

The existing literature addresses these challenges with various strategies. All of them have their advantages and disadvantages. For example, panel data that contain repeated measures for each individual over time can be used for individual fixed-effects models that control for all unobserved heterogeneity among people, including genetic and environmental factors. Unfortunately, individual fixed-effects models do not allow investigating variables that do not vary over time for a particular person, such as the relationship between educational attainment and body height.

The gold standard to address potential bias arising from genetic and family-specific environmental confounds is a comparison among MZ twin pairs. These pairs are (almost) genetically identical and share the same family environment. However, very large samples of MZ twin pairs are necessary for this approach because within MZ twin pair variation tends to be very small or non-existent. Also, this approach does by itself not control for unobserved environmental confounds that are individual-specific.

Probably the most popular approach to identify causal effects in non-experimental data are instrumental variable techniques. Yet, convincing environmental instruments are rare and they limit the scope of research questions to scenarios to which the instruments apply. Furthermore, as discussed earlier, genetic instruments are invalid when they have direct pleiotropic effects on the exposure and the outcome or if they are correlated with other unobserved confounds.

This leaves a broad class of important applied research questions for which GIV regression offers a new approach to obtain more precise estimates than ordinary multiple regression techniques or approaches that use invalid instruments. Table S2.17 provides an overview of different types of applied research questions and our recommended estimation strategy in cross-sectional population samples that lack an experimental design, or valid non-genetic instruments, or relevant natural experiments. We differentiate these research questions based on the expected degree of pleiotropic confounds and whether environmental sources of endogeneity may also exist or not. Unfortunately, environmental endogeneity is hard to rule out in almost all non-experimental research scenarios.

Mendelian Randomization is in principle a great idea for addressing environmental endogeneity, but its application is limited to scenarios where direct pleiotropy between the exposure and the outcome is of no concern. An example may be the influence of number of cigarettes smoked per day on the number of biological offspring – smoking intensity seems to be regulated by a relatively limited number of genes with strong effects and clear biological functions that are unlikely to have direct pleiotropic effects on reproductive success (The Tobacco and Genetics Consortium, 2010). Yet, even in this situation, genes related to smoking may still violate the exclusion restriction via LD with other genes or via their correlation with unobserved environmental confounds, such as parental socioeconomic status. In short, it is difficult to argue convincingly that the assumptions of MR are actually satisfied. The assumptions of MR are less likely to hold the more genetically complex the investigated traits are, the higher their genetic correlation is, and the more likely it is that the genes associated with these traits work via unobserved environmental channels.

We argue that GIV regression is a reasonable estimation strategy whenever pleiotropic confounds are a possible concern. If genetic and environmental confounds are both likely to exist, we recommend the combination of GIV regression with control variables that correct for non-genetic endogeneity as far as possible, ideally in samples that also allow controls for family-fixed effects (e.g. siblings or DZ twins). Examples of research questions with both sources of endogeneity are plentiful, e.g. the relationships between body height and educational attainment (low pleiotropy), diet and body mass (probably with a medium degree of direct pleiotropy), and the returns to schooling (probably with a high degree of direct pleiotropy on educational attainment and personal income, and quite likely mediated by factors such as cognitive ability and personality). GIV regression in combination with environmental controls is a reasonable estimation strategy in all of these cases.

An important practical question is data availability for GIV regression. In addition to a genotyped prediction sample, the researcher will need GWAS summary statistics from nonoverlapping samples to construct the conditional and unconditional scores. Unconditional scores for many traits can often be constructed using publicly available GWAS results from consortia such as GIANT[11], SSGAC[12], PGC[13], or CHARGE[14]. Most of these consortia did not include data from the UKB in their earlier publications. Thus, the publicly available UKB data can often be used to obtain a second score from an independent sample. Unconditional GWAS results for virtually all traits in the UKB are publicly available from the Broad Institute[15]. The UKB, or any other large, publicly available biobank, can also be considered as a source for obtaining conditional GWAS results. If the researcher does not have access to these data or lacks the resources for large-scale GWAS analyses, it is always possible to team up with one of the many

[11] https://portals.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files

[12] https://www.thessgac.org

[13] https://www.med.unc.edu/pgc/results-and-downloads

[14] http://www.chargeconsortium.com/main/results

[15] http://www.nealelab.is/blog/2017/7/19/rapid-gwas-of-thousands-of-phenotypes-for-337000-samplesin-the-uk-biobank

research groups around the world that have the necessary data and resources. Running a conditional GWAS in a large sample like the UKB can often be done in a matter of hours by experienced research teams. Importantly, GIV regression only requires one conditional score which can be instrumented by an unconditional score from a non-overlapping sample. Thus, data access or computational resources should not be a serious practical limitation for GIV regression.

Furthermore, the UKB is large enough to be split into three sub-samples for GIV regression. One particularly appealing approach would be to use the subsample of siblings in the UKB as a prediction sample that allows the researcher to control for family fixed-effects. The remaining unrelated individuals can be split into two, still very large, subsamples to conduct conditional and unconditional GWAS analyses. Because all participants in the UKB have been recruited at about the same time and in the same country, the genetic correlations for a given trait are likely to be perfect for randomly chosen subsets of the data.

An important practical issue is that the prediction sample should not be included in any of the GWAS samples used to construct the scores to avoid overfitting. Reassuringly, this is not a problem either because most GWAS consortia provide meta-analysis results excluding specific samples upon request. If this is not possible, an alternative strategy is to conduct the GWAS on y in the prediction sample and to subtract the effect of each SNP in this cohort from the publicly available results using the meta-analysis formula that the consortium used to aggregate effects. For example, if the meta-analysis used sample size weights to obtain the z-scores of each SNP, the corrected z-scores excluding the prediction sample could be obtained by simply subtracting the z-score in the prediction sample using the appropriate weight (Willer, Li, & Abecasis, 2010). Furthermore, many samples have only recently been genotyped and are therefore not included yet in published GWAS studies. These samples could be readily employed for GIV regression using the approaches described above.

Overall, we believe that GIV regression has substantial practical utility for many researchers and across a wide range of important applied research questions. The usefulness of GIV regression will increase further in the future as a result of the growing availability of accurate, cheap genetic data and GWAS results on many traits from ever growing sample sizes.

S2.7 References

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S2.8 Tables

Table S2.1: Estimating the SNP heritability of *y*

	Number	Total GWAS sample size			
	of SNPs	50,000	100,000	300,000	500,000
$h^2 = 0.1$	1000	0.1002	0.1008	0.0999	0.1016
		(0.00725)	(0.00666)	(0.00621)	(0.00618)
	10000	0.1039	0.0969	0.0988	0.0995
		(0.0165)	(0.0112)	(0.0080)	(0.0073)
	100000	0.1247	0.0964	0.0972	x
		(0.1343)	(0.0475)	(0.0215)	
	300000	0.1822	0.09197*	x	x
		(8.3243)	(0.1512)		
$h^2 = 0.3$	1000	0.2937	0.2968	0.2961	0.2952
		(0.0100)	(0.0095)	(0.0093)	(0.0092)
	10000	0.2999	0.3016	0.2976	0.2982
		(0.0175)	(0.0134)	(0.0106)	(0.0100)
	100000	0.2873	0.3087	0.2999	x
		(0.0889)	(0.0522)	(0.0232)	
	300000	0.2811	0.3558	x	x
		(0.2586)	(0.1713)		
$h^2 = 0.5$	1000	0.4969	0.4951	0.5001	0.5103
		(0.0108)	(0.0103)	(0.0101)	(0.0102)
	10000	0.5039	0.4991	0.5008	0.4974
		(0.0181)	(0.0140)	(0.0114)	(0.0107)
	100000	0.5167	0.5110	0.5024	x
		(0.0988)	(0.0519)	(0.0234)	
	300000	0.6080	0.5460	x	x
		(0.4702)	(0.1536)		

Mean of heritability estimates of twenty simulations for several GWAS sample sizes, varying the number of SNPs and the heritability (h2) of y. Standard errors (in parentheses) are calculated via the delta method. The size of the replication sample is 10,000. * Mean of nineteen simulations, due to one extreme outlier. x Unable to simulate due to memory constraints on the high memory nodes of the high performance computer.

Table S2.2: Endogeneity between *y* and *T* due to Pleiotropic Effects, $h^2 = 0.2$ for both *y* and *T*

	OLS	MR-based			Conditional Proxy PGS			Unconditional Proxy PGS		
		1	MR EMR-2	EMR-	OLS $S(y\|T)$	OLS $S(y_1\|T)$	GIV-C	OLS $S(y)$	OLS $S(y_1)$	GIV-U
$\delta = 1, \rho = 0.2$	1.0405 (0.0001)	1.2018 (0.0010)	0.8247 (0.0017)	1.0522 (0.0011)	1.0190 (0.0001)	1.0249 (0.0001)	1.0081 (0.0001)	0.9525 (0.0001)	0.9744 (0.0001)	0.9100 (0.0001)
$\delta = 1, \rho = 0.5$	1.1004 (0.0001)	1.5040 (0.0012)	1.1240 (0.0023)	1.1155 (0.0015)	1.0473 (0.0001)	1.0617 (0.0001)	1.0131 (0.0001)	0.9891 (0.0001)	1.0150 (0.0001)	0.9419 (0.0001)
$\delta = 1, \rho = 0.8$	1.1602 (0.0001)	1.8058 (0.0014)	1.5649 (0.0040)	1.1880 (0.0051)	1.0764 (0.0001)	1.1011 (0.0001)	1.0094 (0.0001)	1.0275 (0.0001)	1.0567 (0.0001)	0.9761 (0.0001)
$\delta = 0, \rho = 0.2$	0.0405 (0.0001)	0.2018 (0.0010)	0.1083 (0.0009)	0.0522 (0.0011)	0.0190 (0.0001)	0.0249 (0.0001)	0.0092 (0.0001)	0.0139 (0.0001)	0.0127 (0.0001)	0.0015 (0.0001)
$\delta = 0, \rho = 0.5$	0.1004 (0.0001)	0.5040 (0.0012)	0.2922 (0.0012)	0.1155 (0.0015)	0.0473 (0.0001)	0.0617 (0.0001)	0.0180 (0.0001)	0.0349 (0.0001)	0.0519 (0.0001)	0.0016 (0.0001)
$\delta = 0, \rho = 0.8$	0.1602 (0.0001)	0.8058 (0.0014)	0.5956 (0.0021)	0.1880 (0.0051)	0.0764 (0.0001)	0.1011 (0.0001)	0.0164 (0.0001)	0.0585 (0.0001)	0.0857 (0.0001)	0.0015 (0.0001)

Mean of estimated effect for T and its standard error (within parenthesis) of twenty simulations for several methods (columns) and different parameters (rows). The effect for T (δ) is equal to either 1 or 0. The correlation between the true polygenic scores (ρ) varies. See the supplementary text for details.

Table S2.3: Endogeneity between *y* and *T* due to Pleiotropic Effects, $h^2 = 0.4$ for both *y* and *T*

	OLS	MR-based			Conditional Proxy PGS			Unconditional Proxy PGS		
		MR	EMR-1	EMR-2	OLS $S(y\|T)$	OLS $S(y_1\|T)$	GIV-C	OLS $S(y)$	OLS $S(y_1)$	GIV-U
$\delta = 1, \rho = 0.2$	1.0810 (0.0001)	1.2002 (0.0004)	0.6374 (0.0007)	1.0874 (0.0003)	1.0425 (0.0001)	1.0497 (0.0001)	1.0313 (0.0001)	0.8563 (0.0001)	0.8983 (0.0001)	0.7900 (0.0001)
$\delta = 1, \rho = 0.5$	1.2011 (0.0001)	1.5024 (0.0004)	0.9270 (0.0009)	1.2086 (0.0004)	1.1044 (0.0001)	1.1230 (0.0001)	1.0604 (0.0001)	0.9337 (0.0001)	0.9825 (0.0001)	0.8575 (0.0001)
$\delta = 1, \rho = 0.8$	1.3210 (0.0001)	1.8040 (0.0004)	1.4201 (0.0015)	1.3322 (0.0008)	1.1640 (0.0001)	1.2016 (0.0001)	1.0533 (0.0001)	1.0228 (0.0001)	1.0773 (0.0001)	0.9376 (0.0001)
$\delta = 0, \rho = 0.2$	0.0810 (0.0001)	0.2002 (0.0004)	0.0738 (0.0003)	0.0874 (0.0003)	0.0425 (0.0001)	0.0497 (0.0001)	0.0336 (0.0001)	0.0176 (0.0001)	0.0288 (0.0001)	0.0025 (0.0001)
$\delta = 0, \rho = 0.5$	0.2011 (0.0001)	0.5024 (0.0004)	0.2053 (0.0004)	0.2086 (0.0004)	0.1044 (0.0001)	0.1230 (0.0001)	0.0736 (0.0001)	0.0447 (0.0001)	0.0729 (0.0001)	0.0024 (0.0001)
$\delta = 0, \rho = 0.8$	0.3210 (0.0001)	0.8040 (0.0004)	0.4707 (0.0007)	0.3322 (0.0008)	0.1640 (0.0001)	0.2016 (0.0001)	0.0800 (0.0001)	0.0813 (0.0001)	0.1295 (0.0001)	0.0018 (0.0001)

Mean of estimated effect for T and its standard error (within parentheses) of twenty simulations for several methods (columns) and different parameters (rows). The effect for T (δ) is equal to either 1 or 0. The correlation between the true polygenic scores (ρ) varies. See the supplementary text for details.

Table S2.4: Endogeneity between *y* and *T* due to Pleiotropic Effects, h^2 = 0.6 for both *y* and *T*

	OLS	MR-based			Conditional Proxy PGS			Unconditional Proxy PGS		
		MR	EMR-1	EMR-2	OLS $S(y\mid T)$	OLS $S(y_1\mid T)$	GIV-C	OLS $S(y)$	OLS $S(y_1)$	GIV-U
$\delta = 1, \rho = 0.2$	1.1213	1.1999	0.5264	1.1249	1.0798	1.0860	1.0713	0.7222	0.7877	0.6244
	(0.0001)	(0.0002)	(0.0004)	(0.0001)	(<0.0001)	(0.0001)	(0.0001)	(0.0001)	(0.0001)	(0.0001)
$\delta = 1, \rho = 0.5$	1.3016	1.5020	0.8074	1.3056	1.1979	1.2134	1.1573	0.8469	0.9255	0.7263
	(0.0001)	(0.0002)	(0.0005)	(0.0001)	(0.0001)	(0.0001)	(0.0001)	(0.0001)	(0.0001)	(0.0002)
$\delta = 1, \rho = 0.8$	1.4816	1.8033	1.3247	1.4868	1.3136	1.3470	1.1774	1.0101	1.0985	0.8685
	(0.0001)	(0.0002)	(0.0007)	(0.0002)	(0.0001)	(0.0001)	(0.0001)	(0.0001)	(0.0001)	(0.0002)
$\delta = 0, \rho = 0.2$	0.1213	0.1999	0.0562	0.1249	0.0798	0.0860	0.0737	0.0196	0.0331	0.0031
	(0.0001)	(0.0002)	(0.0001)	(0.0001)	(<0.0001)	(0.0001)	(0.0001)	(<0.0001)	(0.0001)	(0.0001)
$\delta = 0, \rho = 0.5$	0.3016	0.5020	0.1586	0.3056	0.1979	0.2134	0.1733	0.0511	0.0867	0.0028
	(0.0001)	(0.0002)	(0.0002)	(0.0001)	(0.0001)	(0.0001)	(0.0001)	(0.0001)	(0.0001)	(0.0001)
$\delta = 0, \rho = 0.8$	0.4816	0.8033	0.3896	0.4868	0.3136	0.3470	0.2267	0.1036	0.1701	0.0019
	(0.0001)	(0.0002)	(0.0003)	(0.0002)	(0.0001)	(0.0001)	(0.0001)	(0.0001)	(0.0001)	(0.0001)

Mean of estimated effect for T and its standard error (within parentheses) of twenty simulations for several methods (columns) and different parameters (rows). The effect for T (δ) is equal to either 1 or 0. The correlation between the true polygenic scores (ρ) varies. See the supplementary text for details.

Table S2.5: Endogeneity between y and T due to Pleiotropic Effects, h2 = 0.8 for both y and T

	OLS	MR-based			Conditional Proxy PGS			Unconditional Proxy PGS		
		MR	EMR-1	EMR-2	OLS $S(y\mid T)$	OLS $S(y_1\mid T)$	GIV-C	OLS $S(y)$	OLS $S(y_1)$	GIV-U
$\delta = 1, \rho = 0.2$	1.1613	1.1998	0.4528	1.1629	1.1323	1.1359	1.1283	0.5309	0.6309	0.3819
	(0.0001)	(0.0002)	(0.0002)	(0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(0.0001)	(0.0001)	(0.0001)
$\delta = 1, \rho = 0.5$	1.4020	1.5018	0.7269	1.4036	1.3303	1.3389	1.3098	0.7034	0.8323	0.4962
	(0.0001)	(0.0001)	(0.0003)	(0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(0.0001)	(0.0001)	(0.0002)
$\delta = 1, \rho = 0.8$	1.6421	1.8030	1.2567	1.6440	1.5292	1.5461	1.4440	0.9822	1.1310	0.7094
	(0.0001)	(0.0001)	(0.0004)	(0.0001)	(<0.0001)	(<0.0001)	(0.0001)	(0.0001)	(0.0001)	(0.0003)
$\delta = 0, \rho = 0.2$	0.1613	0.1998	0.0454	0.1629	0.1323	0.1359	0.1293	0.0208	0.0357	0.0033
	(0.0001)	(0.0002)	(0.0001)	(0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)
$\delta = 0, \rho = 0.5$	0.4020	0.5018	0.1292	0.4036	0.3303	0.3389	0.3179	0.0565	0.0978	0.0028
	(0.0001)	(0.0001)	(0.0001)	(0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(0.0001)
$\delta = 0, \rho = 0.8$	0.6421	0.8030	0.3323	0.6440	0.5292	0.5461	0.4807	0.1325	0.2188	0.0016
	(0.0001)	(0.0001)	(0.0001)	(0.0001)	(<0.0001)	(<0.0001)	(0.0001)	(0.0001)	(0.0001)	(0.0001)

Mean of estimated effect for T and its standard error of twenty simulations for several methods (columns) and different parameters (rows). The effect for T (δ) is equal to either 1 or 0. The correlation between the true polygenic scores (ρ) varies. See the supplementary text for details.

Table S2.6: Endogeneity between y and T due to Pleiotropic Effects, $h^2 = 0.2$ for y and $h^2 = 0.8$ for T

	OLS	MR-based			Conditional Proxy PGS			Unconditional Proxy PGS		
		MR	EMR-1	EMR-2	OLS $S(y\|T)$	OLS $S(y_1\|T)$	GIV-C	OLS $S(y)$	OLS $S(y_1)$	GIV-U
$\delta = 1, \rho = 0.2$	1.0847	1.1033	0.9286	1.0870	1.0795	1.0821	1.0701	0.8836	0.9535	0.6254
	(0.0004)	(0.0006)	(0.0013)	(0.0007)	(0.0004)	(0.0004)	(0.0005)	(0.0007)	(0.0006)	(0.0036)
$\delta = 1, \rho = 0.5$	1.2048	1.2541	1.0996	1.2088	1.1940	1.1988	1.1588	0.9961	1.0686	0.7259
	(0.0004)	(0.0006)	(0.0015)	(0.0008)	(0.0004)	(0.0004)	(0.0005)	(0.0008)	(0.0007)	(0.0043)
$\delta = 1, \rho = 0.8$	1.3244	1.4042	1.3181	1.3321	1.3145	1.3188	1.2156	1.1385	1.2037	0.8799
	(0.0004)	(0.0006)	(0.0018)	(0.0013)	(0.0004)	(0.0004)	(0.0012)	(0.0009)	(0.0007)	(0.0057)
$\delta = 0, \rho = 0.2$	0.0822	0.1012	0.0539	0.0837	0.0715	0.0749	0.0673	0.0301	0.0438	0.0048
	(0.0001)	(0.0002)	(0.0001)	(0.0002)	(0.0001)	(0.0001)	(0.0001)	(0.0001)	(0.0001)	(0.0001)
$\delta = 0, \rho = 0.5$	0.2025	0.2521	0.1457	0.2044	0.1777	0.1852	0.1619	0.0801	0.1140	0.0059
	(0.0001)	(0.0002)	(0.0002)	(0.0002)	(0.0001)	(0.0001)	(0.0001)	(0.0001)	(0.0001)	(0.0002)
$\delta = 0, \rho = 0.8$	0.3224	0.4025	0.2968	0.3257	0.2923	0.3032	0.2442	0.1656	0.2175	0.0087
	(0.0001)	(0.0001)	(0.0002)	(0.0002)	(0.0001)	(0.0001)	(0.0001)	(0.0001)	(0.0001)	(0.0004)

Mean of estimated effect for T and its standard error(within parenthesis) of twenty simulations for several methods (columns) and different parameters (rows). The effect for T (δ) is equal to either 1 or 0. The correlation between the true polygenic scores (ρ) varies. See the supplementary text for details.

Table S2.7: Endogeneity between y and T due to Pleiotropic Effects, $h^2 = 0.8$ for y and $h^2 = 0.2$ for T

	OLS	MR-based			Conditional Proxy PGS			Unconditional Proxy PGS		
		MR	EMR-1	EMR-2	OLS $S(y\|T)$	OLS $S(y_1\|T)$	GIV-C	OLS $S(y)$	OLS $S(y_1)$	GIV-U
$\delta = 1, \rho = 0.2$	1.2005	1.9798	0.4651	1.2273	1.0562	1.0700	1.0396	0.8675	0.9016	0.8253
	(0.0005)	(0.0061)	(0.0022)	(0.0017)	(0.0001)	(0.0001)	(0.0002)	(0.0001)	(0.0002)	(0.0002)
$\delta = 1, \rho = 0.5$	1.5004	3.4922	1.0200	1.5280	1.1304	1.1664	1.0776	0.9427	1.0010	0.8689
	(0.0005)	(0.0093)	(0.0029)	(0.0024)	(0.0001)	(0.0001)	(0.0002)	(0.0001)	(0.0002)	(0.0002)
$\delta = 1, \rho = 0.8$	1.8001	5.0029	2.3902	1.8300	1.1725	1.2414	1.0647	1.0432	1.1262	0.9365
	(0.0005)	(0.0153)	(0.0125)	(0.0074)	(0.0001)	(0.0002)	(0.0002)	(0.0001)	(0.0002)	(0.0002)
$\delta = 0, \rho = 0.2$	0.0898	0.4412	0.1173	0.1048	0.0274	0.0353	0.0187	0.0125	0.0220	0.0015
	(0.0001)	(0.0016)	(0.0008)	(0.0008)	(0.0001)	(0.0001)	(0.0001)	(0.0001)	(0.0001)	(0.0001)
$\delta = 0, \rho = 0.5$	0.2240	1.1174	0.3304	0.2400	0.0648	0.0850	0.0377	0.0310	0.0544	0.0010
	(0.0001)	(0.0023)	(0.0011)	(0.0012)	(0.0001)	(0.0001)	(0.0001)	(0.0001)	(0.0001)	(0.0001)
$\delta = 0, \rho = 0.8$	0.3579	1.7928	0.8247	0.3782	0.0906	0.1290	0.0335	0.0524	0.0917	0.0000
	(0.0001)	(0.0035)	(0.0036)	(0.0034)	(0.0001)	(0.0001)	(0.0001)	(0.0001)	(0.0001)	(0.0001)

Mean of estimated effect for T and its standard error (within parentheses) of twenty simulations for several methods (columns) and different parameters (rows). The effect for T (δ) is equal to either 1 or 0. The correlation between the true polygenic scores (ρ) varies. See the supplementary text for details.

Table S2.8: Genetic-Related Endogeneity, with a Correlation of 0.2 between the Polygenic Score and the Genetically-Related Confounder ($\rho_{vy} = \rho_{vT} = 0.2$)

	OLS	MR-based			Conditional Proxy PGS			Unconditional Proxy PGS		
		MR	EMR-1	EMR-2	OLS $S(y\|T)$	OLS $S(y_1\|T)$	GIV-C	OLS $S(y)$	OLS $S(y_1)$	GIV-U
$\delta = 1, \rho = 0.2$	1.1664	1.2621	0.5575	1.1649	1.1141	1.1201	1.1005	0.7217	0.7938	0.6117
	(0.0001)	(0.0002)	(0.0004)	(0.0001)	(<0.0001)	(0.0001)	(0.0001)	(0.0001)	(0.0001)	(0.0001)
$\delta = 1, \rho = 0.5$	1.3005	1.4781	0.7704	1.3021	1.2043	1.2176	1.1692	0.8158	0.8996	0.6877
	(0.0001)	(0.0002)	(0.0004)	(0.0001)	(<0.0001)	(0.0001)	(0.0001)	(0.0001)	(0.0001)	(0.0002)
$\delta = 1, \rho = 0.8$	1.4390	1.6917	1.0739	1.4361	1.2993	1.3203	1.2130	0.9371	1.0284	0.7906
	(0.0001)	(0.0002)	(0.0005)	(0.0001)	(0.0001)	(0.0001)	(0.0001)	(0.0001)	(0.0001)	(0.0002)
$\delta = 0, \rho = 0.2$	0.1664	0.2621	0.0668	0.1649	0.1141	0.1201	0.1042	0.0250	0.0422	0.0011
	(0.0001)	(0.0002)	(0.0001)	(0.0001)	(<0.0001)	(0.0001)	(0.0001)	(<0.0001)	(0.0001)	(0.0001)
$\delta = 0, \rho = 0.5$	0.3005	0.4781	0.1400	0.3021	0.2043	0.2176	0.1829	0.0457	0.0806	-0.0003
	(0.0001)	(0.0002)	(0.0001)	(0.0001)	(<0.0001)	(0.0001)	(0.0001)	(0.0001)	(0.0001)	(0.0001)
$\delta = 0, \rho = 0.8$	0.4390	0.6917	0.2590	0.4361	0.2993	0.3203	0.2467	0.0817	0.1366	-0.0004
	(0.0001)	(0.0002)	(0.0002)	(0.0001)	(0.0001)	(0.0001)	(0.0001)	(0.0001)	(0.0001)	(0.0001)

Mean of estimated effect for T and its standard error (within parentheses) of twenty simulations for several methods (columns) and different parameters (rows). The effect for T (δ) is equal to either 1 or 0. The correlation between the true polygenic scores (ρ) varies. The heritability for both y and T is 0.5. The variance of both $v_y$and $v_T$equals 0.1. Correlation of $v_y$and $v_T$is 0.4. See the supplementary text for details.

Table S2.9: Genetic-Related Endogeneity, with a Correlation of 0.5 between the Polygenic Score and the Genetically-Related Confounder ($\rho_{vy} = \rho_{vT} = 0.5$

	OLS	MR-based			Conditional Proxy PGS			Unconditional Proxy PGS		
		MR	EMR-1	EMR-2	OLS $S(y\|T)$	OLS $S(y_1\|T)$	GIV-C	OLS $S(y)$	OLS $S(y_1)$	GIV-U
$\delta = 1, \rho = 0.2$	1.1878	1.2789	0.5538	1.1878	1.1357	1.1411	1.1221	0.6942	0.7741	0.5730
	(0.0001)	(0.0002)	(0.0003)	(0.0001)	(<0.0001)	(<0.0001)	(0.0001)	(0.0001)	(0.0001)	(0.0002)
$\delta = 1, \rho = 0.5$	1.3106	1.4609	0.7257	1.3101	1.2235	1.2334	1.1922	0.7825	0.8726	0.6422
	(0.0001)	(0.0002)	(0.0004)	(0.0001)	(<0.0001)	(<0.0001)	(0.0001)	(0.0001)	(0.0001)	(0.0002)
$\delta = 1, \rho = 0.8$	1.4359	1.6493	0.9807	1.4336	1.3111	1.3285	1.2449	0.8918	0.9910	0.7334
	(0.0001)	(0.0002)	(0.0004)	(0.0001)	(<0.0001)	(0.0001)	(0.0001)	(0.0001)	(0.0001)	(0.0002)
$\delta = 0, \rho = 0.2$	0.1878	0.2789	0.0675	0.1878	0.1357	0.1411	0.1259	0.0265	0.0449	0.0002
	(0.0001)	(0.0002)	(0.0001)	(0.0001)	(<0.0001)	(<0.0001)	(0.0001)	(<0.0001)	(<0.0001)	(0.0001)
$\delta = 0, \rho = 0.5$	0.3106	0.4609	0.1252	0.3101	0.2235	0.2334	0.2037	0.0466	0.0797	-0.0002
	(0.0001)	(0.0002)	(0.0001)	(0.0001)	(<0.0001)	(<0.0001)	(0.0001)	(<0.0001)	(0.0001)	(0.0001)
$\delta = 0, \rho = 0.8$	0.4359	0.6493	0.2186	0.4336	0.3111	0.3285	0.2717	0.0747	0.1274	0.0003
	(0.0001)	(0.0002)	(0.0001)	(0.0001)	(<0.0001)	(0.0001)	(0.0001)	(0.0001)	(0.0001)	(0.0001)

Mean of estimated effect for T and its standard error (within parentheses) of twenty simulations for several methods (columns) and different parameters (rows). The effect for T (δ) is equal to either 1 or 0. The correlation between the true polygenic scores (ρ) varies. The heritability for both y and T is 0.5. The variance of both $v_y$and $v_T$equals 0.1. Correlation of $v_y$and $v_T$is 0.4. See the supplementary text for details.

Table S2.10: Genetic-Related Endogeneity, with a Correlation of 0.8 between the Polygenic Score and the Genetically-Related Confounder (ρ_{vy} = ρ_{vT} = 0.8)

	OLS	MR-based			Conditional Proxy PGS			Unconditional Proxy PGS		
		MR	EMR-1	EMR-2	OLS $S(y\|T)$	OLS $S(y_1\|T)$	GIV-C	OLS $S(y)$	OLS $S(y_1)$	GIV-U
δ = 1, ρ = 0.2	1.2084 (0.0001)	1.2951 (0.0002)	0.5550 (0.0003)	1.2087 (0.0001)	1.1559 (<0.0001)	1.1612 (<0.0001)	1.1427 (0.0001)	0.6734 (0.0001)	0.7603 (0.0001)	0.5423 (0.0002)
δ = 1, ρ = 0.5	1.3193 (0.0001)	1.4520 (0.0002)	0.7034 (0.0003)	1.3192 (0.0001)	1.2383 (<0.0001)	1.2471 (<0.0001)	1.2109 (0.0001)	0.7540 (0.0001)	0.8510 (0.0001)	0.6031 (0.0002)
δ = 1, ρ = 0.8										
δ = 0, ρ = 0.2	0.2084 (0.0001)	0.2951 (0.0002)	0.0697 (0.0001)	0.2087 (0.0001)	0.1559 (<0.0001)	0.1612 (<0.0001)	0.1465 (0.0001)	0.0283 (<0.0001)	0.0484 (<0.0001)	0.0005 (0.0001)
δ = 1, ρ = 0.5	0.3193 (0.0001)	0.4520 (0.0002)	0.1181 (0.0001)	0.3192 (0.0001)	0.2383 (<0.0001)	0.2471 (<0.0001)	0.2209 (0.0001)	0.0462 (<0.0001)	0.0793 (<0.0001)	0.0000 (0.0001)
δ = 0, ρ = 0.8										

Mean of estimated effect for T and its standard error (within parentheses) of twenty simulations for several methods (columns) and different parameters (rows). The effect for T (δ) is equal to either 1 or 0. The correlation between the true polygenic scores (ρ) varies. The heritability for both y and T is 0.5. The variance of both v_y and v_T equals 0.1. Correlation of v_y and v_T is 0.4. The empty lines were unobtainable parameter combinations. See the supplementary text for details.

Table S2.11: Genetic-Unrelated Endogeneity, with a Correlation of 0.4 between the Error Terms (ρ_e)

	OLS	MR-based			Conditional Proxy PGS			Unconditional Proxy PGS		
		MR	EMR-1	EMR-2	OLS $S(y\|T)$	OLS $S(y_1\|T)$	GIV-C	OLS $S(y)$	OLS $S(y_1)$	GIV-U
δ = 1, ρ = 0.2	1.3017 (0.0001)	1.2004 (0.0003)	0.6241 (0.0006)	1.3040 (0.0002)	1.3436 (0.0001)	1.3385 (0.0001)	1.3490 (0.0001)	1.0720 (0.0001)	1.1165 (0.0001)	0.9992 (0.0001)
δ = 1, ρ = 0.5	1.4520 (0.0001)	1.5032 (0.0002)	0.9145 (0.0006)	1.4545 (0.0002)	1.4306 (<0.0001)	1.4346 (0.0001)	1.4259 (0.0001)	1.1992 (0.0001)	1.2481 (0.0001)	1.1193 (0.0001)
δ = 1, ρ = 0.8	1.6019 (0.0001)	1.8051 (0.0002)	1.4138 (0.0007)	1.6055 (0.0002)	1.5225 (0.0001)	1.5391 (0.0001)	1.4684 (0.0001)	1.3539 (0.0001)	1.4032 (0.0001)	1.2721 (0.0001)
δ = 0, ρ = 0.2	0.3017 (0.0001)	0.2004 (0.0003)	0.0618 (0.0002)	0.3040 (0.0002)	0.3436 (0.0001)	0.3385 (0.0001)	0.3517 (0.0001)	0.2222 (0.0001)	0.2342 (0.0001)	0.2064 (0.0001)
δ = 0, ρ = 0.5	0.4520 (0.0001)	0.5032 (0.0002)	0.1778 (0.0002)	0.4545 (0.0002)	0.4306 (<0.0001)	0.4346 (0.0001)	0.4267 (0.0001)	0.2713 (0.0001)	0.3002 (0.0001)	0.2302 (0.0001)
δ = 0, ρ = 0.8	0.6019 (0.0001)	0.8051 (0.0002)	0.4271 (0.0003)	0.6055 (0.0002)	0.5225 (0.0001)	0.5391 (0.0001)	0.4838 (0.0001)	0.3648 (0.0001)	0.4093 (0.0001)	0.2949 (0.0001)

Mean of estimated effect for T and its standard error (within parentheses) of twenty simulations for several methods (columns) and different parameters (rows). The effect for T (δ) is equal to either 1 or 0. The correlation between the true polygenic scores (ρ) varies. The heritability for both y and T is 0.5. See the supplementary text for details.

Table S2.12: Genetic-Unrelated Endogeneity, with a Correlation of -0.1 between the Error Terms (ρ_e)

	OLS	MR-based			Conditional Proxy PGS			Unconditional Proxy PGS		
		MR	EMR-1	EMR-2	OLS $S(y\|T)$	OLS $S(y_1\|T)$	GIV-C	OLS $S(y)$	OLS $S(y_1)$	GIV-U
$\delta = 1, \rho = 0.2$	1.0509 (0.0001)	1.1968 (0.0003)	0.5579 (0.0005)	1.0546 (0.0002)	0.9886 (0.0001)	0.9980 (0.0001)	0.9706 (0.0001)	0.7253 (0.0001)	0.7791 (0.0001)	0.6431 (0.0001)
$\delta = 1, \rho = 0.5$	1.2012 (0.0001)	1.4988 (0.0003)	0.8404 (0.0006)	1.2047 (0.0002)	1.0741 (0.0001)	1.0950 (0.0001)	1.0174 (0.0001)	0.8188 (0.0001)	0.8832 (0.0001)	0.7200 (0.0001)
$\delta = 1, \rho = 0.8$	1.3512 (0.0001)	1.8003 (0.0003)	1.3490 (0.0011)	1.3537 (0.0005)	1.1531 (0.0001)	1.1962 (0.0001)	1.0074 (0.0001)	0.9331 (0.0001)	1.0066 (0.0001)	0.8179 (0.0002)
$\delta = 0, \rho = 0.2$	0.0509 (0.0001)	0.1968 (0.0003)	0.0625 (0.0002)	0.0546 (0.0002)	-0.0114 (0.0001)	-0.0020 (0.0001)	-0.0240 (0.0001)	-0.0314 (0.0001)	-0.0192 (0.0001)	-0.0479 (0.0001)
$\delta = 0, \rho = 0.5$	0.2012 (0.0001)	0.4988 (0.0003)	0.1773 (0.0002)	0.2047 (0.0002)	0.0741 (0.0001)	0.0950 (0.0001)	0.0386 (0.0001)	-0.0068 (0.0001)	0.0258 (0.0001)	-0.0544 (0.0001)
$\delta = 0, \rho = 0.8$	0.3512 (0.0001)	0.8003 (0.0003)	0.4234 (0.0005)	0.3537 (0.0005)	0.1531 (0.0001)	0.1962 (0.0001)	0.0520 (0.0001)	0.0249 (0.0001)	0.0852 (0.0001)	-0.0718 (0.0001)

Mean of estimated effect for T and its standard error (within parentheses) of twenty simulations for several methods (columns) and different parameters (rows). The effect for T (δ) is equal to either 1 or 0. The correlation between the true polygenic scores (ρ) varies. The heritability for both y and T is 0.5. See the supplementary text for details.

Table S2.13: Genetic-Unrelated Endogeneity, Partially Controlling for 20% of the Confounds.

	OLS	MR-based			Conditional Proxy PGS			Unconditional Proxy PGS		
		MR	EMR-1	EMR-2	OLS $S(y\|T)$	OLS $S(y_1\|T)$	GIV-C	OLS $S(y)$	OLS $S(y_1)$	GIV-U
$\delta = 1, \rho = 0.2$	1.2433 (0.0001)	1.2051 (0.0002)	0.6221 (0.0005)	1.2948 (0.0002)	1.2878 (<0.0001)	1.2822 (0.0001)	1.2967 (0.0001)	0.9814 (0.0001)	1.0319 (0.0001)	0.8989 (0.0001)
$\delta = 1, \rho = 0.5$	1.4008 (0.0001)	1.5056 (0.0002)	0.9103 (0.0005)	1.4456 (0.0002)	1.3792 (<0.0001)	1.3828 (0.0001)	1.3720 (0.0001)	1.1078 (0.0001)	1.1646 (0.0001)	1.0154 (0.0001)
$\delta = 1, \rho = 0.8$	1.5582 (0.0001)	1.8046 (0.0002)	1.4053 (0.0007)	1.5961 (0.0002)	1.4735 (<0.0001)	1.4908 (0.0001)	1.4046 (0.0001)	1.2638 (0.0001)	1.3226 (0.0001)	1.1667 (0.0001)
$\delta = 0, \rho = 0.2$	0.2433 (0.0001)	0.2051 (0.0002)	0.0552 (0.0002)	0.2948 (0.0002)	0.2878 (<0.0001)	0.2822 (0.0001)	0.2968 (0.0001)	0.1590 (<0.0001)	0.1717 (0.0001)	0.1429 (0.0001)
$\delta = 0, \rho = 0.5$	0.4008 (0.0001)	0.5056 (0.0002)	0.1704 (0.0002)	0.4456 (0.0002)	0.3792 (<0.0001)	0.3828 (0.0001)	0.3742 (0.0001)	0.2053 (0.0001)	0.2361 (0.0001)	0.1617 (0.0001)
$\delta = 0, \rho = 0.8$	0.5582 (0.0001)	0.8046 (0.0002)	0.4178 (0.0003)	0.5961 (0.0002)	0.4735 (<0.0001)	0.4908 (0.0001)	0.4267 (0.0001)	0.2904 (0.0001)	0.3403 (0.0001)	0.2121 (0.0001)

Mean of estimated effect for T and its standard error (within parentheses) of twenty simulations for several methods (columns) and different parameters (rows). The effect for T (δ) is equal to either 1 or 0. The correlation between the true polygenic scores (ρ) varies. The heritability for both y and T is 0.5. Controlling for 20% of the original endogeneity. Remaining correlation between error terms is 0.27. See the supplementary text for details.

Table S2.14: Genetic-Unrelated Endogeneity, Partially Controlling for 50% of the Confounds.

	OLS	MR-based			Conditional Proxy PGS			Unconditional Proxy PGS		
		MR	EMR-1	EMR-2	OLS $S(y\|T)$	OLS $S(y_1\|T)$	GIV-C	OLS $S(y)$	OLS $S(y_1)$	GIV-U
$\delta = 1, \rho = 0.2$	1.2075	1.2057	0.6227	1.2962	1.2521	1.2466	1.2638	0.9349	0.9872	0.8495
	(0.0001)	(0.0002)	(0.0004)	(0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(0.0001)	(0.0001)	(0.0001)
$\delta = 1, \rho = 0.5$	1.3643	1.5064	0.9110	1.4469	1.3431	1.3467	1.3346	1.0555	1.1151	0.9587
	(0.0001)	(0.0002)	(0.0004)	(0.0001)	(<0.0001)	(<0.0001)	(0.0001)	(0.0001)	(0.0001)	(0.0001)
$\delta = 1, \rho = 0.8$	1.5210	1.8054	1.4062	1.5973	1.4355	1.4530	1.3563	1.2042	1.2673	1.1002
	(0.0001)	(0.0002)	(0.0005)	(0.0001)	(<0.0001)	(<0.0001)	(0.0001)	(0.0001)	(0.0001)	(0.0001)
$\delta = 0, \rho = 0.2$	0.2075	0.2057	0.0562	0.2962	0.2521	0.2466	0.2617	0.1233	0.1360	0.1073
	(0.0001)	(0.0002)	(0.0001)	(0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)
$\delta = 0, \rho = 0.5$	0.3643	0.5064	0.1712	0.4469	0.3431	0.3467	0.3378	0.1656	0.1969	0.1215
	(0.0001)	(0.0002)	(0.0001)	(0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(0.0001)
$\delta = 0, \rho = 0.8$	0.5210	0.8054	0.4183	0.5973	0.4355	0.4530	0.3839	0.2407	0.2928	0.1591
	(0.0001)	(0.0002)	(0.0002)	(0.0001)	(<0.0001)	(<0.0001)	(0.0001)	(<0.0001)	(<0.0001)	(0.0001)

Mean of estimated effect for T and its standard error (within parentheses) of twenty simulations for several methods (columns) and different parameters (rows). The effect for T (δ) is equal to either 1 or 0. The correlation between the true polygenic scores (ρ) varies. The heritability for both y and T is 0.5. Controlling for 50% of the original endogeneity. Remaining correlation between error terms is 0.20. See the supplementary text for details.

Table S2.15: Genetic-Unrelated Endogeneity, Partially Controlling for 80% of the Confounds.

	OLS	MR-based			Conditional Proxy PGS			Unconditional Proxy PGS		
		MR	EMR-1	EMR-2	OLS $S(y\|T)$	OLS $S(y_1\|T)$	GIV-C	OLS $S(y)$	OLS $S(y_1)$	GIV-U
$\delta = 1, \rho = 0.2$	1.1736	1.2067	0.6237	1.2981	1.2187	1.2132	1.2332	0.8876	0.9425	0.7978
	(0.0001)	(0.0002)	(0.0003)	(0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(0.0001)	(0.0001)
$\delta = 1, \rho = 0.5$	1.3312	1.5074	0.9121	1.4487	1.3102	1.3138	1.3003	1.0040	1.0672	0.9012
	(0.0001)	(0.0001)	(0.0003)	(0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(0.0001)
$\delta = 1, \rho = 0.8$	1.4887	1.8065	1.4079	1.5989	1.4017	1.4195	1.3121	1.1477	1.2157	1.0353
	(<0.0001)	(0.0001)	(0.0003)	(0.0001)	(<0.0001)	(<0.0001)	(0.0001)	(<0.0001)	(<0.0001)	(0.0001)
$\delta = 0, \rho = 0.2$	0.1736	0.2067	0.0577	0.2981	0.2187	0.2132	0.2291	0.0888	0.1016	0.0728
	(0.0001)	(0.0002)	(0.0001)	(0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)
$\delta = 0, \rho = 0.5$	0.3312	0.5074	0.1725	0.4487	0.3102	0.3138	0.3045	0.1276	0.1596	0.0825
	(0.0001)	(0.0001)	(0.0001)	(0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)
$\delta = 0, \rho = 0.8$	0.4887	0.8065	0.4195	0.5989	0.4017	0.4195	0.3450	0.1940	0.2488	0.1082
	(<0.0001)	(0.0001)	(0.0001)	(0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)

Mean of estimated effect for T and its standard error (within parentheses) of twenty simulations for several methods (columns) and different parameters (rows). The effect for T (δ) is equal to either 1 or 0. The correlation between the true polygenic scores (ρ) varies. The heritability for both y and T is 0.5. Controlling for 80% of the original endogeneity. Remaining correlation between error terms is 0.13. See the supplementary text for details.

Table S2.16: List of Parameters, Variances and Heritability

								True	std.
Name	δ	h_y^2	h_y^2	ρ	$\rho_{vy/T}$	ρ_e	var(y)	h_y^2	δ
Pleiotropic Endogeneity	1	0.2	0.2	0.2	0	0	2.08	0.23	0.48
	1	0.2	0.2	0.5	0	0	2.2	0.27	0.45
	1	0.2	0.2	0.8	0	0	2.32	0.31	0.43
	0	0.2	0.2	0.2	0	0	1	0.2	0
	0	0.2	0.2	0.5	0	0	1	0.2	0
	0	0.2	0.2	0.8	0	0	1	0.2	0
	1	0.4	0.4	0.2	0	0	2.16	0.44	0.46
	1	0.4	0.4	0.5	0	0	2.4	0.5	0.42
	1	0.4	0.4	0.8	0	0	2.64	0.55	0.38
	0	0.4	0.4	0.2	0	0	1	0.4	0
	0	0.4	0.4	0.5	0	0	1	0.4	0
	0	0.4	0.4	0.8	0	0	1	0.4	0
	1	0.6	0.6	0.2	0	0	2.24	0.64	0.45
	1	0.6	0.6	0.5	0	0	2.6	0.69	0.38
	1	0.6	0.6	0.8	0	0	2.96	0.73	0.34
	0	0.6	0.6	0.2	0	0	1	0.6	0
	0	0.6	0.6	0.5	0	0	1	0.6	0
	0	0.6	0.6	0.8	0	0	1	0.6	0
	1	0.8	0.8	0.2	0	0	2.32	0.83	0.43
	1	0.8	0.8	0.5	0	0	2.8	0.86	0.36
	1	0.8	0.8	0.8	0	0	3.28	0.88	0.3
	0	0.8	0.8	0.2	0	0	1	0.8	0
	0	0.8	0.8	0.5	0	0	1	0.8	0
	0	0.8	0.8	0.8	0	0	1	0.8	0
	1	0.2	0.8	0.2	0	0	5.76	0.2	0.17
	1	0.2	0.8	0.5	0	0	6	0.23	0.17
	1	0.2	0.8	0.8	0	0	6.24	0.26	0.16
	0	0.2	0.8	0.2	0	0	1	0.2	0
	0	0.2	0.8	0.5	0	0	1	0.2	0
	0	0.2	0.8	0.8	0	0	1	0.2	0
	1	0.8	0.2	0.2	0	0	7.9	0.91	0.13
	1	0.8	0.2	0.5	0	0	10.9	0.94	0.09
	1	0.8	0.2	0.8	0	0	13.9	0.95	0.07
	0	0.8	0.2	0.2	0	0	1	0.8	0
	0	0.8	0.2	0.5	0	0	1	0.8	0
	0	0.8	0.2	0.8	0	0	1	0.8	0

Table S2.16 - continued

Name	δ	h_y^2	h_y^2	ρ	$\rho_{vy/T}$	ρ_e	var(y)	True h_y^2	std. δ
Genetic-	1	0.5	0.5	0.2	0.2	0	2.53	0.47	0.4
Related	1	0.5	0.5	0.5	0.2	0	2.83	0.53	0.35
Endogeneity	1	0.5	0.5	0.8	0.2	0	3.13	0.57	0.32
	0	0.5	0.5	0.2	0.2	0	1.09	0.46	0
	0	0.5	0.5	0.5	0.2	0	1.09	0.46	0
	0	0.5	0.5	0.8	0.2	0	1.09	0.46	0
	1	0.5	0.5	0.2	0.5	0	2.91	0.41	0.34
	1	0.5	0.5	0.5	0.5	0	3.21	0.47	0.31
	1	0.5	0.5	0.8	0.5	0	3.51	0.51	0.29
	0	0.5	0.5	0.2	0.5	0	1.22	0.41	0
	0	0.5	0.5	0.5	0.5	0	1.22	0.41	0
	0	0.5	0.5	0.8	0.5	0	1.22	0.41	0
	1	0.5	0.5	0.2	0.8	0	3.28	0.37	0.3
	1	0.5	0.5	0.5	0.8	0	3.58	0.42	0.28
	1	0.5	0.5	0.8	0.8	0	3.88	0.46	0.26
	0	0.5	0.5	0.2	0.8	0	1.36	0.37	0
	0	0.5	0.5	0.5	0.8	0	1.36	0.37	0
	0	0.5	0.5	0.8	0.8	0	1.36	0.37	0
Genetic-	1	0.5	0.5	0.2	0	0.4	2.6	0.46	0.38
Unrelated	1	0.5	0.5	0.5	0	0.4	2.9	0.52	0.34
Endogeneity	1	0.5	0.5	0.8	0	0.4	3.2	0.56	0.31
	0	0.5	0.5	0.2	0	0.4	1	0.5	0
	0	0.5	0.5	0.5	0	0.4	1	0.5	0
	0	0.5	0.5	0.8	0	0.4	1	0.5	0
	1	0.5	0.5	0.2	0	-0.1	2.1	0.57	0.48
	1	0.5	0.5	0.5	0	-0.1	2.4	0.63	0.42
	1	0.5	0.5	0.8	0	-0.1	2.7	0.67	0.37
	0	0.5	0.5	0.2	0	-0.1	1	0.5	0
	0	0.5	0.5	0.5	0	-0.1	1	0.5	0
	0	0.5	0.5	0.8	0	-0.1	1	0.5	0

List of parameters and the corresponding variance of y. The variance of T is always equal to 1. The effect sizes of the genetic markers are kept constant in each table, so there is no compensation for an increase in genetic correlation or for the correlation with the confounds. Hence the true heritability of y changes. δ is the effect of T, ρ is the genetic correlation, ρ_e is the correlation between the error terms in y and T (to create environmental confounds) and ρ_{vy} is the correlation between the genetic confounds for y and polygenic score for y. In all simulations $\rho_{vy} = \rho_{vT}$. The last two columns show the actual heritability for y and the standardized effect size for T.

Table S2.17: Guidance for applications

Direct pleiotropy	Environment endogeneity	Recommended method	Example
No / very low	Yes	MR	Smoking intensity on number of children
	No	OLS	Randomized controlled trials
Low	Yes	GIV + FFE + Controls*	Body height on educational attainment
	No	GIV	x
Medium	Yes	GIV + FFE + Controls*	Diet on body mass
	No	GIV	x
High	Yes	GIV + FFE + Controls*	Returns to schooling
	No	GIV	x

MR – Mendelian Randomization, OLS – Ordinary Least Squares, GIV – Genetic Instrumental Variable regression, FFE – Family fixed-effects, ideally estimated in pairs of dizygotic twins. *How well this strategy works depends on the strength of the residual environmental endogeneity after adjusting for controls and FFE; more residual environmental endogeneity will lead to more bias in the estimates of treatment T and outcome y. x No good example is known to us.

Table S2.18: Cohort List for Educational Attainment Score from SSGAC

Study	Full name	Sampling	Country	Sample size
ACPRC	Manchester Studies of Cognitive Ageing	Population-based	England	1713
AGES	Age, Gene / Environment Susceptibility-Reykjavik Study	Population-based	Iceland	3212
ALSPAC	Avon Longitudinal Study of Parents and Children	Population-based birth cohort	England	2877
ASPS	Austrian Stroke Prevention Study	Population-based	Austria	777
BASE-II	Berlin Aging Study II	Population-based	Germany	1619
CoLaus	Cohorte Lausannoise	Population-based	Switzerland	3269
COPSAC2000	Copenhagen Studies on Asthma in Childhood 2000	Case-control birth cohort	Germany	318
CROATIA-Korčula	Croatia Korčula	Population-based (Isolate)	Croatia	842
deCODE	deCODE genetics	Population-based	Iceland	46758
DHS	Dortmund Health Study	Population-based	Germany	953
DIL	Wellcome Trust Diabetes and Inflammation Laboratory	Population-based	England	2578
EGCUT1	Estonian Genome Center, University of Tartu	Population-based	Estonia	5597
EGCUT2	Estonian Genome Center, University of Tartu	Population-based	Estonia	1328
EGCUT3	Estonian Genome Center, University of Tartu	Population-based	Estonia	2047
ERF	Erasmus Rucphen Family Study	Family-based	Netherlands	2433
FamHS	Family Heart Study	Family-based	USA	3483
FINRISK	The National FINRISK Study	Case-control (Cardiovascular health)	Finland	1685
FTC	Finnish Twin Cohort	Family-based	Finland	2418
GOYA	Genetics of Overweight Young Adults	Case-control (Obesity)	Denmark	1459

GRAPHIC	Genetic Regulation of Arterial Pressure in Humans	Population-based	England	727
GS	Generation Scotland	Population-based	Scotland	8776
H2000 Cases	Health 2000	Case-control (Metabolic syndrome)	Finland	797
H2000 Controls	Same as above	Case-control (Metabolic syndrome)	Finland	819
HBCS	Helsinki Birth Cohort Study	Population-based birth cohort	Finland	1617
HCS	Hunter Community Study	Population-based	Australia	1946
HNRS (CorexB)	Heinz Nixdorf Recall Study	Population-based	Germany	1401
HNRS (Oexpr)	Same as above	Same as above	Germany	1347
HNRS (Omni1)	Same as above	Same as above	Germany	778
Hypergenes	Hypergenes	Case-control	Italy/ UK/ Belgium	815
INGI-CARL	Italian Network of Genetic Isolates - Carlantino	Population-based (Isolate)	Italy	947
INGI-FVG	Italian Network of Genetic Isolates - Friuli Venezia Giulia	Population-based (Isolate)	Italy	943
KORA S3	Kooperative Gesundheitsforschung in der Region Augsburg	Population-based	Germany	2655
KORA S4	Same as above	Population-based	Germany	2721
LBC1921	Lothian Birth Cohort 1921	Population-based birth cohort	Scotland	515
LBC1936	Lothian Birth Cohort 1936	Population-based birth cohort	Scotland	1003
LifeLines	The LifeLines Cohort Study	Population-based	Netherlands	12539
MCTFR	Minnesota Center for Twin and Family Research	Family-based, but only founders used.	USA	3819
MGS	Molecular Genetics of Schizophrenia	Population-based	USA	2313
MoBa	Mother and Child Cohort of NIPH	Population-based (Nested case-control)	Norway	622
NBS	Nijmegen Biomedical Study	Population-based	Netherlands	1808

NESDA	Netherlands Study of Depression and Anxiety	Case-control (Mental health)	Netherlands	1820
NFBC66	Northern Finland Birth Cohort 1966	Population-based	Finland	5297
NTR	Netherlands Twin Register	Family-based	Netherlands	5246
OGP	Ogliastra Genetic Park	Population-based	Italy	370
OGP-Talana	Ogliastra Genetic Park-Talana	Population-based (Isolate)	Italy	544
ORCADES	Orkney Complex Disease Study	Population-based (Isolate)	Scotland	1828
PREVEND	Prevention of Renal and Vascular End-stage Disease	Population-based	Netherlands	3578
QIMR	Queensland Institute of Medical Research	Family-based	Australia	8006
RS-I	Rotterdam Study Baseline	Population-based	Netherlands	6108
RS-II	Rotterdam Study Extension of Baseline	Population-based	Netherlands	1667
RS-III	Rotterdam Study Young	Population-based	Netherlands	3040
Rush-MAP	Rush University Medical Center - Memory and Aging Project	Community based	USA	887
Rush-ROS	Rush University Medical Center - Religious Orders Study	Community based	USA	808
SardiNIA	SardiNIA Study of Aging	Family-based	Italy	5616
SHIP	Study of Health in Pomerania	Population-based	Germany	3556
SHIP-TREND	Study of Health in Pomerania	Population-based	Germany	901
STR - Salty	Swedish Twin Registry	Family-based	Sweden	4832
STR - Twingene	Swedish Twin Registry	Family-based	Sweden	9553
THISEAS	The Hellenic Study of Interactions between SNPs & Eating in Atherosclerosis Susceptibility	Case-control	Greece	829
TwinsUK	St Thomas UK Adult Twin Registry	Population-based	England	4012
WTCCC58C	1958 British Birth Cohort	Population-based	England	2804

YFS	The Cardiovascular Risk in Young Finns Study	Population-based	Finland	2029

This table contains the list of cohorts used in the GWAS of Educational Attainment of (Okbay, Beauchamp, et al., 2016), excluding the Health and Retirement Study and 23andMe cohorts. A more detailed list and description can be found in the supplementary materials of (Okbay, Beauchamp, et al., 2016)

Table S2.19: Cohort List for Height Score from GIANT

Study	Full name	Sampling	Country	Sample size
ACTG	The AIDS Clinical Trials Group	Population-based	International	1055
ADVANCE	Atherosclerotic Disease, VAscular FunctioN, and GenetiC Epidemiology	Population-based case-control	USA	584
AE	Athero-Express Biobank Study	patient-cohort	The Netherlands	686
AGES	Age, Gene/Environment SusceptibilityReykjavik Study	Population-based	Iceland	3219
Amish HAPI Heart Study	Amish Heredity and Phenotype Intervention Heart Study	Founder population	USA	907
ARIC	Atherosclerosis Risk in Communities Study	Population-based	USA	8110
ASCOT	AngloScandinavian Cardiac Outcome Trial	"Randomised control clinical trial"	UK, Ireland and Nordic Regions	3802
B58C-T1DGC	British 1958 birth cohort (Type 1 Diabetes Genetic Consortium controls)	Populationbased birth cohort	UK	2591
B58C-WTCCC	British 1958 birth cohort (Wellcome Trust Case Control Consortium controls)	Populationbased birth cohort	UK	1479
BHS	Busselton Health Study	Population-based	Australia	1328
BLSA	Baltimore Longitudinal Study on Aging	Population-based	USA	844
B-PROOF	Baltimore Longitudinal Study on Aging	"Randomised control clinical trial"	Netherlands	2669
BRIGHT	British Genetic of Hypertension (BRIGHT) study	Hypertension cases	UK	1806
CAD-WTCCC	WTCCC Coronary Arteryt Disease cases	Case series	UK	1879

CAPS1 cases	Cancer Prostate in Sweden 1	Case-control	Sweden	489
CAPS1 controls	Cancer Prostate in Sweden 1	Case-control	Sweden	491
CAPS2 cases	Cancer Prostate in Sweden 2	Case-control	Sweden	1483
CAPS2 controls	Cancer Prostate in Sweden 2	Case-control	Sweden	519
CHS	Cardiovascular Health Study	Population-based	USA	3228
CoLaus	Cohorte Lausannoise	Population-based	Switserland	5409
Corogene	Genetic Predisposition of Coronary Heart Disease in Patients Verified with Coronary Angiogram	Population-based	Finland	3758
deCODE	deCODE genetics sample set	Population-based	Iceland	26799
DESIR	Data from an Epidemiological Study on the Insulin Resistance syndrome	Population-based	France	716
DGI cases	Diabetes Genetics Initiative	Case-control	Scandinavia	1317
DGI controls	Diabetes Genetics Initiative	Case-control	Scandinavia	1090
DNBC	Danish National Birth Cohort - Preterm Delivery Study	Case-control	Denmark	1802
EGCUT	Estonian Genome Center, University of Tartu	Population-based	Estonia	1417
EGCUT-370	Estonian Genome Center, University of Tartu	Population-based	Estonia	866
EGCUTOMNI	Estonian Genome Center, University of Tartu	Population-based	Estonia	1356
EPIC-Obesity Study	European Prospective Investigation into Cancer and Nutrition - Obesity Study	Population-based	UK	3552
ERF	Erasmus Rucphen Family Study	Family-based	Netherlands	2726
FamHS	Family Heart Study	Population-based	USA	1463
Fenland	Fenland Study	Population-based	UK	1402
FINGESTURE cases	Finnish Genetic Study of Arrhythmic Events	Disease cohort (MI cases only)	Finland	943

FRAM	Framingham Heart Study	Population-based, multigenerational	USA	8089
FTC	Finnish Twin Cohort	Monozygotic twins	Finland	125
FUSION cases	Finland-United States Investigation of NIDDM Genetics	Case-control	Finland	1082
FUSION controls	Finland-United States Investigation of NIDDM Genetics	Case-control	Finland	1167
GENMETS cases	Health 2000 / GENMETS substudy of Metabolic syndrome	Case-control	Finland	824
GENMETS controls	Health 2000 / GENMETS substudy of Metabolic syndrome	Case-control	Finland	823
GerMiFSI (cases only)	German Myocard Infarct Family Study I	Case-control	Germany	600
GerMiFSII (cases only)	German Myocard Infarct Family Study II	Case-control	Germany	1124
GOOD	Gothenburg Osteoporosis and Obesity Determinants Study	Population-based	Sweden	938
HBCS	Helsinki Birth Cohort Study	Birth cohort study	Finland	1726
Health ABC	Health, Aging, and Body Composition Study	longitudinal cohort study	USA	1655
HERITAGE Family Study	Health, Risk Factors, Training and Genetics (HERITAGE) Family Study	Family Study, baseline data from an exercise training intervention	USA	500
HYPER-GENES Cases	HYPERGENES	Case-control	Italy/ UK/ Belgium	1841
HYPER-GENES Controls	HYPERGENES	Case-control	Italy/ UK/ Belgium	1900
InCHIANTI	Invecchiare in Chianti	Population-based	Italy	1138

IPM Mount Sinai BioMe	The Charles Bronfman Institute for Personalized Medicine BioMe Biobank Program	Hospital-based	USA	2867
KORA S3	Cooperative Health Research in the Region of Augsburg, Kooperative Gesundheitsforschu ng in der Region Augsburg	Population-based	Germany	1643
KORA S4	Cooperative Health Research in the Region of Augsburg, KOoperative Gesundheitsforschu ng in der Region Augsburg	Population-based	Germany	1811
LifeLines	LifeLines Cohort study	Population-based	Netherlands	8118
LLS	Leiden Longevity Study	Family based	Netherlands	1903
LOLIPOP _EW610	London Life Sciences Prospective Population Study	Population-based	UK	927
LOLIPOP _EWA	London Life Sciences Prospective Population Study	Population-based with some enrichment	UK	513
LOLIPOP _EWP	London Life Sciences Prospective Population Study	Population-based with some enrichment	UK	651
MGS	Molecular Genetics of Schizophrenia/NIMH Repository Control Sample	Population-based (survey research method)	USA	2597
MICROS	MICROS (EUROSPAN)	Population-based	Italy	1079
MIGEN	Myocardial Infarction Genetics Consortium	Case-control	USA / Finland / Italy / Spain / Sweden	2652
NBS-WTCCC	WTCCC National Blood Service donors	Population-based	UK	1441
NELSON	Dutch and Belgian Lung Cancer Screening Trial		Netherlands and Belgium	2668

NFBC1966	Northern Finland Birth Cohort 1966	Population-based	Finland	4499
NHS	The Nurses' Health Study	Nested case-control	USA	3217
NSPHS	Northern Sweden Population Health Study (EUROSPAN)	Population-based	Sweden	652
NTRNESDA	Netherlands Twin Register & the Netherlands Study of Depression and Anxiety	Case-control	Netherlands	3522
ORCADES	Orkney Complex Disease Study (part of EUROSPAN)	Population-based	Scotland	695
PLCO	The Prostate, Lung Colorectal and Ovarian Cancer Screening Trial	Case-control	USA	2244
PLCO2 controls	Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial	Population-based case-control	USA	1193
PREVEND	Prevention of REnal and Vascular ENdstage Disease (PREVEND) Study	Population-based	Netherlands	3624
PROCARDIS	Precocious Coronary Artery Disease	Population-based	UK	7000
PROSPER/ PHASE	The PROspective study of Pravastatin in the Elderly at Risk for vascular disease	Randomized controlled trial	Netherlands, Scotland and Ireland	5244
QFS	Quebec Family Study	Family-based???	Canada	860
QIMR	Twin study at Queensland Institute of Medical Research	Population-based	Australia	3627
RISC	Relationship between Insulin Sensitivity and Cardiovascular disease Study	Population-based	Europe	1031
RS-I	Rotterdam Study I	Population-based	Netherlands	5744
RS-II	Rotterdam Study II	Population-based	Netherlands	2124
RS-III	Rotterdam Study III	Population-based	Netherlands	2009

RUNMC	Nijmegen Bladder Cancer Study (NBCS) & Nijmegen Biomedical Study (NBS), Radboud University Nijmegen Medical Centre	Population-based	Netherlands	2873
SardiNIA	SARDINIA	Population-based	Italy	4298
SASBAC cases	Swedish And Singapore Breast Association Consortium	Case-control	Sweden	794
SASBAC controls	Swedish And Singapore Breast Association Consortium	Case-control	Sweden	758
SEARCH / UKOPS	Studies of Epidemiology and Risk factors in Cancer Heredity / UK Ovarian Cancer Population Study	Population-based	UK	1592
SHIP	Study of Health in Pomerania	Population-based	Germany	4092
SHIP-TREND	Study of Health in Pomerania - TREND	Population-based	Germany	986
Sorbs	Sorbs are selfcontained population from Eastern Germany, European Descent	Population-based	Germany	907
T2D-WTCCC	WTCCC Type 2 Diabetes cases	case series	UK	1903
TRAILS	Tracking Adolescents' Individual Lives Survey	Population-based (measured at 18yrs of age)	Netherlands	1139
TWINGENE	TWINGENE	Population-based	Sweden	9380
TwinsUK	TwinsUK	Twins pairs	UK	1479
VIS	VIS (EUROSPAN) and KORCULA	Population-based	Croatia	784
WGHS	Women's Genome Health Study	Population-based	USA	23099
YFS	The Cardiovascular Risk in Young Finns Study	Population-based cohort	Finland	1995

This table contains the list of cohorts used in the GWAS of height from (Wood et al., 2014). A more detailed list and description can be found in the supplementary materials of (Wood et al., 2014) and (Allen et al., 2010)

Chapter 3

A comparison of heritability estimates from GIV regression and GREML

Based on unpublished work by C.A.P. Burik, R. de Vlaming and P.D. Koellinger

Abstract

We compare heritability estimates from genetic instrumental variables (GIV) regression and genome-based restricted maximum likelihood (GREML) in various simulated scenarios. We simulate phenotypes using real genotypes from the UK Biobank (N= 408,741). We simulate phenotypes using three different models, a baseline model adhering to the GREML assumptions and two models that deviate from the GREML assumptions. GIV regression and GREML perform well in all scenarios. GREML performs well even when the simulation model strongly deviates from the assumptions of GREML.

3.1 Introduction

Heritability is one of the core concepts of quantitative genetics, as it describes the proportion of phenotypic variance that may be attributed to genetic effects. Traditionally, heritability is estimated within families, with particular emphasis on twin studies, which have been utilized since the 1970s. Over the last two decades, technological advancements have made it possible to estimate heritability using different methods from molecular genetic data and in the last decade, three main classes of methods have emerged. Here, we provide a short summary of the most used methods from each class.

The first class of methods uses individual-level genotype and phenotype data directly (Yang et al., 2010). This class contains the well-established method genome-based restricted maximum likelihood (GREML). GREML is a method that uses a mixed-effects model, where the phenotypic variance is explained by a genetic component and an idiosyncratic noise component. The genetic variance component is built around a genomic-relatedness matrix (GRM), which reflects genetic similarity between individuals. The two variance components are estimated using restricted maximum likelihood estimation. The heritability then equals the share of the total variance explained by the genetic component. GREML assumes a model where all SNPs are causal and the SNP effects are normally distributed with an inverse relation between effect size and minor allele frequency (MAF). GREML is usually performed in a sample of unrelated individuals using common single nucleotide polymorphisms (SNPs) with a MAF above 1 percent.

The second class of methods, which includes LD-score (LDSC) regression, uses genome-wide association study (GWAS) summary statistics (Bulik-Sullivan et al., 2015). While LDSC was not originally designed to estimate heritability, it is often used for this purpose, as one only needs GWAS summary statistics and can thus be done without direct access to the genotypes or phenotypes. Bulik-Sullivan et al. (2015) show that the heritability of a trait can be estimated by regressing GWAS χ^2-statistics on the linkage-disequilibrium (LD) score of a SNP, which measures the degree to which a SNP is correlated to neighboring SNPs. LDSC and other methods in this category all rely on LD being present in the data. For reasons discussed below, we will use genetic data that is heavily pruned on LD and thus methods in this category cannot be included in the comparison. A detailed comparison of LDSC and other methods has been done by Evans et al. (2018).

The third and final class uses a polygenic index (PGI) constructed from summary statistics. The only method in this class is the recently developed genetic instrumental-variable (GIV) regression (DiPrete, Burik, & Koellinger, 2018). The starting point for GIV regression is the following observation: if it would be possible to construct a perfect PGI without any estimation error, then heritability of a phenotype could be estimated by regressing the phenotype on that PGI and taking the share of explained variance from that regression. When using PGIs in practice, the estimates are attenuated by estimation error in the PGI. This can be compensated by creating two PGIs using GWAS summary statistics from independent GWAS samples and regressing the phenotype on one PGI using two-stage least squares estimation, where the second PGI is used as an instrument for the first PGI.

When the estimation errors in the two PGIs are independent, this methodology corrects the attenuation found in a regular regression of the phenotype on the PGI. From this instrumental-variables approach, a heritability estimate can then be recovered. The key assumption here is that the estimation errors in the two PGI are independent from each other. Any violations (e.g., by not accounting for LD structure or sample overlap) from independence may bias the estimator. A big advantage of GIV regression is the absence of assumptions on the distribution of SNP effects that are required for most estimators in the first two classes.

In this paper, we compare the newly developed GIV regression to the long-established GREML estimation. First, we compare the methods in a baseline scenario where both methods should provide unbiased estimates. Next, we consider scenarios where GIV regression may be preferred over GREML, as those scenarios violate the assumptions of GREML. Specifically, scenarios where very few SNPs are causal and scenarios where the relation between effect size and MAF deviates from the GREML assumptions. The simulations are carried out using real genetic data from the UK Biobank (Fry et al., 2017; Sudlow et al., 2015) with simulated SNP effects and phenotypes.

3.2 Materials and Methods

3.2.1 Genetic Data

We use genetic data from the UK Biobank participants. The UK Biobank is a large population-based longitudinal study, designed to study health in middle aged and older UK citizens (Fry et al., 2017; Sudlow et al., 2015).

To avoid spurious associations in our simulations we perform quality control (QC) on the genetic data. We remove individuals that are related, using relatedness estimates provided by the UK Biobank. We restrict our analyses to individuals of European descent, to simplify the simulations. We filter SNPs based on low MAF (i.e., below 1%), high missingness (i.e., above 1%), and deviations from Hardy-Weinberg equilibrium (p-values below 10^{-6}). We also remove long-range LD regions.

As correcting for LD (e.g., using LDpred; Vilhjálmsson et al., 2015) is computationally intensive we perform LD pruning on SNPs, using an r^2 threshold of 0.03. To further simplify the simulations, we fill missing SNP observations by drawing randomly from a binomial distribution with 2 draws and probability of 'success' equal to the empirical MAF of the given SNP. After these QC steps, we are left with 54,280 SNPs for 408,741 individuals. QC is carried out using Plink 1.9 (Chang et al., 2015; Purcell et al., 2007).

The genetic data is divided into three subsamples, two GWAS samples consisting of 90 percent of the total sample, creating samples of 183,933 individuals each, and a hold-out sample of the remaining 10 percent of the sample—40,875 individuals. The GWAS samples are used to perform two separate GWASs. The estimated effects from these GWAS are then used to construct two PGIs in the hold-out sample. The hold-out sample is used for heritability estimation using both GREML estimation and GIV regression, where the former uses individual-level genotypes and phenotypes in the hold-out sample, whereas the latter only makes use of the two aforementioned PGIs and the phenotype in the hold-out sample.

We also construct twenty leading principal components (PCs) from the genetic data that we use in our simulations to account for further population structure in the data. The PCs are created from all SNPs after the QC steps, as long-range LD regions are removed and SNPs pruned on LD during the QC steps. The PCs are created separately for each subsample. The PCs are calculated using FlashPCA2 (Abraham, Qiu, & Inouye, 2017).

For GREML we also calculate a GRM in the hold-out sample. This GRM is used in the simulations. The GRM is created using Plink 1.9, also using the full set of SNPs after QC.

3.2.2 Simulations

We compare the heritability estimates from GREML and GIV regression using simulations. We use genotypes from the UK Biobank and simulate phenotypes by drawing SNP effects from a normal distribution when the SNP is causal. Effect sizes increase or decrease with MAF depending on parameter settings. The distribution of SNP effects can be given as follows:

$$\beta_j \sim \begin{cases} 0, & \text{with probability } 1-\pi, \\ \mathcal{N}(0,\sigma_j^2), & \text{with probability } \pi, \end{cases} \tag{3.1}$$

$$\sigma_j^2 = \left(2\, f_j(1-f_j)\right)^{\alpha}, \tag{3.2}$$

where β_j is the effect of SNP j, π is the probability for each SNP being causal, f_j is the MAF of SNP j, α is the parameter that determines the relationship between MAF and effect size. Note that $\alpha = -1$ corresponds to standard GREML assumptions, where standardized SNPs have homoscedastic effects.

The phenotype is then created from the drawn effect sizes by post-multiplying the matrix of SNP data by the column vector of SNP effects. Next, we set our outcome, **y**, as a linear combination of the genetic term, **g**, and the error term, **ε**, such that the proportion of variance of **y** accounted for by **g** equals the desired heritability, h^2. More specifically, we set

$$\mathbf{y} = \sqrt{\frac{h^2}{\mathrm{Var}(\mathbf{g})}}\mathbf{g} + \boldsymbol{\epsilon}, \tag{3.3}$$

$$\mathbf{g} = \mathbf{X}\boldsymbol{\beta}, \text{ and} \tag{3.4}$$

$$\boldsymbol{\epsilon} \sim \mathcal{N}(0,(1-h^2)\mathbf{I}), \tag{3.5}$$

where **y** is the vector of phenotypes, h^2 is the heritability, **X** is the matrix of SNPs, **I** the identity matrix, and $\boldsymbol{\epsilon}$ is the error term. Furthermore, we orthogonalize the phenotype from the first twenty principal components of the genetic data to remove population structure.

After the phenotype simulation, we carry out a GWAS in each of the two GWAS samples. Then both GIV regression and GREML estimation are performed in the hold-out sample. In the base simulations, we vary h^2 between 10% and 90%. Here, the share of causal SNPs (π) is set to 100% and the relation between MAF and effect size follows the GREML assumptions ($\alpha = -1$). Following the base simulations, we set $h^2 = 50\%$. Next, we vary the polygenicity (i.e., the share of causal SNPs), denoted by π. We consider π between 0.002%, which corresponds to only one causal SNP, and 100%, which corresponds to full polygenicity. As GREML assumes $\pi = 100\%$ (i.e., all SNPs being causal), we expect GREML estimation performs worse than GIV regression if π is very low, as GIV regression places no assumptions on π.

Next, we carry out simulations where we change the relationship between effect size and MAF. We do this by changing the α parameter in Equation 3.2. Again, we set $h^2 = 50\%$. In addition, we $\pi = 100\%$. Importantly, GREML assumes $\alpha = -1$. We vary this parameter between −2 and 0.5. GIV regression makes no assumptions about the relationship between effect size and MAF. Hence, we expect that GIV regression performs better than GREML estimation when we deviate from this assumption.

For every distinct simulation setting, we perform 50 simulations.

3.3 Results

Figure 3.1 shows the results of the baseline simulations. The heritability varies between 10 percent and 90 percent. GREML is unbiased in all cases. GIV regression shows a slight downward bias that grows with the heritability. While the SNPs were pruned on LD, LD was not fully eliminated from the genetic data and it was not otherwise accounted for due to computational constraints. Hence, a small downward bias is not unexpected. In simulated data, where all SNPs are fully independent GIV regression does not show this slight downwards bias (DiPrete et al., 2018).

Figure 3.2 shows the results where we vary the share of causal SNPs. Surprisingly, GREML is very resilient to deviations from the model where all SNPs are causal, even when we go down to a single causal SNP at $\pi = 0.00002$. Similar to the results in Figure 3.1, the GIV results are slightly downwards biased.

Finally, Figure 3.3 shows the results where we vary the relationship between MAF and effect size. We see similar results compared to the first two sets of simulations, again GREML is very resilient to the deviations of its assumptions across all simulations considered. The GIV results are again slightly biased downwards.

3.4 Discussion

Our results show that GREML is a reliable method which is very resilient to the deviations from the assumptions that we considered (i.e., polygenicity, π, and the relationship between MAF and effect size, α). GIV regression also works as expected in these simulations. It has a slight bias downwards due to LD not being fully accounted for. In practice, it can be combined with methods like LDpred (Vilhjálmsson et al., 2015) to create PGIs. Such an approach, however, is computationally infeasible in our simulation study.

The advantage of GREML is that it can be applied without performing any GWAS prior to the analysis. It also has smaller standard errors in each of the scenarios we simulated. Therefore, it remains the recommended method to estimate heritability here. However, as GIV regression does not require many assumptions it remains a very flexible method that might have advantages when applied elsewhere. One possibility is extending the method so it can be applied to within-family GWAS to estimate both heritability and genetic nurture (Kong et al., 2018). Currently, however, the within-family samples sizes are not big enough yet to conduct the type of large-scale within-family GWASs needed to potentially extend the GIV regression method further.

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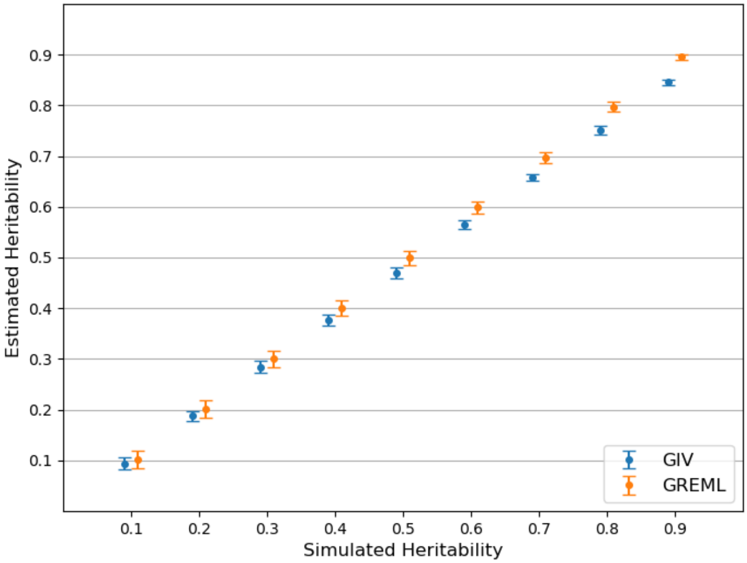
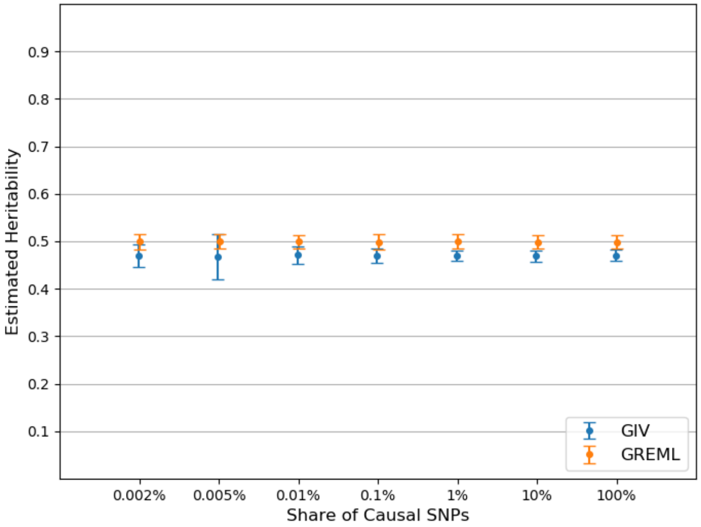
3.6 Figures

Figure 3.1. Baseline simulations



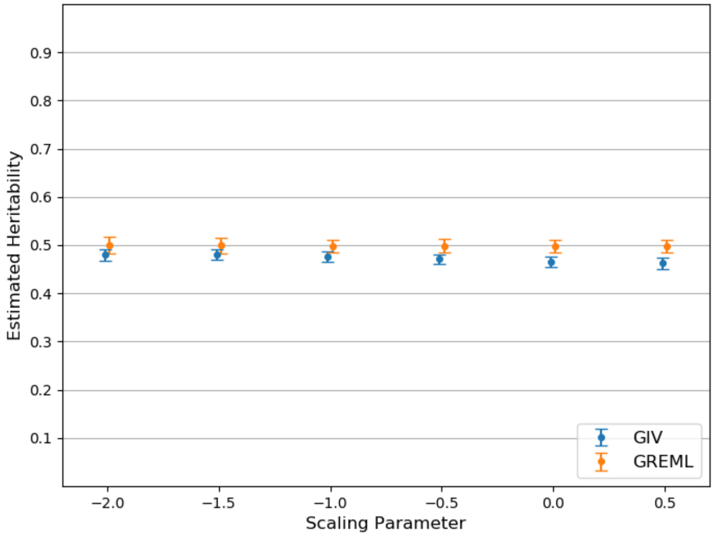
This figure shows the results of the baseline simulations, as described by equations (3.1) to (3.5). The results are based on 50 simulations for each parameter setting. GIV and GREML are estimated in a hold-out sample from the UK Biobank using simulated phenotypes. The GWASs for GIV are run in two independent subsamples of the UK Biobank.

Figure 3.2. Simulations with varied share of causal SNPs



This figure shows the results of simulations where the share of causal SNPs is varied between 0.002 percent (i.e., one causal SNP) and 100 percent. The simulations are described by equations (3.1) to (3.5). In this set of simulations, the results are based on 50 simulations for each parameter setting. GIV and GREML are estimated in a hold-out sample from the UK Biobank using simulated phenotypes. The GWASs for GIV are run in two independent subsamples of the UK Biobank.

Figure 3.3. Simulations with varied scaling parameter



This figure shows the results of simulations where the relationship between SNP effect size and minor allele frequency is varied. The simulations are described by equations (3.1) to (3.5). The results are based on 50 simulations for each parameter setting. GIV and GREML are estimated in a hold-out sample from the UK Biobank using simulated phenotypes. The GWASs for GIV are run in two independent subsamples of the UK Biobank.

Chapter 4

Resource Profile and User Guide of the Polygenic Index Repository

Published as:

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This publication contains online supplements not included in this chapter

Abstract

Polygenic indexes (PGIs) are DNA-based predictors. Their value for research in many scientific disciplines is rapidly growing. As a resource for researchers, we used a consistent methodology to construct PGIs for 47 phenotypes in 11 datasets. To maximize the PGIs' prediction accuracies, we constructed them using genome-wide association studies—some not previously published—from multiple data sources, including 23andMe and UK Biobank. We present a theoretical framework to help interpret analyses involving PGIs. A key insight is that a PGI can be understood as an unbiased but noisy measure of a latent variable we call the "additive SNP factor." Regressions in which the true regressor is the additive SNP factor but the PGI is used as its proxy therefore suffer from errors-in-variables bias. We derive an estimator that corrects for the bias, illustrate the correction, and make a Python tool for implementing it publicly available.

4.1 Main

The ability to predict complex outcomes from genotype data alone is rapidly increasing. The main catalyst behind the increases is the success of genome-wide association studies (Visscher et al., 2017) (GWAS). GWAS estimate the relationship between a trait, called a "phenotype," and each of millions of genetic variants. The "summary statistics" (coefficients and standard errors) from GWAS can be used to construct a DNA-based predictor of the phenotype, calculated essentially as a coefficient-weighted sum of allele counts (Purcell et al., 2009; Wray, Goddard, & Visscher, 2007). There are a variety of terms used for such DNA-based predictors. In this paper, we will refer to them as "polygenic indexes"[1].

As GWAS sample sizes have grown, coefficients are estimated more precisely, enabling the construction of more predictive PGIs. One example is the PGI for educational attainment. The original PGI was constructed from a GWAS of ~100,000 individuals and predicted ~2% of the variance in years of schooling across individuals (C. A. Rietveld et al., 2013). The third and most recent PGI for educational attainment (EA) predicts ~12% of the variance (Lee et al., 2018). Qualitatively similar patterns have been

[1] In this paper, we use the term "polygenic index" instead of the commonly used terms "polygenic score" and "polygenic risk score." Most of us prefer the term polygenic index because we are persuaded by the argument that it is less likely to give the impression of a value judgment where one is not intended. The term polygenic index was first proposed by Martha Minow at a meeting of the Trustees of the Russell Sage Foundation.

observed in PGIs for other complex-trait phenotypes (Cesarini & Visscher, 2017; Visscher et al., 2017), including height, fertility, personality traits, and risk of many common diseases.

PGIs became mainstream in human genetics remarkably quickly. While predictive genetic indexes have a long history in plant and animal genetics (Wray, Kemper, Hayes, Goddard, & Visscher, 2019), the idea of using GWAS summary statistics to generate a PGI for humans was first proposed in 2007 (Wray et al., 2007). The first study to empirically construct and validate a PGI was a GWAS of bipolar disorder and schizophrenia published in 2009 (Purcell et al., 2009). Soon thereafter, command of methods used to construct PGIs became a standard part of the skill repertoire of analysts specializing in genome-wide data.

Today, PGIs are profoundly impacting research across the disciplinary spectrum. In medicine, much of the discussion revolves around their potential use as tools for identifying individuals who could benefit from enhanced screening and preventive therapies (Green & Guyer, 2011). Though much uncertainty remains about their ultimate clinical utility (Wray et al., 2013), one recent study of polygenic risk for five common diseases concluded that the science is sufficiently far along to contemplate incorporating polygenic prediction into clinical care (Khera et al., 2018). Researchers working at the intersection of the social and natural sciences have articulated visions of how PGIs could be productively leveraged in a number of ways to advance knowledge about important questions (Belsky & Harden, 2019; Benjamin et al., 2012; Freese, 2018). Already, the various iterations of the EA PGI have been used, among other things, to trace out pathways for genetic influences that develop with age (Belsky et al., 2016) and through school (Harden et al., 2020), study assortative mating (Robinson et al., 2017; Yengo, Robinson, et al., 2018), trace recent migration patterns (Abdellaoui et al., 2019; Domingue, Rehkopf, Conley, & Boardman, 2018), and improve analyses of the relationship between education and earnings (Papageorge & Thom, 2020). As PGIs become more predictive and available for more phenotypes, potential applications will multiply, and novel areas of research are likely to open up.

To depict the rapid growth in research using PGIs, Figure 4.1 shows the percentage of PGI-related papers presented at the annual meetings of the Behavior Genetics Association. The percentage increased from zero in 2009 to 20% in 2019. The figure also shows how the percentages of papers classified as candidate-gene studies and twin/family/adoption studies—two other commonly used approaches—have evolved over time. The declining fraction of candidate-gene studies in the figure is consistent with the hypothesis of a paradigm shift, with candidate-gene-based approaches gradually being displaced by PGI-based approaches (Freese, 2018). This shift occurred, at least in part, because PGIs are not subject to some well-known methodological limitations of candidate-gene studies (Duncan & Keller, 2011; Hewitt, 2012; C. A. Rietveld et al., 2014).

In this paper, we hope to promote productive behaviour-genetic research using PGIs in three ways. First and most centrally, we make a broad array of PGIs available via a Polygenic Index Repository, covering a number of datasets that may be useful to social scientists. By constructing the PGIs ourselves and making them available as variables downloadable from the data providers, our resource eliminates a number of roadblocks for researchers who would like to use PGIs in their research, as we detail below. The Repository contains PGIs for 47 phenotypes. To maximize prediction accuracy of the PGIs, we meta-analysed summary statistics from multiple sources, including several large-scale GWASs conducted in UK Biobank and the personal genomics company 23andMe. 23andMe shared summary statistics from 37 separate association analyses, 9 of which have not been reported previously. Therefore, almost all PGIs in our initial release perform at least as well as currently available PGIs in terms of prediction accuracy. We will update the Repository regularly with additional PGIs and datasets.

Second, we present a theoretical framework for interpreting associations with a PGI. Using this framework, we show that a PGI can be understood as an unbiased but noisy measure of what we call the "additive SNP factor," which is the best linear predictor of the phenotype from the measured genetic variants. Because the PGI is a noisy measure, regressions that use the PGI as an explanatory variable suffer from errors-in-variables bias. Since different papers use different versions of a PGI, the magnitude of this bias varies. We hope that the theoretical framework helps establish a common language for discussions about the interpretation of PGIs and their effect sizes.

Third, we propose an approach that improves the interpretability and comparability of research results based on PGIs: to use in place of ordinary least squares (OLS) regression, we derive an estimator that corrects for the errors-in-variables bias. (We are aware of four papers to date that have implemented a measurement-error correction along the lines we propose here (Beauchamp, 2016; DiPrete, Burik, & Koellinger, 2018; Kong et al., 2017; Tucker-Drob, 2017). Our approach is most similar to that of ref. (Tucker-Drob, 2017), who develops a nearly identical framework using a psychometrics modeling approach but focuses on the univariate case.) The estimator produces coefficients in units of the standardized additive SNP factor, which has a more meaningful interpretation than units of some particular PGI. We illustrate by applying the estimator to multivariate and gene-by-environment regressions from a recently published paper (Papageorge & Thom, 2020). We make a Python command-line tool publicly available for implementing the estimator.

4.2 Results

4.2.1. The Polygenic Index Repository

The Polygenic Index Repository is a resource that addresses several practical obstacles that researchers interested in using PGIs must often confront. These include:

1. Constructing PGIs from individual genotype data can be a time-consuming process, even for researchers trained to work with large datasets.
2. Since the prediction accuracy of a PGI is increasing in the sample size of the underlying GWAS, it is generally desirable to generate PGI weights from GWAS summary statistics based on the largest available samples. However, privacy and IRB restrictions often create administrative hurdles that limit access to summary statistics and force researchers to trade off the benefit of summary statistics from a larger sample against the costs of overcoming the hurdles. In practice, researchers often end up constructing PGIs using only publicly available summary statistics.
3. Publicly available GWAS summary statistics are sometimes based on a discovery sample that includes the target cohort (or close relatives of cohort members) in which the researcher wishes to produce the PGI. Such sample overlap causes overfitting, which can lead to highly misleading results (Wray et al., 2013). (Sometimes, when GWAS consortia provide summary statistics upon request from a GWAS that is restricted so as to exclude the cohort, this barrier is surmounted at low cost.)
4. Because different researchers construct PGIs from GWAS summary statistics using different methodologies, it is hard to compare and interpret results from different studies.

We overcome #1 by constructing the PGIs ourselves and releasing them to the data providers, who in turn will make them available to researchers. This simultaneously addresses #2 because we use all the data available to us that may not be easily available to other researchers or to the data providers, including genome-wide summary statistics from 23andMe. Using these genome-wide summary statistics from

23andMe is what primarily distinguishes our Repository from existing efforts by data providers to construct PGIs and make them available, such as the effort by the Health and Retirement Study (https://hrs.isr.umich.edu/data-products/genetic-data/products#pgs). It also distinguishes our Repository from efforts to make publicly available PGI weights directly available for download (Lambert et al., 2020) (although we also do that, for weights constructed without 23andMe data). To deal with #3, for each phenotype and each dataset, we construct a PGI from GWAS summary statistics that excludes that dataset. We overcome #4 by using a uniform methodology across the phenotypes. In Methods, we detail how the Repository disseminates the PGIs, as well as the principal components of the genetic data in each dataset (which often should be used as controls for ancestry; see Supplementary Methods).

Figure 4.2 depicts the algorithm that determined which PGIs we constructed. In a preliminary step, we obtained GWAS summary statistics for a comprehensive list of 53 candidate phenotypes (see Supplementary Tables 1 and 2, meta-analysed the summary statistics for each candidate phenotype, and calculated the expected R^2 for an out-of-sample regression of each candidate phenotype on a PGI derived from its GWAS summary statistics. We calculated this expected R^2 from the GWAS summary statistics (see Methods for details). If it exceeded $R^2 = 0.01$, then we used the meta-analysis output to construct a PGI for the phenotype. We call these the "single-trait PGIs." For each candidate phenotype, we also identified a list of supplementary phenotypes: any other phenotype whose pairwise genetic correlation with the candidate exceeds 0.6 in absolute value. For each candidate with at least one supplementary phenotype, we then calculated the out-of-sample expected R^2 of a PGI derived from a joint analysis of the candidate and supplementary phenotype summary statistics. If the expected R^2 exceeded 0.01, then we used the joint-analysis output to construct a "multi-trait PGI" for the phenotype. When both single-trait and multi-trait PGIs are available, the multi-trait PGI generally has greater predictive power, but the single-trait PGI may be better suited for some applications (see Supplementary Methods).

For each of the 47 phenotypes for which we constructed a single-trait and/or multi-trait PGI, Table 4.1 lists the total sample size included in the GWAS summary statistics (Total N), followed by the sample-size contributions from three separate sources. For comparison, we also report the sample size of the largest GWAS whose summary statistics are in the public domain (Public N). With three exceptions, Total N exceeds Public N. Two exceptions are height and BMI, where our UKB sample inclusion filters lead to a slightly smaller sample size than the Public N. The remaining exception is cognitive performance, where the sample size of our GWAS is smaller due to overlap between the discovery sample in the largest GWAS with publicly available summary statistics and some of our Repository cohorts. For the remaining phenotypes, the gains in sample size relative to the public N are often substantial, and driven by our inclusion of summary statistics from large-scale GWASs conducted in 23andMe, UKB, or both. Table 4.1 also shows the 36 and 35 phenotypes for which we created single-trait and multi-trait PGIs, respectively.

We created PGIs for these phenotypes in 11 Repository cohorts that shared their individual-level genetic data with us (regardless of whether the phenotype itself is measured in the cohort). Table 4.2 lists the datasets and some of their basic characteristics. Each data provider will make these PGIs available to researchers through their own data access procedures (see Supplementary Note).

The UK Biobank is among the 11 cohorts included in the Polygenic Index Repository. Because of its large sample size (see Table 4.2), the UK Biobank contributes substantially to the available sample for the GWAS for many phenotypes. We therefore did not want to exclude the entire UK Biobank from the GWASs used to create the PGIs. Instead, we split the UK Biobank sample into three equal-sized partitions. We ran three 1/3-sample GWASs for each phenotype. To create the PGI for each partition, we included results from the other two partitions in the meta-analysis. Consequently, researchers can conduct analyses of a PGI in any one of the partitions and obtain unbiased results. However, we caution researchers against conducting analyses in two or three of the partitions and meta-analyzing across partitions; because the other partitions are used to create the PGI, the results obtained across different partitions (although individually unbiased) will be correlated. Meta-analysis standard errors will therefore be anticonservative, and this bias can be substantial (see Methods). Therefore, to maximize the usefulness of our PGIs for research involving related individuals or brain-scan data, we assigned to the same partition all pairs of individuals that are related up to second degree (and some pairs of third degree), as well as all individuals with brain-scan data.

For validating the predictive power of the PGIs, we used five cohorts for which we had access to individual-level genetic and phenotypic data: the Health and Retirement Study, a representative sample of Americans over the age of 50; the Wisconsin Longitudinal Study, a sample of individuals who graduated from high school in Wisconsin in 1957; the Dunedin Multidisciplinary Health and Development Study, a sample of residents of Dunedin, New Zealand, born in 1972-1973; the

Environmental Risk (E-Risk) Longitudinal Twin Study, a birth cohort of twins born in England and Wales in 1994-1995; and the UKB (our third partition). The top panel of Figure 4.3 shows the observed R^2 and 95% confidence intervals for the single-trait PGIs in one or more validation cohorts, depending on which had a measure of the phenotype. Height, BMI, and educational attainment are shown separately because the *y*-axis scale is different. The bottom panel of Figure 4.3 shows the difference between the R^2 of the single-trait Repository PGI and that of a PGI we constructed using the largest non-overlapping GWAS whose summary statistics are in the public domain. The Repository PGIs are almost always at least as predictive as the PGIs based on publicly available GWAS results. For the corresponding results for the multi-trait PGIs, see Supplementary Figure 1. The multi-trait PGIs are usually at least as predictive as the single-trait PGIs (Supplementary Figure 1C and Supplementary Table 3).

We have written a User Guide (reproduced in the Supplementary Methods) that will be distributed by participating cohorts along with the Repository PGIs. It discusses interpretational issues, including those relevant for whether researchers should use the single-trait or multi-trait PGIs when both are available.

4.2.2 Theoretical Framework for Polygenic Indexes

To help interpret PGIs, we lay out a theoretical framework. Denote individual i's phenotype value by $y_i^\star$. Denote individual i's allele count at genetic variant j by $x_{ij}^\star \in \{0,1,2\}$. Without loss of generality, we use a mean-centred transformation of the phenotype and allele counts, such that $y_i \equiv y_i^\star - E(y_i^\star)$ and $x_{ij} \equiv x_{ij}^\star - E\left(x_{ij}^\star\right)$ for each SNP j. We denote the vector of mean-centered allele counts at J genetic variants by $\boldsymbol{x}_i = \left(x_{i1}, x_{i2}, \dots, x_{iJ}\right)'$. As a benchmark, consider the standardized best linear predictor of the phenotype based on the allele counts:

$$g_i \equiv \frac{\boldsymbol{x}_i'\boldsymbol{\gamma}}{sd\left(\boldsymbol{x}_i'\boldsymbol{\gamma}\right)},$$

where

$$\boldsymbol{\gamma} = \arg\min_{\widetilde{\boldsymbol{\gamma}}} E[(y_i - \boldsymbol{x}_i'\widetilde{\boldsymbol{\gamma}})^2].$$

That is, the optimal weight vector $\boldsymbol{\gamma}$ is the vector of coefficients from the population regression of y_i on $\boldsymbol{x}_i$. This population regression may also include control variables; we omit them here to avoid cluttering notation, but in the Supplementary Methods we extend the framework to include them and explain why they do not affect the results in this paper. In the User Guide (also in the Supplementary Methods), we explain how control variables do matter for the interpretation of a PGI.

When the set of genetic variants in $\boldsymbol{x}_i$ is all variants in the genome, g_i is referred to as the "standardized additive genetic factor." The variance in the phenotype explained by g_i is called the "(narrow-sense) heritability," often the object of interest in twin, family, and adoption studies that draw inferences without access to molecular genetic data.

In studies with molecular genetic data—our focus here—the set of genetic variants in $\boldsymbol{x}_i$ is restricted to those measured or imputed from the single-nucleotide polymorphisms (SNPs) assayed by standard genotyping platforms (and which pass quality-control filters). In that case, the variance in the phenotype explained by g_i is called the "SNP heritability" (Yang et al., 2010), which we denote h^2_{SNP}. We will refer to g_i as the standardized "additive SNP factor."

Since the population regression cannot be run, the vector $\boldsymbol{\gamma}$ is unknown, so g_i cannot be constructed empirically. What can be constructed empirically is a "polygenic index (PGI)," $\hat{g}_i$, which is a standardized, weighted sum of allele counts using some other weight vector $\hat{\boldsymbol{\gamma}}$ calculated from GWAS summary statistics:

$$\hat{g}_i \equiv \frac{\boldsymbol{x}_i'\hat{\boldsymbol{\gamma}}}{sd(\boldsymbol{x}_i'\hat{\boldsymbol{\gamma}})}.$$

In general, $\hat{\boldsymbol{\gamma}}$ will not be equal to $\boldsymbol{\gamma}$ because $\hat{\boldsymbol{\gamma}}$ is calculated from GWAS summary statistics that are estimated in a finite sample. The key observation for our framework is that when $\hat{\boldsymbol{\gamma}}$ is calculated using standard methods (that include all the SNPs in $\boldsymbol{x}_i$), such as LDpred (Vilhjálmsson et al., 2015) and PRS-CS (Ge, Chen, Ni, Feng, & Smoller, 2019), the resulting PGI can be expressed as

$$\hat{g}_i = \frac{(g_i + e_i)}{\rho},$$

where e_i is mean-zero estimation error that is uncorrelated with g_i, and $\rho \equiv sd(\boldsymbol{x}_i'\hat{\boldsymbol{\gamma}})/sd(\boldsymbol{x}_i'\boldsymbol{\gamma})$ is a scaling factor that standardizes $\hat{g}_i$. In words, the PGI is a standardized, noisy measure of the additive SNP factor, where the noise is classical measurement error.

One way to characterize the amount of measurement error is the value ρ. In Methods, we show that

$$\rho^2 = 1 + Var(e_i) = \frac{h_{SNP}^2}{R^2} \geq 1,$$

where h_{SNP}^2 is the SNP heritability (the predictive power of g_i) and R^2 is the fraction of variance explained in a regression of the phenotype y_i on the PGI $\hat{g}_i$ (the predictive power of $\hat{g}_i$). The ratio h_{SNP}^2/R^2 is greater than or equal to one because the weights that define g_i maximize the variance explained in y_i, and therefore any other weights—including those used to construct the PGI—explain at most h_{SNP}^2 of the variation. Furthermore, the amount of measurement error ρ would achieve its minimum value of one only if the PGI weights were based on GWAS summary statistics from an infinite sample. Across studies, ρ^2 varies. For example, R^2 depends on the sample size of the GWAS underlying the PGI weights and the method of constructing PGI weights (e.g., LDpred vs. PRS-CS). However, ρ^2 can usually be estimated using estimates of h_{SNP}^2 and R^2 from the sample at hand or other samples that are sufficiently similar.

4.2.3 Measurement-Error-Corrected Estimator for PGI Regressions

Typical research with a PGI involves running a regression with the PGI as an explanatory variable and reporting results in units of standard deviations of the PGI. This approach, however, has two shortcomings. First, it is often unclear how to interpret these units, which depend on the amount of measurement error. Second and relatedly, the effect sizes are not comparable across PGIs that differ in their amount of measurement error.

We argue that such a regression should be interpreted as aiming to approximate a regression with the standardized additive SNP factor as the explanatory factor. The PGI serves as an empirically feasible proxy for the standardized additive SNP factor. An analysis of the standardized additive SNP factor has a clearer interpretation than an analysis of the PGI and puts results in comparable units, regardless of which specific PGI was used in the analysis. Here we extend known results from errors-in-variables models to derive a consistent estimator for the coefficients from a regression with the standardized additive SNP factor as an explanatory variable.

The "theoretical regression" is what we call a regression with the (unobserved) standardized additive SNP factor as an explanatory variable. Consider an OLS regression of a phenotype ϕ_i on the standardized additive SNP factor g_i, a vector of covariates $\boldsymbol{z}_i$, and a vector $\boldsymbol{w}_i$ of interactions between g_i and a subset of the regressors in $\boldsymbol{z}_i$ (possibly all of them):

$$\phi_i = g_i\beta_g + \boldsymbol{z}_i\boldsymbol{\zeta}_g + \boldsymbol{w}_i\boldsymbol{\delta}_g + \epsilon_{g,i}, \tag{4.1}$$

where the g subscripts indicate that these are parameters from the theoretical regression. (Note that the phenotype ϕ_i need not be the same phenotype y_i for which the standardized additive SNP factor is the best linear predictor. For example, some papers have studied the relationship between the PGI for educational attainment and test scores at younger ages (Belsky et al., 2016). Note also that the covariates in $\boldsymbol{z}_i$ may be measured with error; equation (4.1) represents whatever regression is run by a researcher except that g_i is measured without error.) The "feasible regression" is what we call the regression using the PGI $\hat{g}_i$ in place of g_i:

$$\phi_i = \hat{g}_i\beta_{\hat{g}} + \boldsymbol{z}_i\boldsymbol{\zeta}_{\hat{g}} + \widehat{\boldsymbol{w}}_i\boldsymbol{\delta}_{\hat{g}} + \epsilon_{\hat{g},i}, \tag{4.2}$$

where $\widehat{\boldsymbol{w}}_i$ is the vector of interactions with $\hat{g}_i$ in place of g_i. We denote the vectors of coefficients from the theoretical and feasible regressions by $\boldsymbol{\alpha}_g \equiv \left(\boldsymbol{\beta}_g, \boldsymbol{\zeta}_g, \boldsymbol{\delta}_g\right)'$ and $\boldsymbol{\alpha}_{\hat{g}} \equiv \left(\boldsymbol{\beta}_{\hat{g}}, \boldsymbol{\zeta}_{\hat{g}}, \boldsymbol{\delta}_{\hat{g}}\right)'$, respectively.

In what follows, we sketch the derivation of an estimator for $\boldsymbol{\alpha}_g$ (for details, see the Supplementary Methods). The derivation assumes that the error in the PGI, e_i, is uncorrelated with $\boldsymbol{z}_i$ and $\boldsymbol{w}_i$. In the Supplementary Methods, we show that this condition holds exactly if the PGI weights $\hat{\boldsymbol{\gamma}}$ are unbiased estimates of $\boldsymbol{\gamma}$. We also show that if the PGI weights $\hat{\boldsymbol{\gamma}}$ are estimated using LDpred-inf—as is true for the Repository PGIs—then the bias in our estimator due to plausible violations of this condition will typically be negligible.

Extending the standard formula for errors-in-variables bias (Spearman, 1904) in a multivariate regression to this setting, and under the assumption that e_i is uncorrelated with $\boldsymbol{z}_i$ and $\boldsymbol{w}_i$, the feasible-regression coefficients can be shown to be biased:

$$\boldsymbol{\alpha}_{\hat{g}} = \boldsymbol{P}\left(\boldsymbol{V}_g + \boldsymbol{\Omega}\right)^{-1}\boldsymbol{V}_g\boldsymbol{\alpha}_g \neq \boldsymbol{\alpha}_g, \tag{4.3}$$

where $\boldsymbol{P} \equiv \begin{pmatrix} \rho\boldsymbol{I}_{1+|\boldsymbol{w}|} & 0 \\ 0 & \boldsymbol{I}_{|\boldsymbol{z}|} \end{pmatrix}$, $\boldsymbol{I}_{|\boldsymbol{x}|}$ is the identity matrix with the dimensionality of $\boldsymbol{x}$, $\boldsymbol{V}_g$ is the variance-covariance matrix of $(g_i, \boldsymbol{w}_i, \boldsymbol{z}_i)'$, and $\boldsymbol{\Omega}$ is the component of the variance-covariance matrix of $(\hat{g}_i, \widehat{\boldsymbol{w}}_i, \boldsymbol{z}_i)'$ that is due to error (see Supplementary Methods). In the special case of a univariate regression, in which the only covariate is a constant term, equation (4.3) implies that the regression slope coefficient $\beta_{\hat{g}}$ converges to $\frac{1}{\rho}\beta_g$. This is a familiar form of attenuation bias, in which the degree of attenuation toward zero is greater the larger the amount of measurement error. In the multivariate case, however, the amount of attenuation bias for $\beta_{\hat{g}}$ will also depend on the covariance matrix of g_i with $\boldsymbol{z}_i$.

Moreover, the other coefficients, $\boldsymbol{\zeta}_{\hat{g}}$ and $\boldsymbol{\delta}_{\hat{g}}$, will be biased as well, not necessarily toward zero. For example, a covariate whose coefficient in equation (4.1) is zero can have a coefficient in equation (4.2) that is non-zero, leading to an incorrect rejection of the null hypothesis (Abel (2017), unpublished manuscript).

The idea underlying our "corrected" estimator follows immediately from equation (4.3) by inverting the bias term:

$$\boldsymbol{\alpha}_{corr} = \boldsymbol{V}_g^{-1}(\boldsymbol{V}_g + \boldsymbol{\Omega})\boldsymbol{P}^{-1}\boldsymbol{\alpha}_{\hat{g}} = \boldsymbol{\alpha}_g. \tag{4.4}$$

This expression is called a regression-disattenuation estimator. It cannot be implemented directly, however, because $\boldsymbol{V}_g$ involves the variance and covariances of the unobserved standardized additive SNP factor g_i. However, the variance and covariances involving g_i differ from analogous terms involving $\hat{g}_i$ only due to measurement error, and the amount of measurement error is given by ρ. Therefore, the variance and covariances involving g_i can be inferred from estimable quantities. In the Supplementary Methods, we derive an expression for $\boldsymbol{\alpha}_{corr}$ in terms of ρ and population parameters that can be estimated consistently using the observed data. That expression is stated in Methods. We implement that version of the estimator. In the Supplementary Methods, we also derive standard errors for the regression coefficients, under the assumption that ρ is known.

If the PGI is uncorrelated with the covariates, then the estimator will inflate the naïve OLS estimate $\hat{\beta}_g$ and its standard error by the factor ρ. If, in addition, the covariates are uncorrelated with each other, then the estimator will also inflate $\hat{\boldsymbol{\delta}}_g$ and its standard error by the factor ρ. Because the regression coefficients and standard errors are inflated by the same factor, the t-statistics and p-values for the corrected estimates will be identical to those for the uncorrected estimates. Correlation between the PGI and the covariates and correlation among the covariates will lead to deviations from this "rule of thumb" adjustment (and can lead to the adjustment being different across regression coefficients and standard errors).

In the univariate case where ρ is estimated within the same dataset as the PGI analysis is conducted, we show that while uncertainty in $\hat{R}^2$ causes downward bias in the standard error, uncertainty in $\hat{h}^2_{SNP}$ causes upward bias, and the net effect is likely to be standard errors that are slightly conservative. We conjecture that the standard errors will also typically be conservative in multivariate settings. If the ρ estimate is from a different dataset, then ignoring the uncertainty in ρ will unambiguously cause the standard errors to be anticonservative. In such settings and in settings when there is meaningful uncertainty in the estimate of ρ, we recommend that users calculate bootstrapped standard errors. The bootstrapped standard errors correctly account for uncertainty in ρ and will be larger than the unbootstrapped standard errors.

We provide a Python command-line tool that implements the measurement-error correction based on a user-specified value of ρ. The package can also estimate ρ by calculating estimates of h_{SNP}^2 (using the GREML method(Yang et al., 2010; Yang, Lee, Goddard, & Visscher, 2011) or, for larger datasets, BOLT-REML(P. R. Loh et al., 2015)) and R^2. The package can calculate standard errors either treating ρ as known or (at some computational cost) by bootstrapping. When possible, we recommend users estimate ρ within the dataset they use to analyse the PGI. If the dataset is too small to reliably estimate ρ or lacks a measure of the phenotype corresponding to the PGI, an estimate of ρ from another dataset can be used under the assumption of perfect genetic correlation of the phenotype across datasets. In the Polygenic Index Repository, we provide pre-specified estimates of ρ for three participating datasets for which we have access to the phenotypic data corresponding to the PGI: HRS, WLS, and the third partition of UKB (see Supplementary Table 4). For many of the cohorts, the standard error on the h_{SNP}^2 estimate is large, so we recommend a value of ρ based on existing h_{SNP}^2 and R^2 estimates from a larger sample.

Although our estimator is derived for an OLS estimation framework, it will be approximately correct for logistic regression (Rosner, Spiegelman, & Willet, 1992) and survival models (Hughes, 1993) as long as the coefficient on the standardized additive SNP factor, β_g, is not too large. For example, applying a measurement-error correction that would be correct for OLS will be a very accurate approximation for the coefficient in a survival model when the hazard ratio associated with a one-standard deviation difference in the variable measured without error is 1.11 (Hughes, 1993). However, the correction is roughly 20% too small when the hazard ratio is 1.65 (Hughes, 1993).

4.2.4 Illustrative Application

To illustrate our proposed measurement-error correction, we apply it to several analyses reported in a recent paper relating educational attainment (and labour market outcomes) to a PGI for educational attainment (Papageorge & Thom, 2020). The paper uses data from the HRS, one of our validation cohorts (*N*= 8,537; 58.3% female; median age = 83). As a preliminary analysis, the paper reports some straightforward tests of the relationship between educational attainment (EA) and the EA PGI. In Panel A of Table 4.3, we reproduce their univariate regression of EA on the PGI and their multivariate regression that additionally includes controls for mother's and father's EA. In the univariate regression, shown in column (1), a 1-standard-deviation increase in the PGI is associated with 0.844 (95% confidence interval = [0.793, 0.895]) additional years of schooling. This association is reduced to 0.619 (95% confidence interval = [0.572, 0.666]) years in column (2), once the controls are included.

The measurement-error-corrected univariate regression is shown in column (3) of Panel A. We estimate that a 1-standard-deviation increase in the additive SNP factor is associated with 1.318 (95% confidence interval = [1.238, 1.398]) additional years of schooling. Relative to the PGI coefficient in column (1), this coefficient is larger by a factor of 1.318 / 0.844 = 1.56. In the regression with controls for parental education, shown in column (4), we estimate a corrected coefficient of 1.104 (95% confidence interval = [1.022, 1.186]) additional years. Relative to column (2), this is an increase by a factor of 1.104 / 0.619 = 1.78. Since for EA in the HRS, $\hat{h}^2_{SNP} \approx 0.25$ and $\hat{R}^2 \approx 0.10$, according to the rule of thumb mentioned above, both coefficients should be expected to have increased by a factor of 1.58 ($\approx \sqrt{0.25/0.10}$). The increase is larger than that from column (2) to (4) due to the positive correlations between the PGI, the controls, and the dependent variable.

The results in Panel A illustrate a general implication of the measurement-error correction for mediation analyses: the correction deflates estimates of how much covariates mediate the effect of the PGI. There have been several mediation analyses in which researchers study how much the coefficient on a PGI is reduced when control variables—which are usually positively correlated with both the PGI and the dependent variable—are added to the regression (Elliott et al., 2018; Okbay, Beauchamp, et al., 2016; Stergiakouli et al., 2016). Going from column (1) to (2), the drop in the coefficient on the PGI would lead a researcher to conclude that parental education mediates (0.844 – 0.619) / 0.844 = 27% of the effect of the PGI. Going from column (3) to (4) shows the corrected estimate of mediation is only (1.318 – 1.104) / 1.318 = 16%. The drop is larger for the uncorrected regressions because in those regressions, the control variables are proxying for part of the additive SNP factor that is not well captured by the PGI. Therefore, studies that do not correct for measurement error will tend to overestimate the extent to which the control variables mediate the effect of the PGI.

The results in Panel B illustrate a fairly general implication of the measurement-error correction for PGI-by-environment interaction analyses: in contrast to how it affects mediation estimates, the correction tends to increase the magnitude of PGI-by-environment interaction estimates. A main result of Papageorge and Thom is about two such interactions: a higher PGI is associated with a weaker relationship between childhood SES and high school completion but a stronger relationship between childhood SES and college completion (Papageorge & Thom, 2020). Columns (1) and (2) reproduce two specifications that show this result: a regression of high school completion on the PGI, self-reported childhood SES, their interaction, and controls; and the analogous regression for college completion. The key finding is that the interaction term is negative in column (1) but positive in column (2). As shown in columns (3) and (4), once the additive SNP factor is considered instead of the PGI, the interaction coefficients for both the high school and college regressions move farther away from zero, strengthening the main result of the paper. In general, PGI-by-environment interaction studies that do not correct for measurement error will tend to underestimate the magnitude of the interaction because the interaction term will tend to be attenuated by the measurement error. Note, however, that this conclusion may not hold if other regressors are correlated with the interaction term.

4.3 Discussion

We described the initial release of the Polygenic Index Repository, which contains PGIs for 47 phenotypes. A major goal of this effort is to disseminate PGIs with greater predictive power than the PGIs typically used. To maximize prediction accuracy of the PGIs, we meta-analysed data from multiple sources, including 23andMe and the UK Biobank.

We also derived a measurement-error-corrected estimator that can be used instead of OLS regressions where the independent variables include a PGI or a PGI and its interactions. While some lack of comparability of results across studies is inevitable (e.g., due to differences across samples in SNP heritabilities), one goal of both the Repository and the proposed estimator is to increase comparability. For example, when constructing the PGIs, we applied to each cohort uniform sets of inclusion criteria for individuals and markers in the genotype data. The estimator contributes to improving comparability by putting regression coefficients in units of the additive SNP factor, regardless of the predictive power of the particular PGI available to the researchers.

Because genetic associations are easily misinterpreted, researchers who use PGIs should be especially careful to understand and convey the appropriate interpretation of their findings. For example, it is important to keep in mind that PGI associations may be mediated by environmental factors, and these factors may be modifiable. To facilitate understanding of these and other interpretational issues, we have written a User Guide that cohorts will distribute to users of the Repository PGIs (see Supplementary Methods).

As more GWAS summary statistics become available in the years ahead, and better methods for constructing PGIs are developed, we plan to update the Repository regularly with more predictive PGIs that leverage these advances. For example, future releases will incorporate PGIs of novel phenotypes for which it is not currently feasible to construct PGIs with meaningful predictive power. We emphasize, however, that although PGIs have attained levels of predictive power that can be useful to researchers, the limited heritability of behavioural phenotypes such as those in the Repository implies that the PGIs will never be able to predict any individual's phenotype with much precision. Additionally, since GWAS summary statistics have only been available in large samples of individuals from European ancestries, currently available PGIs have limited portability to individuals of non-European ancestries (Martin et al., 2017). In future releases of the Repository, once sufficient data becomes available to create PGIs that have non-negligible predictive power for other ancestry groups, we will update the Repository to contain such PGIs.

4.4 Methods

The polygenic indexes (PGIs) shared through the Repository are based on summary statistics from three types of sources: GWASs conducted in UK Biobank (UKB), GWASs conducted in samples of volunteer research participants from 23andMe, and other published genome-wide association studies (GWAS). In Section 4.4.1 below, we begin by detailing how the Repository facilitates researchers' access to the PGIs. In Section 4.4.2, we describe how the summary statistics used in our main analyses were generated, quality-controlled and meta-analysed to generate a set of files used as inputs into construction of the single-trait and multi-trait PGIs. In Section 4.4.3, we define and justify the R^2 criterion we used to determine which PGIs to include in the first release of the Repository. We then describe quality-control filters applied to the individual-level genotype data supplied by each Repository cohort. We conclude by describing the methods used to construct the cohort PGIs. In Section 4.4.4 we state our measurement-error-corrected estimator and its standard error in terms of estimable quantities. Section 4.4.5 describes our estimation of ρ in the HRS, WLS and UKB. Section 4.4.6 describes the data underlying Figure 4.1.

4.4.1 PGI Dissemination Strategies

Recall from the main text that the PGI Repository aims to overcome four obstacles: (1) Constructing PGIs can be time-consuming and requires specialized knowledge; (2) Researchers face administrative hurdles in accessing all the genome-wide summary statistics for constructing PGIs; (3) Publicly available summary statistics may include the target dataset (which should be omitted when constructing the PGI); and (4) PGIs are often constructed with a variety of methods and idiosyncratic analysis decisions.

Disseminating PGSIs through participating datasets

As described in the main text, we overcome all four obstacles by constructing PGIs that include both publicly available data and restricted data (including genome-wide summary statistics from 23andMe) and releasing them to the data providers, who in turn will make them available to researchers. We omit the participating dataset from the summary statistics used to construct that dataset's PGIs, and we construct all the PGIs using a uniform methodology. We similarly construct principal components (PCs) of the genome-wide data using a uniform methodology and release them to the data providers to make available. Our methodology is described below in Sections 4.4.2 and 4.4.3. Upon publication, we will post the code we used for constructing the PGIs and PCs on the SSGAC website (https://www.thessgac.org/data).

To access the PGIs and PCs in a dataset, researchers will need to follow the usual data access procedures for that dataset (typically including a Data Use Agreement and approval from an IRB). The current procedures for each dataset are in the Supplementary Note, and up-to-date procedures will be maintained on the SSGAC website.

Data providers can join the Repository if: (i) they share their individual-level genetic data with the SSGAC so that we can construct the PGIs and PCs on our secure servers; and (ii) they have procedures by which external researchers can gain access to the dataset.

Disseminating PGI weights based on public data

For datasets not participating in the Repository, we cannot overcome obstacles (1)-(4). However, for researchers who wish to construct the PGIs in a non-participating dataset, we will facilitate this effort by posting on the SSGAC website (www.thessgac.org/data) the weights underlying the PGIs constructed from publicly available data (i.e., that have no 23andMe data). As mentioned above, we will also post the code we used for constructing the PGIs and PCs. In addition, we refer researchers to 23andMe's

"Publication Dataset Access Request Form" (https://research.23andme.com/dataset-access/#how-to), which allows researchers to gain access to GWAS results used in published papers (after signing a Data Use Agreement with 23andMe). In this way, researchers can gain access to the same 23andMe data that we used, and use it to construct the PGIs that are wholly or partly based on data from 23andMe.

4.4.2 Summary Statistics

UKB GWAS

Supplementary Table 5 lists all UKB phenotypes for which we ran GWASs. Before running the GWASs, we filtered out poor-quality genotypes: (i) samples identified as putatively carrying sex-chromosome configurations that are neither XX nor XY, (ii) samples identified as outliers in heterozygosity and missingness rates, (iii) samples whose sex inferred from sex chromosomes does not match self-reported gender, and (iv) samples with missing sex, birth year, genotyping batch, or PC information. We also restricted the sample to individuals we will refer to as of "European ancestries," defined as the first genetic PC provided by UKB being greater than 0 and individual self-reporting to be of "British", "Irish", or "Any other white background."

In order to make PGIs for the UK Biobank (UKB) without having to exclude the entire UKB from the discovery GWAS, we split the UK Biobank sample into three equal-sized partitions and, for each partition, used the summary statistics from the other two partitions when generating its PGI. The first partition (UKB1) is composed of UKB participants with brain-scan data (as indicated by data field 12188), all pairs of UKB participants related up to second degree, and the pairs of relatives of third-degree relatedness with greatest relatedness. Pairs of individuals of third-degree relatedness were ordered based on the maximum relatedness coefficient they have with another participant and assigned to the first partition in decreasing relatedness order until the partition was full. Remaining individuals with third-degree relatives were assigned to the second partition. Finally, individuals with no third degree or closer relatives were randomly assigned to the second (UKB2) or third (UKB3) partition.

For all phenotypes in Supplementary Table 5, we ran three separate GWASs, one for each partition. Briefly, each GWAS in UKB was conducted using mixed-linear models implemented by the software BOLT-LMM (P.-R. Loh et al., 2015). The dependent variable in each analysis is a phenotype that has been residualized on sex, a third-degree polynomial in birth year (defined as $(birthyear - 1900)/10$), their interactions, 106 genotyping batch dummies, and the first 40 of the PCs released by the UK Biobank. Details on how each phenotype is coded are provided in Supplementary Table 5. For the variance-component estimation in BOLT-LMM (but not the association analyses), we restricted the set of markers to the set of 622,788 hard-called SNP genotypes that remained after filtering for 1% minor allele frequency and 60% imputation accuracy and pruning with an r^2 threshold of 0.3. Our subsequent association analyses were performed on imputed SNP dosages provided by UKB.

Using the UK Biobank split-sample PGI

Splitting the UKB into thirds as described above increases the predictive power of the PGI within each third (relative to omitting the UKB from the GWAS sample). Researchers may desire to conduct analyses that simultaneously include individuals from different partitions of the data or to meta-analyse results across different partitions. Such analyses will produce estimates that are unbiased, but the standard errors will be incorrectly calibrated. To see why, consider a linear model

$$Y_i = \boldsymbol{X}_i\boldsymbol{\beta} + \varepsilon_i,$$

where $\boldsymbol{X}_i$ is a vector of covariates that includes a PGI. Imagine that the data $(\boldsymbol{Y}, \boldsymbol{X})$ include individuals from different partitions of the data. As a result of the sample-splitting procedure above, $\mathrm{Cov}(\boldsymbol{X}_i, \varepsilon_i) = 0$, which implies that the OLS estimator for $\boldsymbol{\beta}$ will be unbiased. However, because some of the individuals in the data were used to generate the PGI for other individuals in the data, $\mathrm{Cov}(\boldsymbol{X}_i, \varepsilon_j) \neq 0$ whenever individuals i and j are in different partitions. As a result,

$$\mathrm{Var}(\widehat{\boldsymbol{\beta}}) = \mathrm{Var}[(\boldsymbol{X}'\boldsymbol{X})^{-1}\boldsymbol{X}'\boldsymbol{Y}]$$

$$= \mathrm{Var}[(\boldsymbol{X}'\boldsymbol{X})^{-1}\boldsymbol{X}'\boldsymbol{\varepsilon}] \qquad (5)$$

$$\neq (\boldsymbol{X}'\boldsymbol{X})^{-1}\boldsymbol{X}'\mathrm{Var}(\boldsymbol{\varepsilon})\boldsymbol{X}(\boldsymbol{X}'\boldsymbol{X})^{-1}. \qquad (4.6)$$

The expression (6) is the standard general formula for the sampling variance of OLS estimates. It is not equal to (5) due to the correlation between $(\boldsymbol{X}'\boldsymbol{X})^{-1}\boldsymbol{X}'$ and $\boldsymbol{\varepsilon}$. If we knew the correlation between these two vectors, we could calculate correct standard errors in this setting, but the correlation structure is complex, and we are unaware of any current method that produces correct standard errors. For this reason, we recommend that researchers only do analyses on sets of individuals within a partition. If researchers choose to do analyses with individuals across different partitions, they should include the strong caveat that their standard errors may be poorly calibrated.

23andMe GWAS

Our analyses use summary statistics from GWASs conducted by 23andMe in samples of European-ancestry volunteer research participants for 37 different phenotypes. Supplementary Table 6 provides an overview of these summary statistics. 28 out of the 37 are from previously published studies (Day et al., 2015; Demontis et al., 2019; Ferreira et al., 2017; Hinds et al., 2013; Hu et al., 2016; Hyde et al., 2016; Karlsson Linnér et al., 2019; Lee et al., 2018; Liu et al., 2019; Lo et al., 2016; Pasman et al., 2018; Pickrell et al., 2016; Sanchez-Roige et al., 2017, 2018; Warrier et al., 2018). For these, we cite the original study in the column labelled "Citation". The remaining 9 are based on previously unreported GWASs. Two of these GWASs are for phenotypes (Subjective Well-Being and Risk) for which GWASs had been previously published by 23andMe but with a smaller sample. The remaining summary statistics have not been previously published by 23andMe. Supplementary Table 6 describes the details of the association model used for each phenotype. For details on 23andMe's genotyping and imputation, see Supplementary Tables 17 and 18 in Lee et al.(Lee et al., 2018)

Quality control of summary statistics

We applied a uniform set of quality-control filters to each original file with summary statistics (both those from previously unpublished and previously published GWASs). We closely followed the quality-control pipeline detailed in section 1.5.1 of Okbay, Beauchamp, et al. (2016) and implemented in the software EasyQC (Winkler et al., 2014). Our QC protocol departed from Okbay, Beauchamp, et al. (2016) in the following steps:

- We used data from the Haplotype Reference Consortium reference panel (r1.1) (McCarthy et al., 2016) to check for strand misalignment, allele mismatch, chromosome and base pair position concordance, and allele frequency discrepancies (instead of using data from the 1000 Genomes Phase 1 (Abecasis et al., 2010)). (Mapping file and allele frequency data were downloaded from the EasyQC website, from the following urls, respectively: https://homepages.uni-regensburg.de/~wit59712/easyqc/HRC/HRC.r1-1.GRCh37.wgs.mac5.sites.tab.rsid_map.gz , https://homepages.uni-regensburg.de/~wit59712/easyqc/HRC/HRC.r1-1.GRCh37.wgs.mac5.sites.tab.cptid.maf001.gz .)
- For simplicity and uniformity, we applied a more conservative imputation accuracy filter of 0.7 to all input files irrespective of the software that was used for imputation.

- We applied a uniform minor allele frequency filter of 0.01 to all input files. Stricter filters varying by sample size were not necessary because the studies that we analysed were much larger than some of those in Okbay, Beauchamp, et al. (2016)
- We filtered out standard-error outliers. To do so, we first estimated the standard deviation ($\hat{\sigma}_y$) of the phenotype in each input file by regressing the reported standard errors on the following approximation to the standard error of a coefficient estimated by OLS when the phenotype is standardized:

  $$SE_{pred,j} = \frac{1}{\sqrt{N}} \times \frac{1}{\sqrt{2 \times MAF_j \times \left(1 - MAF_j\right)}},$$

  where MAF_j is the minor allele frequency of SNP j and N is the GWAS sample size. We filtered out markers with $\frac{SE_{pred,j}}{SE_j} < \frac{\hat{\sigma}_y}{2}$ or $\frac{SE_{pred,j}}{SE_j} > 2\hat{\sigma}_y$. This filter allowed us to identify and remove markers for which the reported GWAS sample size deviated considerably from the sample size implied by the marker's standard error. This filter was particularly relevant for publicly available summary statistics, where marker-specific sample sizes were typically not reported. (Having an accurate number for the sample size is important for LDpred (Vilhjálmsson et al., 2015).)

Before each filtered file was cleared for subsequent meta-analyses, we also prepared and visually inspected a number of diagnostic plots, as described in Okbay et al. Our final analyses are limited to files whose diagnostic plots did not suggest any anomalies. Finally, we examined the genetic correlation between input files (estimated using the LDSC software package (Bulik-Sullivan et al., 2015)) for each phenotype to make sure phenotype coding was in the same direction across 23andMe, UKB, and published studies. Supplementary Table 7 summarizes the number of SNPs dropped in each filtering step in the files that passed all diagnostic checks.

Single-Trait Input GWAS

In this section, we describe the construction of single-trait input GWASs used in several of our downstream analyses, including as inputs for the single-trait and multi-trait PGIs. The single-trait input GWAS for a phenotype is obtained by meta-analysing summary statistics from up to three sources of information: analyses in UKB, analyses in 23andMe, and summary statistics from a previously published study of the phenotype (Barban et al., 2016; Day et al., 2015; de Moor et al., 2012, 2015; Demontis et al., 2019; Doherty et al., 2018; Ferreira et al., 2017; Furberg et al., 2010; Kunkle et al., 2019; Lee et al., 2018; Liu et al., 2019; Locke et al., 2015; Okbay, Baselmans, et al., 2016; Perry et al., 2014; Stringer et al., 2016; Trampush et al., 2017; van den Berg et al., 2016; Wood et al., 2014; Wray et al., 2018). The input GWAS for a phenotype is the same across most cohorts. However, when there is overlap between a Repository cohort and cohorts that contributed to summary statistics from previously published studies, or in order to construct a PGI for a UKB partition that is based on summary statistics including the rest of the UKB sample, we restrict the meta-analyses to summary statistics based on non-overlapping data. Details on the construction of single-trait input GWAS are in Supplementary Table 8.

To illustrate the general procedure, consider the single-trait input GWAS for neuroticism in ELSA and EGCUT. Supplementary Table 8 shows that the largest meta-analysis of neuroticism (NEURO1) yielded a final sample of $N = 484{,}560$ individuals by combining data from UKB ($N = 361{,}688$), 23andMe ($N = 59{,}206$) and a previously published study ($N = 63{,}666$). Since the column does not indicate any overlap with ELSA, the single-trait input GWAS for neuroticism in ELSA is the set of summary statistics from this meta-analysis. EGCUT, however, is listed in Supplementary Table 8 as overlapping with the NEURO1 meta-analysis. The reason is that EGCUT contributed to the summary statistics of the previously published study (it is one of the cohorts in de Moor et al. (de Moor et al., 2015)). To eliminate overlap, EGCUT's single-trait input is therefore generated by meta-analysing the summary statistics from UKB ($N = 361{,}688$) and 23andMe ($N = 59{,}206$) only. This restricted meta-analysis is listed in the table as NEURO2. Similarly, the largest single-trait input GWAS for neuroticism includes the UKB, so all three UKB partitions are listed as overlapping with it. To eliminate overlap, the single-trait input for each UKB partition (which are labelled NEURO3, NEURO4, and NEURO5) is generated by meta-analysing 23andMe, de Moor et al., and the remaining two UKB partitions.

Each input GWAS is conducted by meta-analysing the relevant input files in MTAG (Turley et al., 2018). All analyses are conducted allowing for sample overlap and setting all genetic correlations equal to unity. However, we allow the SNP-heritability parameter to vary across input files. Even though MTAG produces a separate output file for each input file, the assumption of perfect genetic correlation ensures that the SNP coefficients in each output file are a constant multiple of each other (hence the PGIs generated by the output files are the same). In all analyses that follow, we adopt the convention of designating the output file with the highest estimated SNP heritability as the input GWAS (this matters for the expected R^2 calculation but nothing else). The details of the heritability estimation are described below, in the subsection "Criterion for Inclusion in Repository" in Section III.

Multi-Trait Input GWAS

For several phenotypes in the first-wave release of the Repository, we provide multi-trait PGIs. Here, we describe the multi-trait input GWAS used to generate each of these.

In a first step, we used LDSC (Bulik-Sullivan et al., 2015) to estimate genetic correlations between the phenotypes in Supplementary Table 8. For phenotypes with multiple single-trait input GWAS files, we used the version with the largest Total N. This restriction leaves 53 single-trait input GWAS files, each of which is associated with a distinct phenotype. Because there may be sample overlap between the meta-analysed summary statistics, we used GWAS-equivalent sample sizes as reported by MTAG when estimating genetic correlations. (This was the case for Age First Birth, Number Ever Born (men), Number Ever Born (women), and Asthma/Eczema/Rhinitis. For the first three phenotypes, we meta-analysed the publicly available summary statistics from Barban et al. (Barban et al., 2016), which included the first release of UKB, with UKB full release. Similarly, for Asthma/Eczema/Rhinitis, we meta-analysed publicly available summary statistics from Ferreira et al., (2017), which included the first release of UKB, with UKB full release.) The set of pairwise genetic correlations is reported in Supplementary Table 9.

In a second step, we identified each Repository phenotype's supplementary phenotypes. A phenotype is supplementary to a target phenotype (and vice versa) if the pairwise genetic correlation between the phenotypes exceeds 0.6 in absolute value. Under this definition, the estimates in Supplementary Table 9 identify each target phenotype's supplementary phenotypes. These are listed in the column "Input files" of Supplementary Table 10 (set to "No Supplementary Phenotypes" if the phenotype has genetic correlation less than 0.6 with all other phenotypes). For 37 of the 53 Repository phenotypes, we identified at least one supplementary phenotype.

In a final step, for each of these 37 phenotypes, and for each Repository cohort, we ran a multivariate MTAG analysis on the target phenotype together with its supplementary phenotypes, using the version of the target phenotype and each supplementary phenotype for which the cohort is listed in the column "Repository Datasets Sumstats are Used For" in Supplementary Table 8. (In some cases, the same version of the target phenotype and each supplementary phenotype were used for more than one cohort; in those cases, we ran the MTAG analysis only once for that group of cohorts.)

Each MTAG analysis produces multiple output files—one for the target phenotype and one for each of the supplementary phenotypes—but we only retain the summary statistics for the target phenotype. In what follows, we refer to each such file as a multi-trait input GWAS.

For multi-trait MTAG analyses, in order to understand which traits drive results from using multi-trait PGIs, in Supplementary Table 10, we report the average weight that MTAG assigned to each input file in the multi-trait MTAG analyses. These weights may vary by SNP when there is variation in the sample size across SNPs, but the average weights summarize the relative contributions to predictive power.

4.4.3 Constructing Repository PGIs

Criterion for Inclusion in Repository

The previous section described how we generated single-trait and multi-trait input GWASs from which it is straightforward to generate single-trait and multi-trait PGIs for a large number of phenotypes. We now describe how we determined, for each candidate phenotype, whether to include neither the single- nor multi-trait PGI, both PGIs, or one of the two in the initial release of the Repository. The structure of our algorithm is outlined in Figure 4.2. This section provides the details.

For both single- and multi-trait PGIs, we limited the initial set of PGIs released to those with an out-of-sample expected R^2 above 1%. While the threshold itself is arbitrary, the decision to have a threshold was driven by two considerations: the value of a PGI for research is increasing in its predictive power, and we worried that a PGI with low predictive power could cause more harm than good if researchers are tempted to conduct underpowered studies.

We calculated the expected predictive power of each PGI (that might potentially be included in the Repository) using the following formula from Daetwyler, Villanueva, & Woolliams (2008):

$$E(R^2) = \frac{(h_{SNP}^2)^2}{h_{SNP}^2 + \frac{M}{N}},$$

where h_{SNP}^2 is the phenotype's SNP heritability, M is the effective number of independent SNPs which we assume to be equal to 60,000 (Wray et al., 2013), and N is the GWAS sample size for the phenotype.

We first used the formula above to project the expected predictive power of each potential single-trait PGI. Our projections for the 53 potential PGIs and the underlying parameter values assumed are shown in Supplementary Table 1. We set h^2_{SNP} equal to the SNP heritability estimated by LDSC in the summary statistics from the single-trait input GWAS file with the largest sample size for a phenotype. We set N equal to the GWAS-equivalent sample size reported in the MTAG output. For the 37 phenotypes with at least one supplementary phenotype, we generated similar projections for the multi-trait PGIs, using the Multi-Trait Input GWAS files instead. The results of the 37 projections, and the underlying parameter values assumed, are shown in Supplementary Table 2.

We find that our criterion results in 47 phenotypes with at least one PGI in the Repository (see Figure 4.2). For 12 phenotypes, our procedure results in the release of a single-trait PGI but no multi-trait PGI; these are the phenotypes with no supplementary phenotypes. For 11 other phenotypes, our procedure results in the release of a multi-trait PGI but no single-trait PGI; these are typically phenotypes without large GWASs but for which we have multiple supplementary phenotypes with large GWASs. Finally, our procedure yields 24 phenotypes with both single- and multi-trait PGIs that satisfy our inclusion criterion (Table 4.1) and 6 phenotypes for which neither PGI qualifies.

Genotype Data QC in Repository Cohorts

We restricted the set of markers to the SNPs present in the third phase of the international HapMap project (HapMap 3) (International HapMap 3 Consortium et al., 2010) in order to reduce computational burden (relative to using all reported SNPs) while keeping a set of markers that covers most of the common variation in individuals with European ancestries.

Subject-level QC in Repository Cohorts

We restricted the samples to individuals with European ancestries. Exclusion criteria were based on the first four principal components of the genetic data. In order to obtain the principal components, for each cohort, we first converted the imputed genotype dosages for HapMap3 SNPs into hard calls. We then merged the data with all samples from the third phase of the 1000 Genomes Project, restricting to SNPs that had a call rate greater than 99% and minor allele frequency greater than 1% in the merged sample. We calculated the principal components (PCs) in the 1000 Genomes subsample and projected these onto the remaining individuals in the merged data. In order to select European-ancestry samples, we plotted the first four PCs against each other and visually identified the individuals that cluster together with the 1000 Genomes EUR sample.

Creation of PCs in Repository Cohorts

In the Repository cohorts, before constructing PCs, we removed markers with imputation accuracy less than 70% or minor allele frequency less than 1%, as well as markers in long-range LD blocks (chr5:44mb-51.5mb, chr6:25mb-33.5mb, chr8:8mb-12mb, chr11:45mb-57mb). Next, we restricted the sample to individuals with European ancestries, as described immediately above. We further pruned the markers to obtain a set of approximately independent markers, using a 1Mb rolling window (incremented in steps of 5 variants) and an R^2 threshold of 0.1. We used this set of markers to estimate a genetic relatedness matrix. We identified all pairs of individuals with a relatedness coefficient greater than 0.05 as calculated by Plink1.9 (Chang et al., 2015). We excluded one individual from each pair, calculated the first 20 PCs for the resulting sample of unrelated individuals using Plink 1.9, and projected the PCs onto the sample of unrelated individuals. In HRS, we re-labeled the PCs in sets of five in order to address identifiability concerns.

Constructing PGIs

All PGIs in the initial release of the Repository were constructed in Plink2 (Chang et al., 2015) using imputed genotype probabilities. Prior to constructing the PGIs, we adjusted the SNP weights for linkage disequilibrium (LD) using LDpred (Vilhjálmsson et al., 2015). We estimated the LD patterns using genotype data from the public release of the HRC Reference Panel (version 1.1) after applying the following quality-control filters. First, we limited the set of variants to HapMap3 SNPs and filtered out variants with genotyping call rate <0.98 and individuals with genotype missingness rate >0.02. Next, we calculated the genomic relatedness matrix and dropped one individual out of each pair with relatedness coefficient >0.025. We clustered the remaining individuals based on their identity-by-state distances using Plink1.9 and dropped an individual if the Z-score corresponding to their distance to their nearest neighbour is less than -5. In the remaining sample that we fed into LDpred for LD estimation, there were 1,214,408 SNPs and 14,028 individuals. At the coordination step of LDpred, we used the option "--max-freq-discrep" in order to exclude markers that have a frequency discrepancy greater than 0.1 between the summary statistics and genotype data. We also used the "--z-from-se" option so that Z statistics were obtained from the GWAS coefficient estimates and their standard errors rather than from P values (the default) because the latter led to issues in LDpred for markers with extremely small P values. For each PGI, we used the LD window recommended by Vilhjálmsson et al. (2015), i.e., the number of markers common between the LD reference data, cohort genotype data and summary statistics left after the remaining LDpred quality control filters (MAF > 0.01, no allele mismatch, no ambiguous alleles), divided by 3,000. The fraction of causal markers was set to 1 for each phenotype to ensure consistency across phenotypes.

Prediction Analyses

We conducted a validation exercise for our PGIs in the HRS (*N*= 10,978; 57% female; median age = 82), WLS (*N*= 8,937; 52% female; median age = 82), Dunedin (*N*= 887; 49% female; 1972 birth cohort), E-Risk (*N*= 1,968; 51% female; 1994 birth cohort), and UKB (third partition; *N*= 148,662; 54% female; median age = 71) cohorts. The HRS sample used in our validation exercise (2006-2010) is smaller than the HRS sample for which we are releasing PGIs (2006-2012) because we only had access to phenotype data in the former. Supplementary Table 12 describes the phenotypes used as outcomes in these analyses for all cohorts except UKB. The UKB phenotypes are described in Supplementary Table 5. (The UKB phenotypes used in the prediction exercise differ slightly from the GWAS phenotypes described in Supplementary Table 5 in that they were not residualized on the PCs and genotyping batch dummies. Instead, we have controlled for these covariates in the regressions when calculating incremental R^2 as described below.) As a general rule, if a single measurement in time was available, we residualized the phenotype on a second-degree polynomial in age, sex, and their interactions. If multiple measurements were available, we either did the same residualization in each wave and took the mean across waves or we took the maximum across waves and then residualized on birth year, sex, and their interactions.

Supplementary Table 3 shows the results from the prediction analyses. The incremental R^2 was calculated as the difference in explained variance when adding the PGI to a regression of the residualized phenotype on the first 10 principal components of the genetic data. In the UKB prediction analyses, we included an additional 10 principal components and 106 genotyping batch dummies. We obtained 95% confidence intervals around the incremental R^2's by bootstrapping with 1000 repetitions. Supplementary Table 3 also shows the predictive power of "public PGIs", which are PGIs constructed using our Repository pipeline based on the largest publicly available GWAS on the phenotype that does not have sample overlap with the prediction cohort (Barban et al., 2016; Day et al., 2015; de Moor et al., 2012, 2015; Demontis et al., 2019; Doherty et al., 2018; Ferreira et al., 2017; Furberg et al., 2010; Howard et al., 2019; Jones et al., 2019; Karlsson Linnér et al., 2019; Lee et al., 2018; Liu et al., 2019; Locke et al., 2015; Nagel et al., 2018; Okbay, Baselmans, et al., 2016; Okbay, Beauchamp, et al., 2016;

Perry et al., 2014; C. A. C. A. Rietveld et al., 2013; Savage et al., 2018; Stringer et al., 2016; Trampush et al., 2017; van den Berg et al., 2016; Wood et al., 2014; Wray et al., 2018; Yengo, Sidorenko, et al., 2018) (we also use http://www.nealelab.is/uk-biobank/). The details of the input GWAS used for each validation cohort for the construction of the "public PGIs" are in Supplementary Table 13.

4.4.4 Measurement-Error-Corrected Estimator

Equation (4.4) in the main text gives an expression for our measurement-error-corrected estimator, but it cannot be implemented directly because $\boldsymbol{V}_g$ and $\boldsymbol{\Omega}$ are based on unobserved variables. In the Supplementary Methods we derive an equivalent expression in terms of variables that can all be consistently estimated using sample analogues:

$$\boldsymbol{\alpha}_{\text{corr}} = \boldsymbol{P}\begin{bmatrix} \frac{1}{\rho^2}\boldsymbol{\Sigma}_G & \boldsymbol{\Sigma}_{\hat{G},z} \\ & \boldsymbol{\Sigma}_z \end{bmatrix}^{-1} \boldsymbol{V}_g\boldsymbol{\alpha}_{\hat{g}}, \tag{4.7}$$

where

$$\boldsymbol{\Sigma}_G \equiv \begin{bmatrix} 1 & \rho^2\text{Cov}(\widehat{\boldsymbol{w}}, \hat{g}_i) \\ & \rho^2\boldsymbol{\Sigma}_{\widehat{w}} - (\rho^2 - 1)\boldsymbol{\Sigma}_{\text{int},z} \end{bmatrix},$$

$\boldsymbol{\Sigma}_{\hat{G},z} \equiv \text{Cov}[(\hat{g}_i, \widehat{\boldsymbol{w}}_i), \boldsymbol{z}_i], \boldsymbol{\Sigma}_z \equiv \text{Var}(\boldsymbol{z}_i), \boldsymbol{\Sigma}_{\widehat{w}} \equiv \text{Var}(\widehat{\boldsymbol{w}}_i), \boldsymbol{\Sigma}_{\text{int},z} \equiv \text{Var}(\boldsymbol{z}_{\text{int},i})$, and $\boldsymbol{z}_{\text{int},i}$ is the vector of the covariates that are interacted with g_i to form the vector $\boldsymbol{w}_i$.

To obtain standard errors for $\boldsymbol{\alpha}_{\text{corr}}$, we calculate

$$\text{Var}(\boldsymbol{\alpha}_{\text{corr}}) = \boldsymbol{C}\boldsymbol{A}_{\hat{g}}\boldsymbol{C}', \tag{4.8}$$

where $\boldsymbol{A}_{\hat{g}} \equiv \text{Var}(\boldsymbol{\alpha}_{\hat{g}})$ and

$$\boldsymbol{C} \equiv \boldsymbol{P}\begin{bmatrix} \frac{1}{\rho^2}\boldsymbol{\Sigma}_G & \boldsymbol{\Sigma}_{\hat{G},z} \\ & \boldsymbol{\Sigma}_z \end{bmatrix}^{-1} \boldsymbol{V}_g. \tag{4.9}$$

The standard errors are the square root of the diagonal of $\text{Var}(\boldsymbol{\alpha}_{\text{corr}})$. Note that equations (4.7) – (4.9) are written in terms of population variance-covariance matrices, model coefficients, and the parameter ρ. To implement this correction, we replace each of these terms with its sample counterpart.

4.4.5 Estimation of $\boldsymbol{\rho}$ in HRS, WLS and UKB

We estimated the value of ρ for all PGIs satisfying the criterion for inclusion in the Repository in three of our validation datasets: HRS, WLS and UKB (partition 3). Recall from the main text that ρ is defined as

$$\rho = \sqrt{\frac{h_{SNP}^2}{R^2}},$$

where h_{SNP}^2 is the SNP heritability and R^2 is the fraction of variance explained in a regression of the phenotype on the PGI.

In order to estimate h_{SNP}^2 and R^2, we first took the residualized phenotypes described in section "Prediction Analyses" and additionally residualized these on 20 PCs in HRS and WLS, and 40 PCs and batch effects in UKB3. We did the same for the PGIs. In HRS and WLS, we estimated h_{SNP}^2 with genomic-relatedness-matrix restricted maximum likelihood (GREML) implemented in GCTA v1.93.0beta(Yang et al., 2010, 2011) using HapMap3 SNPs with MAF > 1%. Prior to the h_{SNP}^2 estimation, we dropped one individual from each pair with a relatedness greater than 0.025. We estimated R^2 as the explained variance in a simple regression of the residualized phenotype on the residualized PGI. Standard errors for R^2, h_{SNP}^2, and ρ were estimated with a 100-block jackknife procedure.

In UKB3, because of the large sample size, we faced computational constraints. We therefore used the REML implementation in BOLT v2.3(P. R. Loh et al., 2015) (with the `--remlNoRefine` option). Moreover, we estimated standard errors only for three phenotypes: friend satisfaction, educational attainment, and height. We chose these three phenotypes so as to have one each corresponding to a single-trait PGI with low (friend satisfaction), medium (educational attainment) and high predictive power (height).

Supplementary Table 4 lists the estimates of ρ for HRS, WLS and UKB3, along with the underlying h_{SNP}^2 and R^2 estimates and standard errors where available.

4.4.6 Categorization of BGA Annual Meeting Presentations

To obtain the data for Figure 4.1, we first created a dataset containing the titles, authors, and abstracts of all presentations at the 2009-2019 Behavior Genetics Association Annual Meetings. The information about the presentations is printed each year in issue six of the association journal Behavior Genetics. There were 2,034 presentations in this initial dataset. Included in the initial dataset were 36 symposia and 5 papers that were submitted as a part of symposia; all 41 of these are omitted from the final dataset. The final dataset contains a total of 1,993 presentations.

After some trial-and-error and visual inspection of several dozen abstracts, we arrived at the algorithm below for categorizing studies:

- We categorized a presentation as a "PGI study" if the title or the abstract contains at least one of the following keywords: 'PGS', 'PRS', 'PGRS', 'polygenic score', 'polygenic risk score', 'genetic risk score', 'GRS'.
- We categorized a presentation as a "twin, family, or adoption study" if it satisfies at least one of the following conditions:
    - The abstract contains 'twin' at least twice.
    - The title contains the word 'twin'.
    - The title or abstract contain at least one of the following keywords: 'twin registry', 'center for twin research', 'twin project', 'twin panel', 'twin study at the', ‘twin study (LTS)', '(RFAB) twin study', 'twin register', 'twin pairs', 'nonidentical twins', 'identical twins', 'pairs of twins', 'twin sample', ' MZ', ' DZ', 'monozygotic', 'dizygotic', 'pairs of twins', 'adopted', 'adoptee', 'adoptive', 'adoption design', 'biological parent', 'adoptive parent', 'adoption-sibling', 'genetically-unrelated', 'genetically-related', 'siblings reared together', 'siblings reared apart', 'mother and child', 'father and child', 'parent and child', 'intergenerational', 'transracial', 'biometric', 'path analy', 'Cholesky', 'children-of-twins', 'children of twins', 'common environment', 'unique environment', 'ACE', 'ACDE'.
- We categorized a presentation as a "candidate-gene study" if it satisfies at least one of the following conditions:
    - The title contains ‘candidate gene’ or at least one of the following candidate gene keywords: 'HTR2', 'MAOA', '5-HTT', '5HTT', 'DRD', 'SLC6', 'BDNF', 'COMT', 'TPH', 'MTHFR', 'APOE', 'DTNBP1', 'DBH', 'ABCB1', 'VNTR', 'CRHR', 'AKT', 'NRG', 'AVP', 'rs0', 'rs1', 'rs2', 'rs3', 'rs4', 'rs5', 'rs6', 'rs7', 'rs8', 'rs9'.
    - The abstract contains at least one of the above candidate-gene keywords.
    - The abstract contains 'candidate' at least twice and 'candidate gene' at least once.

However, a presentation was removed from the candidate-gene study category if the abstract contains GWAS keywords: 'wide association analysis', 'wide association study', 'GWAS'.

To quantify how accurately the algorithmic classifications predict categorizations based on human evaluations, we asked two researchers with expertise in behaviour genetics to categorize 65 randomly sampled presentations. The raters worked independently, without any external assistance, and based their categorizations solely on information supplied about the title and abstract. Each rater assigned three yes/no labels—representing candidate-gene study; twin, family or adoption study; or PGI study—to each presentation. Raters sought to make labelling decisions consistent with the labels' typical usage in the literature. We defined "agreement" on a presentation as an identical judgment about each of the three labels (i.e., if the raters disagreed about any of the three categories, they were considered as not agreeing). Even under this strict definition, we found an interrater agreement of 94%. The agreement between the algorithm's and one rater's categorizations was 86%, and that between the algorithm's and the other rater's categorizations was 83%.

4.5 Data availability

For how to access the Repository PGIs and other data from each participating dataset, see Supplementary Note; upon publication, an up-to-date list of participating datasets and data access procedures will be maintained at https://www.thessgac.org/pgi-repository. For each phenotype that we analyse, we report GWAS and MTAG summary statistics and PGI (LDpred) weights for all SNPs from the largest discovery sample for that analysis, unless the sample includes 23andMe. SNP-level summary statistics from analyses based entirely or in part on 23andMe data can only be reported for up to 10,000 SNPs. Therefore, if the largest GWAS or MTAG analysis for a phenotype includes 23andMe, we report summary statistics for only the genome-wide significant SNPs from that analysis. In addition, we report summary statistics for all SNPs from a version of the largest GWAS analysis that excludes 23andMe. Finally, we also report summary statistics and PGI (LDpred) weights that the "public PGIs" are based on. These summary statistics and PGI weights can be downloaded from https://www.thessgac.org/pgi-repository upon publication. The data underlying Figure 4.1 will also be available at https://www.thessgac.org/pgi-repository. Researchers at non-profit institutions can obtain access to the genome-wide summary statistics from 23andMe used in this paper by completing the 23andMe Publication Dataset Access Request Form, available at https://research.23andme.com/dataset-access/.

4.6 Code availability

Upon publication, the software used for the measurement-error correction will be available at https://github.com/JonJala/pgi_correct. The code for constructing PGIs and principal components, the code for the illustrative application, and the code for analyzing the data displayed in Figure 4.1 will be available at https://www.thessgac.org/pgi-repository.

4.7 References

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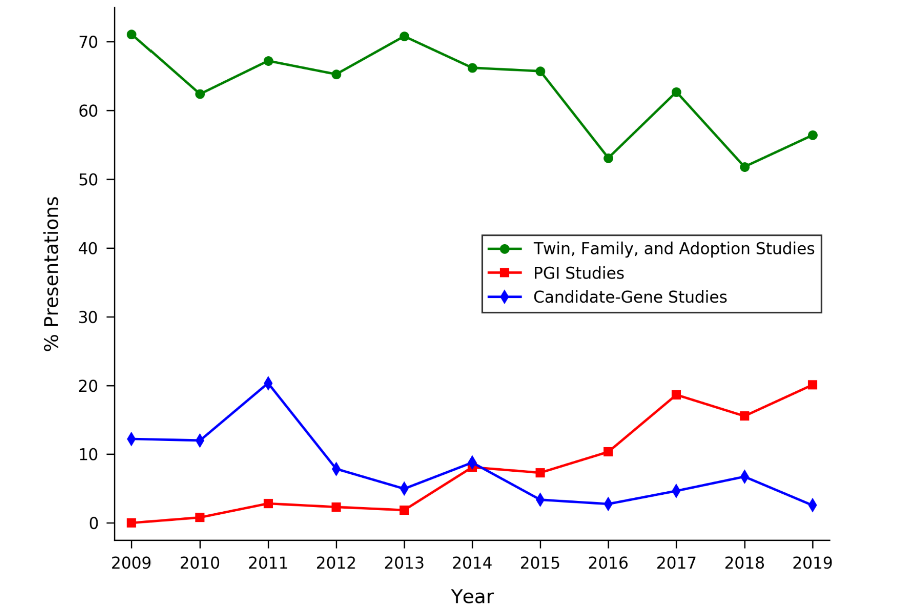
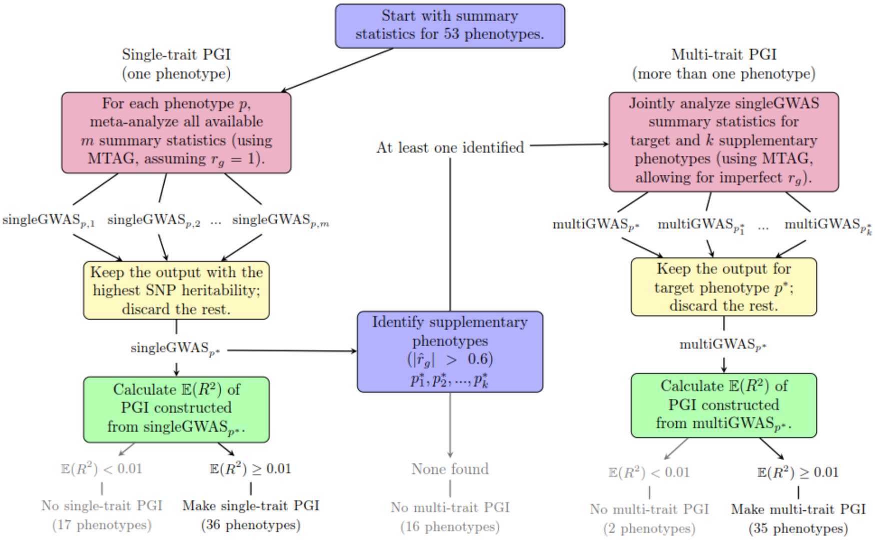
4.8 Figures

Figure 4.1: Type of study in presentations at Behavior Genetics Association Annual Meetings



Notes: For a description of the data underlying this figure, see Methods. Out of 1,993 presentations in total (over the 2009-2019 period), the percentages that are in exactly 0, 1, 2, or 3 categories are 26.76%, 67.56%, 5.5%, and 0.2%, respectively.

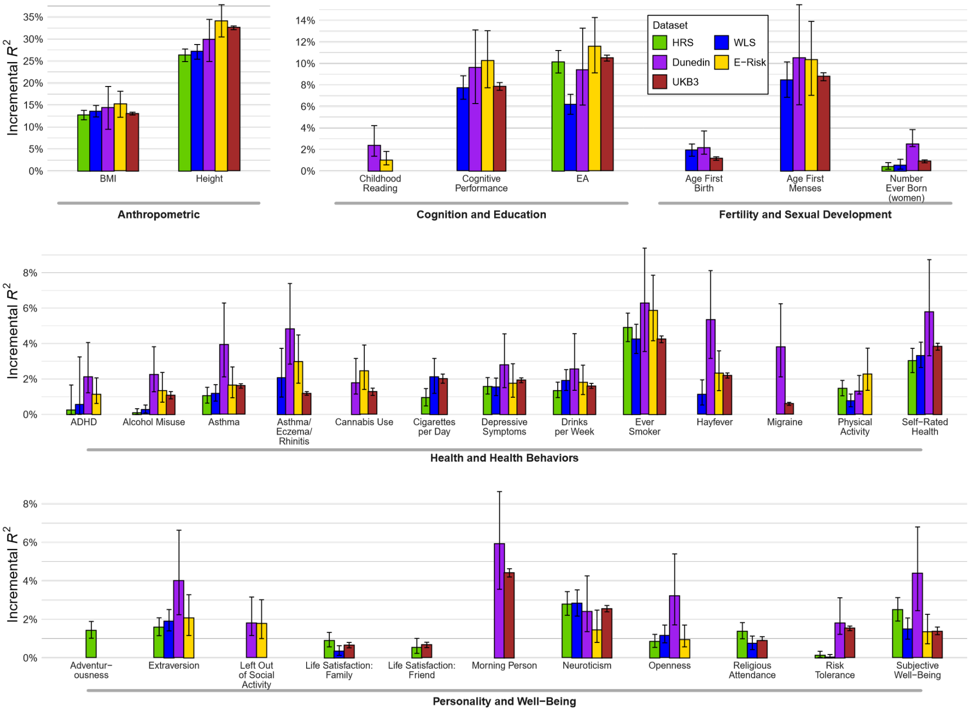
Figure 4.2: Algorithm determining which single-trait and multi-trait PGIs were generated for the Repository


Start with summary statistics for 53 phenotypes.
Single-trait PGI (one phenotype)
Multi-trait PGI (more than one phenotype)
For each phenotype p, meta-analyze all available m summary statistics (using MTAG, assuming $r_g = 1$).
At least one identified
Jointly analyze singleGWAS summary statistics for target and k supplementary phenotypes (using MTAG, allowing for imperfect r_g).
singleGWAS$_{p,1}$
singleGWAS$_{p,2}$
...
singleGWAS$_{p,m}$
multiGWAS$_{p^*}$
multiGWAS$_{p_1^*}$
...
multiGWAS$_{p_k^*}$
Keep the output with the highest SNP heritability; discard the rest.
Keep the output for target phenotype p^*; discard the rest.
singleGWAS$_{p^*}$
Identify supplementary phenotypes ($|\hat{r}_g| > 0.6$) $p_1^*, p_2^*, ..., p_k^*$
multiGWAS$_{p^*}$
Calculate $\mathbb{E}(R^2)$ of PGI constructed from singleGWAS$_{p^*}$.
Calculate $\mathbb{E}(R^2)$ of PGI constructed from multiGWAS$_{p^*}$.
$\mathbb{E}(R^2) < 0.01$
$\mathbb{E}(R^2) \geq 0.01$
None found
$\mathbb{E}(R^2) < 0.01$
$\mathbb{E}(R^2) \geq 0.01$
No single-trait PGI (17 phenotypes)
Make single-trait PGI (36 phenotypes)
No multi-trait PGI (16 phenotypes)
No multi-trait PGI (2 phenotypes)
Make multi-trait PGI (35 phenotypes)

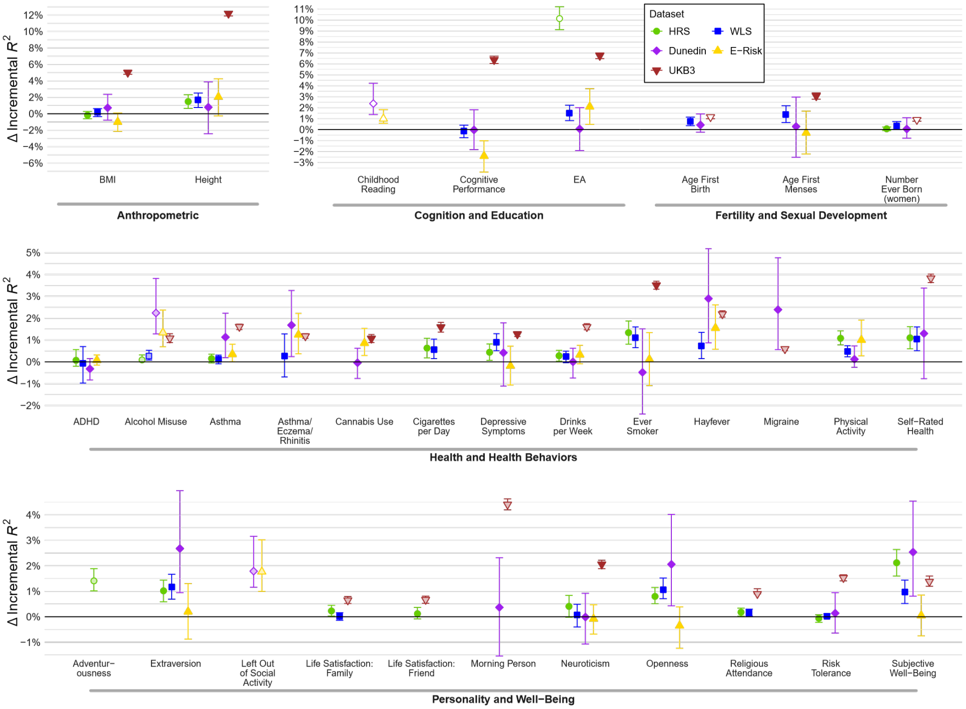
Notes: See Table 4.1 for the 36 single-trait PGIs and 35 multi-trait PGIs included in the Repository.

Figure 4.3: Predictive power of Repository single-trait PGIs

(a)



(b)



Notes: Error bars show 95% confidence intervals from bootstrapping with 1,000 repetitions. Panel (A): Incremental R^2 from adding Repository's single-trait PGI to a regression of the phenotype on 10 principal components of the genetic relatedness matrix for HRS, WLS, Dunedin and ERisk, and on 20 principal components and 106 genotyping batch dummies for UKB. Prior to the regression, phenotypes are residualized on a second-degree polynomial for age or birth year, sex, and their interactions (see

Supplementary Tables 5 and 12). For the sample sizes of the GWAS that the PGIs are based on, see Supplementary Table 478. Panel (B): Difference in incremental R^2 between Repository single-trait PGI and PGI constructed from publicly available summary statistics using our Repository pipeline. (Note that the latter do not include PGI directly available from cohortdatasets, such as the ones accessible from the HRS website.) If no publicly available summary statistics are available for a phenotype, then the difference in incremental R^2 is equal to the incremental R^2 of the single-trait PGI and is represented by an open circle. "Cigarettes per Day" in Dunedin was omitted from the Figure because the confidence interval (-5.99% to 0.94%) around the point estimate (-2.38%) required extending the y-axis substantially, making the figure hard to read. For the GWAS sample sizes of the PGIs based on publicly available summary statistics, see Supplementary Table 13.

4.9 Tables

Table 4.1. Repository phenotypes and GWAS sample sizes

Phenotype	GWAS Sample Size					PGIs Released		Suppl. Phenotypes
	Total	23andMe	UKB	Other	Public N	Single	Multi	
Anthropometric								
1 Body Mass Index (BMI)	760,630	-	438,476	322,154	795,640	X		
2 Height	698,334	-	445,054	253,280	709,706	X		
Cognition and Education								
3 Childhood Reading	172,503	172,503	-	-	-	X		
4 Cognitive Performance	260,354	-	225,056	35,298	269,867	X	X	5, 6, 7
5 Educational Attainment	1,047,538	365,536	-	682,002	766,345	X	X	4, 6, 8, 33, 45
6 Highest Math	430,439	430,439	-	-	-	X	X	4, 5, 7, 8, 33
7 Self-Rated Math Ability	564,692	564,692	-	-	-	X	X	4, 6
Fertility and Sexual Development								
8 Age First Birth	407,884	9,370	156,733*	241,781	241,781	X	X	5, 6, 11, 12, 19, 22
9 Age First Menses (Women)	329,345	76,831	-	252,514	252,514	X	X	10
10 Age Voice Deepened (Men)	55,871	55,871	-	-	-		X	9
11 Number Ever Born (Men)	260,991	-	168,056*	92,935	165,492		X	8, 12
12 Number Ever Born (Women)	399,803	-	188,208*	211,595	211,595	X	X	8, 11
Health and Health Behaviors								
13 Alcohol Misuse	151,067	19,407	131,660	-	-	X	X	24
14 Allergy - Cat	46,646	46,646	-	-	-		X	15, 16, 17, 18, 26
15 Allergy - Dust	46,646	46,646	-	-	-		X	14, 16, 17, 18, 26
16 Allergy - Pollen	46,646	46,646	-	-	-		X	14, 15, 17, 19, 26

17	Asthma	445,965	-	445,965	-	361,141	X	X	14, 15, 16, 18, 26
18	Asthma/Eczema/Rhinitis	685,716	135,538	307,609*	242,569	242,569	X	X	14, 15, 16, 17, 26
19	Attention Deficit Hyperactivity Disorder (ADHD)	117,754	62,380	-	55,374	55,374	X	X	8, 22
20	Cannabis Use	202,180	22,771	144,112	35,297	117,911	X		
21	Cigarettes per Day	340,140	76,186	-	263,954	263,954	X		
22	Chronic Obstructive Pulmonary Disease (COPD)	445,965	-	445,965	-	91,787		X	8, 19, 30
23	Depressive Symptoms	942,579	307,354	404,984	230,241	500,199	X	X	30, 40, 43, 47
24	Drinks per Week	941,287	403,938	-	537,349	537,349	X	X	13
25	Ever Smoker	1,255,948	623,146	-	632,802	632,802	X		
26	Hayfever	445,963		445,963	-	360,527	X	X	14, 15, 16, 17, 18, Eczema†
27	Migraine	693,993	283,985	410,008	-	361,194	X		
28	Nearsightedness	367,906	191,843	176,063	-	360,677	X		
29	Physical Activity	357,039	265,934	-	91,105	91,105	X		
30	Self-Rated Health	1,203,099	758,713	444,386	-	359,681	X	X	22, 23, 37
				-					
Personality and Well-Being				-					
31	Adventurousness	557,923	557,923	-	-	-	X	X	46
32	Cognitive Empathy	46,861	46,861	-	-	-		X	Agreeableness†
33	Delay Discounting	23,217	23,217	-	-	-		X	5, 6
34	Extraversion	122,255	59,225	-	63,030	63,030	X	X	35
35	Left Out of Social Activity	507,804	507,804	-	-	-	X	X	34, 38, 40, 47
36	Life Satisfaction: Family	168,313	-	168,313	-	118,818	X	X	38, 39, 47
37	Life Satisfaction: Finance	169,051	-	169,051	-	119,394		X	30, 40, 47
38	Life Satisfaction: Friends	168,001	-	168,001	-	118,649	X	X	35, 36, 39, 47
39	Life Satisfaction: Work	115,038	-	115,038	-	82,190		X	36, 38, 47
40	Loneliness	439,525	-	439,525	-	355,583		X	23, 35, 37, 43, 47

41	Morning Person	493,043	91,967	401,076	-	449,734	X		
42	Narcissism	452,535	452,535	-	-	-	X		
43	Neuroticism	484,560	59,206	361,688	63,666	380,060	X	X	23, 40, 47
44	Openness	76,551	59,176	-	17,375	17,375	X		
45	Religious Attendance	444,842	-	444,842	-	360,063	X	X	5
46	Risk	1,427,867	969,309	-	458,558	466,571	X	X	31
47	Subjective Well-Being	1,022,510	728,752	169,219	124,539	204,978	X	X	23, 35, 36, 37, 38, 39, 40, 43

Notes: *For Age First Birth, Number Ever Born (Men), Number Ever Born (Women) and

Asthma/Eczema/Rhinitis, the publicly available summary statistics include the first release of UKB. Therefore, there is sample overlap between our UKB GWAS and publicly available summary statistics. For these phenotypes, in the UKB column, we report the UKB sample size excluding samples from the publicly available GWAS. †For Eczema and Agreeableness, both the single- and multi-trait PGIs had an expected predictive power less than 0.01, so they were used only as supplementary phenotypes for other phenotypes. Therefore, they are not included in the table and are not represented by a number. The GWAS sample for Eczema consists of only UKB, with $N = 440{,}177$. The GWAS sample for Agreeableness consists only of 23andMe, with $N = 59{,}176$.

Table 4.2. Datasets participating in the Repository

Dataset	N	Country	Population- or Family-based
Dunedin Multidisciplinary Health and Development Study	887	New Zealand	Population
English Longitudinal Study of Ageing (ELSA)	7,310	UK	Population
Environmental Risk (E-Risk) Longitudinal Twin Study	2,316	UK	Family
Estonian Genome Center, University of Tartu (EGCUT)	51,719	Estonia	Population
Health and Retirement Study (HRS)	12,090	USA	Population
Minnesota Center for Twin and Family Research (MCTFR)	7,654	USA	Family
National Longitudinal Study of Adolescent to Adult Health (Add Health)	5,689	USA	Family
Swedish Twin Registry (STR)	38,072	Sweden	Family
Texas Twin Project	556	USA	Family
UK Biobank (UKB)	445,985	UK	Population
Wisconsin Longitudinal Study (WLS)	8,949	USA	Family

Notes: The "N" column gives the number of participants in each dataset for whom the PGIs in Table 4.1 are supplied in the initial release of the Repository (i.e., those who passed the subject-level exclusion filters described in Methods). "Population- or Family-based" refers to how individuals were recruited to the dataset.

Table 4.3. Application of measurement-error correction

Panel A. Association Between EA and the PGI, Without and With Controls for Parental EA

	Original		Corrected	
	(1)	(2)	(3)	(4)
EA PGI	0.844	0.619	1.318	1.104
	(0.026)	(0.024)	(0.041)	(0.042)
Father's EA	-	0.154	-	0.112
		(0.010)		(0.010)
Mother's EA	-	0.176	-	0.141
		(0.011)		(0.012)
# Obs.	8,537	8,537	8,537	8,537

Panel B. Interaction Between PGI and Family SES Predicting High School and College Completion

	(1)	(2)	(3)	(4)
	High school	College	High school	College
EA PGI	0.095	0.055	0.166	0.103
	(0.008)	(0.008)	(0.014)	(0.014)
Family SES	0.069	0.031	0.063	0.034
	(0.009)	(0.010)	(0.009)	(0.010)
EA PGI X Family SES	-0.047	0.068	-0.084	0.101
	(0.009)	(0.010)	(0.015)	(0.016)
# Obs.	8,387	8,387	8,387	8,387

Notes: Each column reports estimated regression coefficients, with standard errors in parentheses. Panel A: Columns (1) and (2) replicate results from Papageorge and Thom's Table 2 columns 1 and 2. Panel B: Columns (1) and (2) replicate results from Papageorge and Thom's Table B.2 panel B columns 2 and 4. Panels A and B: Columns (3) and (4) apply our measurement-error-corrected estimator to the feasible-regression results in Columns (1) and (2). A value of $\rho = 1.52$ was used in the correction. All regressions include indicators for birth year, sex, interactions of birth year and sex, and 10 principal components of the genetic data (coefficients not reported). The regressions in Panel B also control for mother and father's educational attainment and an indicator for whether these values are missing (these data are missing for 2000 individuals). Our panel B regressions differ from Papageorge and Thom as we do not include a cubic of the PGI as control variables. We omitted the cubic terms because our measurement-error-corrected estimator does not account for non-linear transformations of the PGI.

Chapter 5

Genetic Fortune: Winning or Losing Education, Income, and Health

Published as:

Kweon, H., Burik, C. A. P., Karlsson Linnér, R., de Vlaming, R., Okbay, A., Martschenko, D., Harden, K.P., DiPrete, T.A.,& Koellinger, P. D. (2020). *Genetic Fortune: Winning or Losing Education, Income, and Health* (Tinbergen Institute Discussion Papers No. 20- 053/V). Amsterdam.

Abstract

We develop a polygenic index for individual income and examine random differences in this index with lifetime outcomes in a sample of ~35,000 biological siblings. We find that genetic fortune for higher income causes greater socio-economic status and better health, partly via intervenable environmental pathways such as education. The positive returns to schooling remain substantial even after controlling for now observable genetic confounds. Our findings illustrate that inequalities in education, income, and health are partly due the outcomes of a genetic lottery. However, the consequences of different genetic endowments are malleable, for example via policies that target education.

5.1 Introduction

The origins, extent, and consequences of income inequalities differ across nations, regions, time and social systems (Chetty & Hendren, 2018; Corak, 2013; Kuznets, 1955; Piketty & Saez, 2003; Roine & Waldenström, 2015). However, a universal fact is that parents influence the starting-points of their children by providing them with family-specific environments and by passing down a part of their genes. This phenomenon creates individual-specific social and genetic endowments that are due to luck in the sense that they are exogenously given rather than the result of one's own actions. Thus, inequalities of opportunity (Roemer & Trannoy, 2015) can partly arise from the outcomes of two family-specific "lotteries" that take place during conception — a "social lottery" that determines who our parents are, and a "genetic lottery" that determines which part of their genomes our parents pass on to us. Inequalities in opportunity restrict the extent of intergenerational social mobility (Becker et al., 2018; Belsky et al., 2018; Durlauf & Seshadri, 2018; Jäntti & Jenkins, 2015) and limit how much credit people can claim for achievements such as their education or income (Rawls, 1999; Roemer, 1998). The relative importance of social and genetic luck has policy relevance because the extent to which people are willing to tolerate or endorse inequality partially depends on whether they perceive that disparity originates from differences in effort and choice (e.g., working hard) or from differences in circumstances that are outside of one's control (e.g., luck in the social or genetic lotteries). The empirical results suggest that inequality that can ultimately be traced back to luck may be perceived as unfair and people may favor redistributive policies more strongly if inequality is the result of luck rather than agency (Alesina et al., 2018; Alesina & La Ferrara, 2005; Almås et al., 2010; Cappelen et al., 2013; Clark & D'Ambrosio, 2015; Gromet et al., 2015). It has even been suggested that GDP per capita as a measure of economic development should be replaced with a measure of the degree to which opportunities for income acquisition in a nation have been equalized (Roemer & Trannoy, 2016).

If the outcomes of the genetic or social lottery influence economic outcomes, it can challenge common intuitions about the relative importance of luck and agency. For example, it is tempting to appraise good performance at work due to conscientiousness as rooted in individual agency. However, if genetics partly influence personality traits such as conscientiousness (Lo et al., 2016), luck and agency will be intertwined, and genetic fortune could be expected to affect outcomes throughout the life course not only via direct biological effects, but also through behavioral and environmental channels. It is important for science and policy to understand the extent to which genetic and social fortune contribute to inequality, the mechanisms that are at work, and whether and how the consequences of exogenously given endowments can be altered.

The current paper makes progress in this regard by using large-scale molecular genetic and family data to test the influence of genetic and family-specific endowments on income inequality and its consequences for health. Specifically, we develop a new polygenic index for individual income and exploit random differences between ~35,000 biological siblings in this index to estimate the consequences of the genetic lottery for income on a range of life-time outcomes. We show that the well-known gradient between socioeconomic status and health is partly rooted in exogenously given genetic and social endowments. Furthermore, we demonstrate that a substantial part of genetic luck for income and its link with health appears to operate via educational attainment and its accompaniments, i.e., environmental factors that are in principle malleable through policy interventions. Finally, we show that the effects of schooling on income remain strong and positive even when potential confounds from linear effects of common genetic variants are explicitly controlled for. Our results demonstrate the relevance of exogenously given genetic endowments for inequalities in income, education, and health. They also illustrate that the implications of the genetic lottery are not immutable because they operate at least partly via behavioral and environmental channels. Finally, our results emphasize the importance of education for inequality.

Our paper builds on recent work in social science genetics (Abdellaoui et al., 2019; Hill et al., 2016, 2019; Lee et al., 2018; Okbay et al., 2016; Rietveld et al., 2013) and applications of this work in economics. For example, (Belsky et al., 2018) used family data to explore the links between a genetic index for educational attainment and various measures of social mobility. Furthermore, (Barth et al., 2020) and (Papageorge & Thom, 2019) studied the associations between a genetic index for educational attainment and a variety of economic decisions and outcomes, without, however, using a within-family research design that would allow them to identify causal effects.

We accompany this article with a frequently asked questions (FAQ) document that explains in plain and simple language what we have done, what we found, what our results mean, and — importantly — what they do not mean (https://bit.ly/3f5TXoV). This FAQ document aims to address a wider audience of nonexperts in an effort to responsibly communicate scientific results, which is especially important given the dark history and abuses of social science genetics (Editors, 2013; Nuffield Council on Bioethics, 2002).

5.1.1 Background

One approach researchers have used to quantify the relevance of luck due to genetic and family-specific endowments in the past are twin studies, which decompose observed differences in outcomes into genetic, family-specific, and residual variance components, leveraging the insight that monozygotic (MZ) twins are genetically (almost) completely identical, whereas dizygotic (DZ) twins have a genetic similarity of ≈50% (Falconer & Mackay, 2009; Plomin et al., 2012). The identifying assumptions in classic twin studies include that MZ and DZ twins are different from each other only because of genetic reasons and not, for example, because parents treat MZ twin pairs systematically different from DZ twin pairs. Furthermore, classic twin studies assume that all genetic influences are additively linear and that parents are randomly matched rather than assorted based on similarity. Violations of these assumptions can lead to either upward or downward bias in the estimated variance components and have consequently sparked an extensive debate in the literature (Felson, 2014; Lerner, 2006; Purcell, 2002; Visscher et al., 2008; Zuk et al., 2012). Additionally, the findings from twin studies are typically based on samples from specific Western, educated, industrialized, rich, and democratic (WEIRD) populations (Henrich et al., 2010), thereby missing the importance of factors such as policies, culture, attitudes, institutions or economic development that do not vary much within the considered samples, but that can matter a great deal for differences between groups and over time.

Keeping these limitations in mind, the main conclusion from twin studies is that genetic differences account for a substantial part of the observed differences in income, educational attainment, or occupational choice in the samples analyzed (Nicolaou & Shane, 2010; Polderman et al., 2015; Rietveld et al., 2013; Rowe et al., 1998; Taubman, 1976). For example, according to a meta-analysis of 10 studies based on 24,484 partly overlapping twin pairs, 52% (*SE* = 0.03) of the variance in educational attainment can be attributed to genetic influences and 27% (*SE* = 0.03) to family-specific environments (Polderman et al., 2015; Rietveld et al., 2013; Rowe et al., 1998). The first study of this kind in economics (Taubman, 1976) found a large influence of genetic and family-specific effects on earnings and years of schooling in a sample of white male twins who served in the U.S. Armed Forces during World War II. The article described these findings as "disturbing" given the author's inclination to accept socioeconomic inequalities due to "hard work and effort" much more than those arising from the contributions of one's parents.

Studies that considered genetic factors as potential contributors to socioeconomic inequality tend to trigger controversy, worry, and opposition (Comfort, 2018). These concerns have to be taken seriously because misinterpretations of genetic influences and heritability estimates as measures of "purely biological" and "immutable" factors have been abused to justify ideologies about "natural rank orders" among individuals. This type of thinking has contributed to discrimination and some of the most horrifying atrocities in human history, including the Holocaust, involuntary sterilization programs, and state-sponsored violence targeting minorities and the poor (Kevles, 1995; Ladd-Taylor, 2020; Zimmer, 2018). Unfortunately, these ideologies and dangers still exist today.

Viewing genetic influences as immutable factors that are independent from the environment is not only dangerous but also factually incorrect: the heritability of a trait puts no upper bound on the potential relevance of the environment (Goldberger, 1978, 1979; Jencks, 1980). Indeed, the heritability of a trait can even be entirely caused by environmental conditions.[1] Furthermore, genetic influences on socioeconomic outcomes are most likely indirect, working via social and behavioral pathways that strongly depend on institutions, norms, policies, and incentives that are man-made and mutable (Jencks, 1980). Genetic influences that work via environmental pathways, for example by selection into

[1] For example, a hypothetical society that discriminates against people with red hair in college admissions would induce a heritability of educational attainment and a correlation between genes that influence hair pigmentation and college attendance, even though hair pigmentation may be orthogonal to academic aptitude (Jencks, 1972).

particular surroundings such as colleges, may lead to substantial disparities in outcomes such as income for environmental reasons that are everything but universal, perpetual, or "given by nature". As a result, genetic influences on socioeconomic outcomes can differ across divergent environments, making them neither inalterable nor purely biological factors. Thus, heritability estimates or genetic associations by themselves are uninformative about whether an environmental change such as a policy reform would affect an outcome or not. Rather, they are snapshots of a particular moment in time, a particular context, and most often of a particular ancestral population, one that is traditionally afforded higher income and education.

In response to some of these challenges, it has been suggested that "economists might do well to abandon the enterprise of determining the heritability of socioeconomic achievement measures" altogether (Goldberger, 1978; Manski, 2011). Although interest in the potential contributions of genetic factors to economic outcomes and behaviors has never entirely ceased (Bowles & Gintis, 2002; D. Cesarini et al., 2009; David Cesarini et al., 2010; Sacerdote, 2002; Zax & Rees, 2002), most economists seem to have largely followed Goldberger's advice and turned their attention away from genetics and heritability estimates in the past four decades.[2]

However, genetic influences do not disappear just because one chooses to ignore them. Instead, genetic influences remain both a challenge and an opportunity for attempts to understand economic realities such as the origins and consequences of inequalities in income. First, genetic influences are a challenge because they may induce omitted variable bias in observational, nonexperimental studies. For example, a central issue for understanding the origins of inequality is to grasp the effects of education on income. One of the challenges in attempts to accurately estimate the returns to schooling are unobserved

[2] This development away from genetics in economics is in stark contrast to what happened in psychology, where estimating the heritability of traits and their co-heritability has been an active field of research since the 1970s that produced an extensive body of empirical evidence that can be succinctly summarized as "all human behavioral traits are heritable" (Turkheimer, 2000), with an average heritability estimate of around 50% across all traits (Polderman et al., 2015).

differences in "ability" that may have a genetic component (J. J. Heckman et al., 2006).[3] As a result, unaccounted genetic factors that are related to both educational attainment and income may lead to false conclusions about the extent to which differences in income can be attributed to schooling (DiPrete et al., 2018). Second, ignoring any source of variability of an outcome and relegating it to the error term of a regression necessarily leads to noisier, less precise estimates of the observed variables of interest. This phenomenon also holds for genetic sources of variability. Obviously, both uncertainty and bias can be serious obstacles in attempts to generate useful empirical insights.

Of course, these challenges are not new and economists already have potentially powerful tools to address them. For example, natural experiments and instrumental variable techniques can be used to identify causal effects, but they hinge on the availability of truly exogenous shocks that are relevant and measurable. Another popular way to address potential bias from unobserved heterogeneity is individual fixed-effects models. However, these models require panel data featuring both regressors and regressands that vary among individuals over time, which restricts the type of questions one can ask. When genetic differences among people and their correlations with economic outcomes are observed directly, it opens up new opportunities to avoid unobserved variable bias and to obtain more accurate estimates of nongenetic influences (Benjamin et al., 2012; Harden & Koellinger, 2020).

Furthermore, genetic data have two properties that make them particularly interesting for applied empirical work (Mills et al., 2020). First, the genetic sequence of each person is fixed at conception and does not change throughout one's lifetime. Thus, reverse causality from behavior or environmental exposures to the genome can be ruled out. Therefore, genetic data provide researchers with the potential to construct noisy but exogenously given proxies for individual characteristics and outcomes that will emerge and change over the life course, allowing us to trace development paths. Second, each child is the

[3] "Ability" is often mentioned in economic studies on the returns to schooling, but it is also a historically-burdened term that has been used to validate and carry out violent campaigns against the poor and racially-defined minorities at different points in history (Tabery, 2015). This background contributes to the discomfort and caution applied to current genetics research (Roberts, 2015). We use quotation marks in our mention of the term "ability" to recognize this historical legacy and the potentially misleading nature of this term.

result of a natural experiment that randomly mixes the genetic sequences of her biological parents. Thus, with the possible exception of monozygotic twins, all children who share the same biological parents exhibit random genetic differences. These exogenous shocks of the "genetic lottery" are a natural experiment that may be useful to identify causal relationships (Davies et al., 2019). Here, we provide an example of how random differences between siblings in a genetic score for income lead to inequalities in socioeconomic outcomes and health later in life and we begin to explore the possible mechanisms.

5.2 Data

5.2.1 Genetic data

The genome is encoded in a sequence of DNA (deoxyribonucleic acid) molecules. This sequence contains hereditary information that provides building instructions for all living organisms. In humans, the genome consists of 23 pairs of chromosomes, with one chromosome in each pair passed down by the father and one by the mother. Each chromosome is composed of two connected DNA strands that together resemble a twisted "ladder" (i.e., a double-helix). The "rails" of the "ladder" consist of a sugar-phosphate backbone and a nitrogenous base (adenine [A], cytosine [C], thymine [T], or guanine [G]) is attached to each sugar-phosphate group. Together, these components construct a "nucleotide". The nitrogenous bases bind to each other in a strictly complementary way such that A always binds with T and G always binds with C, forming the "rungs" of the "ladder". The bases of the two copies of each chromosome may vary if father and mother passed down different variants.

Human DNA consists of ≈3 billion nucleotide pairs, the overwhelming majority of which are shared across individuals. Here, we study variations in nucleotide pairs in which some people carry a different base at a particular location (e.g., AT instead of GC). These so-called single nucleotide polymorphisms (SNPs) are the most common form of genetic variation that exists. Relatively common SNPs that vary among >1% of humans make up less than 2% of all ≈3 billion base pairs of human DNA (Auton et al., 2015), rendering these SNPs both informative about common genetic differences between people as well as relatively cheap[4] and easy to measure (e.g., using saliva samples and high-throughput genotyping arrays) (Mills et al., 2020).[5]

Because individuals have two copies of each chromosome, they typically have either two ATs, two GCs, or one AT and one GC at each position in their DNA. Therefore, SNPs can be numerically represented as count variables that indicate the number of copies of a chosen reference molecule (AT or GC), taking the values 0, 1, or 2.

SNP data exhibit two types of correlations that must be taken into account. The first type consists of SNP correlations among the rows in the data (i.e., individuals) which increase if two individuals are related to each other and decrease with the number of generations that lie between them and their last common ancestor. While relatedness among individuals in a dataset can occur simply due to sampling multiple individuals from the same family, there can also be more subtle types of population structures underlying SNP data that can be traced back to shared ancestors many generations ago. Subgroups of the population that have different allele frequencies may also have different outcomes due to nongenetic factors such as cultural norms, policies, geographic environments, or economic circumstances, which can induce bias known as population stratification (Hamer & Sirota, 2000). Thus, many research questions

[4] The collection of a saliva sample, DNA extraction, and genotyping using a machine-readable array can currently be achieved for around $50 or less.

[5] In addition to the common SNPs analyzed here, other types of genetic variation exist such as rare and multiallelic SNPs or structural genetic variants including inversions, deletions, insertions, copy number variants, or translocations (Auton et al. (2015)). To the extent that these unobserved genetic variants are not or only weakly correlated with common SNPs, their influence cannot be detected well using SNP data. Thus, methods that use these data tend to underestimate the extent of genetic influences (Witte, Visscher, and Wray (2014)). To measure structural and rare genetic variants, full genome sequencing would be required, which is much more expensive than the array-based scans of common SNPs that we and the vast majority of all studies in human genetics rely on, and which would imply substantially smaller sample sizes.

that rely on genetic data need to control for unobserved variable bias due to population structure (Price et al., 2006; Young et al., 2018, 2019).

Second, there is also a correlation structure among the SNPs themselves, i.e., the data columns. In molecular genetics, this is called linkage disequilibrium (LD) and it refers to the fact that genetic variants that are in close physical proximity to one another on a chromosome tend to be inherited together, creating persistent correlational patterns. LD is driven by several factors including biological mechanisms such as chromosomal crossover that happens during the formation of egg and sperm cells (i.e., meiosis), but also by mating patterns, selection, or migration events (Mills et al., 2020). We detail below how we addressed potential biases from population structure and how we adjusted for LD in the construction of the genetic indices that are central for our applications.

5.2.2 UK Biobank (UKB)

The UKB is an ongoing population-based longitudinal study that was established to allow investigations of genetic and nongenetic factors that influence health outcomes in middle and old age. The UKB recruited 502,522 participants who were between 40-69 years old when they entered the study between 2006-2010 (Fry et al., 2017; Sudlow et al., 2015). All participants gave consent, answered questions, had physical measurements taken and provided samples of blood, urine and saliva at a baseline assessment center visit.

We use the molecular genetic data (see Appendix VI) and several available measures of SES of the UKB participants (standardized occupation codes, household income, educational attainment, and regional measures of socioeconomic status that were derived by the UKB from home locations and national statistics). We also use the digital health records of all participants, which are provided by UKB via continuously updated data linkage with the National Health Service (NHS). The NHS provides free medical treatment to all UK residents and is funded through general taxation. Thus, in contrast to other countries, access to medical treatment and the availability of digital health records in the UK is not a function of income or SES. Specifically, digital health records for England are available from hospital inpatient episodes (1996-2017), cancer registries (1971-2016), and death registries (2006-2018)[6], providing clinical diagnoses for all instances according to the International Classification of Diseases

[6] See http://biobank.ndph.ox.ac.uk/showcase/exinfo.cgi?src=Data_providers_and_dates

(ICD; 9th or 10th revision), which defines the universe of diseases, disorders, injuries and other related health conditions in a comprehensive, hierarchical fashion (World Health Organization, 2019). We examined all available hospital inpatient records, cancer episodes, and deaths for different types of disease using all major ICD chapters with a prevalence rate higher than 10% (16 in total). As an overall measure of health, we aggregate the available digital health records to examine whether participants had ever been hospitalized for any disease or diagnosed with any type of cancer. The available digital health records are left-censored, which prevents us from observing disease episodes from earlier periods where the participants were younger. It should therefore be kept in mind that our estimates with respect to disease occurrence and hospitalization are likely to be underestimated.

In addition, we use four proxies for health that are not subject to left-censoring and that are continuously distributed: body-mass-index (BMI), waist-to-hip ratio (WHR), blood pressure, and a measure of lung function (Global Burden of Disease Obesity Collaborators et al., 2017; Huxley et al., 2010; Srikanthan et al., 2009). Finally, we use a summary index of overall health that is a weighted sum of all binary and continuously distributed health indicators mentioned above.[7] Table S5.1 provides a list of these variables and their definitions. In addition, Tables S5.2 and S5.3 show relevant descriptive statistics.

5.2.3 Health and Retirement Study (HRS)

The HRS is an ongoing longitudinal survey on health, retirement, and aging that is representative of the US population aged 50 years or older (Sonnega et al., 2014). The survey contains a wide range of socioeconomic outcomes, including income, educational attainment, working hours, and standardized job codes. Since 2006, data collection has expanded to include biomarkers and a subset of the participants has been genotyped (Weir, 2013). We use the second release of the HRS genetic data here (see Appendix VI). Our primary outcome of interest in the HRS is hourly wages, which are constructed from self-reports of income and hours worked. We use a cleaned and harmonized dataset produced by

[7] The summary index of every health measure is constructed by following (Anderson, 2008). This method takes a weighted average of standardized outcomes where weights are determined by the inverse of the correlation matrix. Outcomes highly correlated with each other are assigned less weight, while outcomes receive more weight if they are uncorrelated and therefore represent new information. The weights we used in our study are reported in Table A4.

the RAND corporation[8], which includes twelve waves from 1992 to 2014. We convert nominal wages into real wages using the consumer price index (base =1982-1984).

5.2.4 Polygenic indices

All heritable human behaviors are associated with very many genetic variants, each of which accounts for a very small percentage of the behavioral variability. This stylized fact is known as the "Fourth Law of Behavior Genetics" (Chabris et al., 2015). Due to the sheer number of SNPs that are potentially relevant for human behavior and economic outcomes, it is difficult to incorporate them directly in an econometric model. Instead, an efficient and well-established way of exploiting the SNP data is to construct a polygenic index (PGI) that additively summarizes the effects of more than 1 million SNPs. Formally, a PGI s_i is a weighted sum of SNPs:

$$s_i = \sum_{j=1}^{J} \hat{\beta}_j x_{ij} \tag{5.1}$$

where x_{ij} is individual *i*'s genotype at SNP *j*. The weights $\hat{\beta}_j$ are estimated in a genome-wide association study (GWAS) (see Appendix III) which scans all measured genetic variations among people for associations with the outcome of interest. Since the number of SNPs *J* is typically orders of magnitude greater than the number of individuals in the sample, it is impossible to fit all SNPs simultaneously in a multiple regression. Instead, the outcome is regressed on each SNP separately, resulting in *J* regressions in total. Importantly, in order to avoid overfitting, the GWAS estimation sample does not include individuals for which a PGI is constructed.

PGI for several economic outcomes are already available, thanks to large-scale GWAS on traits such as educational attainment (Lee et al., 2018; Okbay et al., 2016; Rietveld et al., 2013), risk tolerance (Karlsson Linnér et al., 2019), subjective well-being (Turley et al., 2018), and household income (Hill et al., 2016, 2019). However, no PGI for individual income exists until now, despite the fact that individual income is one of the most central topics in economics and one of the most important proxies for well-

[8] Health and Retirement Study, (RAND HRS Longitudinal File, version P) public use dataset. Produced and distributed by the University of Michigan with funding from the National Institute on Aging (grant number NIA U01AG009740). Ann Arbor, MI, 2017.

See https://www.rand.org/well-being/social-and-behavioral-policy/centers/aging/dataprod/hrs-data.html being (Sacks et al., 2012; Stevenson & Wolfers, 2013) and health throughout the lifecourse (Adler et al., 1994; Chetty et al., 2016; Wilkinson & Marmot, 2003). The primary reason for this deficiency is that most datasets that contain genetic information have been collected for medical research purposes and lack measures of individual income. The few existing genetic datasets that do contain high-quality measures of income are, unfortunately, too small to allow conducting statistically well-powered GWAS on individual income (e.g. the Health and Retirement Study and the Wisconsin Longitudinal Study).

We remedy this issue by conducting GWAS on a good proxy for individual income, occupational wages, which we imputed from standardized occupation codes in the UKB, one of the largest existing genotyped datasets in the world. In essence, our imputation algorithm reflects the typical log wage of occupations in the UK, adjusted for demographic characteristics such as sex and age. Appendix I describes the procedure in detail. The income PGI that we created here adds to the growing array of polygenic indices that are useful for economists and other social scientists. Furthermore, a PGI for individual income is crucial for several of the analyses we present below, including our estimates of the returns to schooling.

Specifically, we follow a preregistered analysis plan (https://osf.io/rg8sh/) and conduct GWAS on occupational wages using 252,958 individuals in the UKB, excluding siblings and their close relatives to obtain an independent sample for follow-up analyses using the PGI. In Appendix III, we provide detailed descriptions of the GWAS and discuss the results of the GWAS on occupational wages with the full sample including the sibling sample (N=282,963). In short, our GWAS on occupational wages identified 45 approximately independent genetic loci from 3,920 SNPs that are significant after Bonferroni correction for multiple testing ($p < 5\times10^{-8}$).[9] The estimated effect size of each individual SNP is very small ($R^2 < 0.04\%$), which is consistent with previous GWAS results for socio-economic outcomes (Chabris et al., 2015; Hill et al., 2019; Lee et al., 2018; Rietveld et al., 2013). The effects of 1,197,148 SNPs are then aggregated into a PGI in the sibling sample. We take the correlations between

[9] The summary statistics of the genome-wide association study (GWAS) presented here can be downloaded at https://osf.io/rg8sh/. These data are useful for many purposes such as constructing genetic indices, computing genetic correlations (Bulik-Sullivan et al., 2015), and for genetically informed study designs involving income (Harden & Koellinger, 2020).

SNPs into account by using a Bayseian approach that adjusts the estimated GWAS weights $\hat{\beta}_j$ with information about correlations between SNPs (Vilhjálmsson et al., 2015) (see Appendix IV). The resulting PGI is then standardized to have zero mean and unit variance. This PGI captures approximately 3% of the variation in occupational wages in the UKB sibling sample and 1% of self-reported wages in holdout samples from the U.S. (Table S5.7).[10] For simplicity, we refer to this polygenic index as the "income PGI" below.

Our GWAS results for occupational wages are similar to those for educational attainment, which was previously studied in GWAS sample size of N> 1,000,000 (Lee, Wedow, et al. (2018). The genetic similarity between occupational wages and educational attainment can be quantified by the so-called genetic correlation coefficient between both traits[11], which is 0.923 (SE = 0.01). Thus, occupational wages and educational attainment are genetically very similar but not identical traits (see Appendix III). The genetic similarity between occupational wages and educational attainment can be exploited to improve the accuracy of the income PGI by applying a multivariate statistical method called Multi-Trait Analysis of Genome-wide association summary statistics (MTAG) (Turley et al., 2018). MTAG increases the accuracy of a PGI by "borrowing" information from GWAS estimates of genetically similar traits, which could also be obtained from partly or even completely overlapping GWAS samples. The MTAG approach substantially boosts the accuracy of the income PGI. For instance, the R^2 of the income PGI increases in the UKB holdout sample of siblings from 2.77% to 4.47% for occupational wages and from 0.66% to 1.40% for BMI when MTAG is used (Table S5.9).

[10] The difference in R^2 of the PGI across samples is likely due to differences in heritability and the true genetic architecture of different measures of income (i.e. occupational wages versus self-reported wages) across different environments (i.e. UK versus US), see (de Vlaming et al., 2017).

[11] The genetic correlation between two traits quantifies the extent to which they share the same molecular genetic architecture, ranging from -1 to 1 (Bulik-Sullivan et al., 2015; Harden & Koellinger, 2020; Okbay et al., 2016).

5.3 Statistical considerations

Our main analysis examines the consequence of the genetic lottery for income on socioeconomic and health outcomes, taking advantage of the large sibling sample from the UKB. Consider the following baseline specification for outcome *y* for individual *i* from family *j*:

$$y_{ij} = \delta s_{ij} + z'_{ij}\theta + \alpha_j + e_{ij} \tag{5.2}$$

where s_{ij} is the PGI for income, z_{ij} a vector of covariates, and α_j unobserved family-specific effects. In what follows, we discuss two important sources of potential bias when estimating the effects of the genetic lottery (δ) and how we address these issues.

5.3.1 Confounds due to family environment

Estimates of δ can be confounded due to the fact that the PGI only summarizes genetic associations, which are not necessarily the same as the causal genetic effects. The causal genetic effect can be defined as the average (counterfactual) change in an individual's outcome that would occur as a result of a ceteris paribus change of that individual's genotype at conception. In practice, however, GWAS are typically conducted in population samples and the obtained GWAS results and PGI can, and often do, contain environmental confounds, for example due to the environment that parents provide for their children (Kong et al. 2018).[12] More generally, when $cov(s_{ij}, \alpha_j) \neq 0$ and α_j is not specifically controlled for, estimates of δ will be inflated as a result of family-specific environmental conditions that influence y_{ij}.

[12] Another example is population stratification, i.e. environmental effects that correlate with more distant genetic ancestry that subgroups of the population share with each other such as cultural norms, policies, geographic environments, or economic circumstances (Hamer & Sirota, 2000). GWAS typically try to address bias from population stratification by restricting samples to a relatively homogenous population, e.g. by limiting the study sample to individuals of European descent, and second by controlling for first 40 principal components from the SNP data. This is also the approach we followed here. These strategies help to some extent, but they are typically not sufficient to eliminate bias due to population stratification when socio-economic outcomes are studied in large GWAS samples (Abdellaoui et al., 2019; Haworth et al., 2019).

This bias is particularly relevant for socioeconomic outcomes (Kong et al., 2018; Lee et al., 2018; Young et al., 2018).

To break the link between $s_{ij}$and α_j, the natural experiment of meiosis can be exploited in a sample of siblings who share the same biological parents. During meiosis, the two copies of each parental chromosome are randomly combined and then separated to create a set of two gametes (e.g., two eggs or two sperm), each of which contains only one new, resampled copy of each chromosome. The resulting genetic differences between full siblings and dizygotic twins are therefore random and independent from family-specific ancestry and environmental factors that vary between families.

In a sample of siblings, the unobserved family-specific effects can simply be accounted for by including family fixed effects. Hence, a within-family regression will yield estimates of the coefficient for the PGI (δ) that are immune to parental genetic nurture and the uncontrolled population structure in GWAS that cannot be traced back to causal genetic effects. For this purpose, our main analysis relies on a hold-out sample of approximately 35,000 siblings from the UKB.

5.3.2 Measurement error in the PGI

Empirically estimated PGI are noisy proxies for "true" PGI that would capture the linear effects of all genetic variants in their entirety. The differences between the "true" and the available PGI are primarily due to two reasons. First, currently available genotyping technologies focus on common genetic variants, but they miss rare or structural genetic variants that are not highly correlated with the observed common variants (see footnote 7). For this reason, most empirical work in complex trait genetics is currently limited to studying the effects of common genetic variants, including this study. Second, GWAS estimates of the effect sizes of individual SNPs are noisy because they are obtained from finite sample sizes. The noise in the estimated effects of SNPs translates into noise in the PGI that is akin to classic (i.e. random) measurement error (Daetwyler et al., 2008; de Vlaming et al., 2017) which can be adjusted using instrumental variable regression (DiPrete et al., 2018). In our concrete example, we estimate that a PGI of all common genetic variants could potentially capture up to ≈10% of the variation in occupational wages, which is the share of variance in occupational wages that can be attributed to the combined linear effects of common genetic variants among UKB participants (See Appendix II). Thus, noisy GWAS estimates attenuate the accuracy of the currently available income PGI by more than 50%.

To address attenuation bias due to measurement error, we use genetic instrument variable (GIV) regression (DiPrete et al., 2018), which constructs an instrument for the noisy PGI by randomly splitting the GWAS sample into two independent subsamples that allow for constructing two (even noisier) indicators of the PGI. Under the reasonable assumption that the error terms of both indicators are independent, one of them can be used as an instrument for the other to obtain coefficient estimates that are corrected for measurement error.

More formally, define a PGI $s_i = s_i^* + u_i$, where s_i^* is the true PGI and u_i is additive measurement error. Because the PGI is a linear combination of SNP effects, we can write $u_i = \mathbf{x}'_i(\mathbf{b} - \boldsymbol{\beta})$, where $\mathbf{x}_i$ is the vector of SNP data for individual i, $\boldsymbol{\beta}$ is the vector of true SNP effects, and $\mathbf{b}$ is the vector of estimated SNP effects. That is, the PGI can be decomposed into a true part and the contribution from the estimation error in the GWAS (i.e., $\mathbf{b} - \boldsymbol{\beta}$).

Suppose that we generate two PGI, by randomly splitting the GWAS sample into two independent subsamples to obtain two estimates of $\boldsymbol{\beta}$, where $s_i{}^{(1)}$ is constructed using the estimate from one subsample and $s_i{}^{(2)}$ using the estimate from the other subsample, where the additive measurement error in $s_i{}^{(2)}$ is denoted by $u_i{}^{(2)}$.

Now, if we are to use $s_i{}^{(2)} = s_i^* + u_i{}^{(2)}$ as an instrument for $s_i{}^{(1)}$, $s_i{}^{(2)}$ must capture the true PGI term s_i^* only in the first stage regression. This implies that the noise terms $u_i{}^{(1)}$and $u_i{}^{(2)}$ of the two PGI must be uncorrelated with each other. Thus, the estimation error of GWAS, $\mathbf{b} - \boldsymbol{\beta}$, cannot be correlated across the two subsamples, so that Cov($u_i{}^{(1)}$, $u_i{}^{(2)}$) = 0. In practice, the two most important steps that need to be taken are (1) excluding genetic relatives from all subsamples and (2) adding fairly rigorous controls against population structure to the GWAS. To the extent that Cov($u_i{}^{(1)}$, $u_i{}^{(2)}$) = 0 holds, using one PGI as an instrument for the PGI in a two-stage least squares regression will yield effect size estimates for the PGI that are no longer attenuated by finite GWAS sample sizes (DiPrete et al., 2018). However, even this correction of measurement error in PGI due to finite GWAS sample sizes does not address the fact that the influence of rare and structural genetic variants that are not well tagged by current genotyping arrays remain unobserved. Therefore, estimates of the effects of the genetic lottery that we report below are lower bounds for the influences of all genetic variants.

To obtain GWAS results for GIV analyses, we split the UKB GWAS estimation sample randomly into two subsamples, each containing 126,478 individuals. The subsamples have the same male-female ratio and the individuals in each sample are genetically related to those in the other sample with no more than first degree cousins or great-grandparents. We re-conducted a GWAS of occupational wages on these two subsamples and constructed two PGI for the sibling sample to use for GIV analyses. Note that these GIV PGI are not augmented with the GWAS results of educational attainment using MTAG.

5.4 The SES-health gradient in the UK Biobank

It is well-known that people with high SES also tend to live longer and healthier lives than those with lower SES (Chetty et al., 2016; Piotrowska et al., 2015; Stringhini et al., 2017b; Wilkinson & Marmot, 2003). Natural experiments show that higher education has a positive causal effect on health (Grossman, 2000, 2006). However, studies looking at income and health have produced mixed results about causal effects and come with many methodological challenges (Kawachi et al., 2010; O'Donnell et al., 2015).

The UK Biobank offers a unique opportunity to gain additional insights into the relationship between SES and health thanks to its broad coverage of the UK population; its large sample size, which includes one of the largest samples of genotyped siblings in the world; as well as the availability of detailed health records from assessment center visits and digital health records that are continuously updated and that span the entire universe of medical diagnoses. In addition to descriptive analyses of the SES-health gradient for a variety of health outcomes, this particular type of data also allows us to estimate the extent to which exogenously given endowments from the social and the genetic lottery drive the relationships between SES and health. As a first step, we conduct a family fixed-effects analysis in the sibling sample that allows us to control for the outcomes of the social lottery (i.e., the parental environment that both siblings share) and a part of the genetic lottery (i.e., the genetic similarity of siblings that is due to their descent from the same biological parents). The remaining differences in SES and health outcomes between siblings are the result of their random genetic differences as well as unique environmental influences that are unrelated to their shared genetic endowments.

Table 5.1 shows the relationship between SES, approximated by having a college degree and occupational wage, and health outcomes in the UKB. The first five rows of the table show estimates for the gradient with continuous proxies of health that include the waist-to-hip ratio, BMI, blood pressure, lung function, as well as the summary index for health. The results imply strong health advantages for people with higher SES. For example, a ten percent increase in occupational wages is associated with ≈ 0.12 decrease in BMI (95% CI: 0.09-0.34). The same picture emerges for the digital health records that were grouped into specific disease categories: Individuals with higher occupational wages and a college degree exhibit a lower tendency for severe disease outcomes that would require hospitalization (*ever hospitalized*). High SES is also associated with a lower likelihood of being diagnosed with all major disease categories, with the exception of neoplasms and cancers. The association between SES and health outcomes is particularly strong for endocrine, nutritional, and metabolic diseases; mental, behavioral, and nervous system disorders; and diseases of the circulatory and digestive systems. For example, having a college degree decreases the risk of ever being hospitalized for diseases of the circulatory system by ≈ 8 percentage points (95% CI: 6.12-10.10). These estimates are a lower bound of the SES-health gradient because the well-known healthy volunteer bias in the UK Biobank attenuates the estimates (Fry et al., 2017).

The results in Table 5.1 also clearly demonstrate that exogenously given family-specific endowments are responsible for the majority of the gradient between SES and health. In particular, when we control for family fixed effects, all estimated coefficients between SES and health are closer to zero and only the associations of SES with circulatory system disorders, waist-hip-ratio, lung function, and the summary index across all health outcomes remain statistically distinguishable from zero. The substantial contributions of family-specific genetic and environmental effects that are outside of one's control emphasize moral concerns about these observed health inequalities (Alesina et al., 2018; Alesina & La Ferrara, 2005; Almås et al., 2010; Cappelen et al., 2013; Gromet et al., 2015).

5.5 Consequences of the genetic lottery for income

We now turn to the consequences of the genetic lottery based on the random differences between siblings in their polygenic index for income. Our approach allows us to examine the causal impact of the genetic lottery for income on lifetime outcomes in the present-day UK.

There are 18,807 genetic sibling groups in the UKB (38,698 individuals). Our analyses are restricted to pairs that have the respective outcome variables available for both individuals,[13] leading to varying sample

[13] Only 1,003 sibling groups have more than 2 members. We dropped sibling groups if more than two siblings were available for a given outcome.

sizes between 8,780 and 17,633 pairs per outcome. We regressed each of the SES and health outcomes on the income PGI and covariates.[14] For each outcome, we estimated the regression with and without family fixed effects. In the OLS estimation, the MTAG income PGI is used, whereas GIV estimation uses the ordinary income PGI estimated from the UKB subsamples.[15] All PGIs are standardized to have zero mean and unit variance. We adjusted for multiple hypothesis testing using Holm's method (Holm, 1979) in each set of analyses.[16]

Figure S5.1 shows the distribution of the sibling difference in the MTAG income PGI in absolute value. Most of the sibling pairs exhibit a very small difference.[17] Half of the sibling pairs have a difference in income PGI values smaller than 0.63, measured in standard deviations of PGI in the sibling sample. The results of our within-family PGI analyses are presented in Table 5.2 and 5.3. The OLS estimates reported in the first column of Table 5.2 and 5.3 demonstrate that the MTAG income PGI is associated with all socioeconomic and almost all health-related outcomes we investigated. Furthermore, as reported in the third column, GIV regression estimates, which correct for measurement error in the PGI are typically twice as large as their corresponding OLS estimates.

Across the board, we find that a higher income PGI is associated with more favorable lifetime outcomes including higher educational attainment, higher occupational wages, living in a better neighborhood, a lower BMI and waist-to-hip ratio, lower blood pressure, a lower chance of having ever been hospitalized, and a lower probability of being diagnosed with all disease categories in the digital health records that that we investigated, again with the exception of cancer and neoplasms (Figure S5.2). When we correct for the attenuation bias in our results due to the measurement error in the PGI using GIV regression (but before we control for family fixed effects), our estimates show that a one-standard-deviation increase in the genetic propensity for higher income is associated with a 15% increase in occupational wages, a 7-percentage-point-increase in the likelihood of having a university education, an almost one-

[14] See the note in Table 2 and 3 for the included covariates.
[15] This is because the GWAS results for educational attainment are from a meta-analysis of many cohorts.
[16] Holm's method controls the familywise error rate like Bonferroni correction, while it offers a uniformly more powerful correction by sequentially adjusting rejection criteria.
[17] 22% of the variation in the MTAG income PGI comes from within-family differences, while 78% comes from between-family variation. The correlation of a genotype between two siblings is 0.5 in expectation, which implies that 25% of the variation in the PGI is due to within-family differences in expectation. However, in the presence of assortative mating, the PGI of siblings can be more similar to each other than in expectation, which can lower the share of the within-family variation to below 25%.

point-decrease in BMI, and a 4-percentage-point decrease in the likelihood of ever being hospitalized for the given age. Thus, the phenotypic associations between SES and health are mirrored in the associations between the PGI for income and health.

This pattern of results is consistent with the finding that measures of SES such as educational attainment show pervasive and often substantial genetic correlations with health outcomes that range between -0.3 for Alzheimer's disease, depressive symptoms, and body fat percentage to 0.6 with Mother's age at death (Bulik-Sullivan et al., 2015; Harden & Koellinger, 2020), illustrating that health and SES are also tightly intertwined at a genetic level.

However, a substantial part of the correlations between PGI for socioeconomic outcomes and disease is likely to be due to indirect genetic effects such as genetic nurture (Kong et al., 2018) or subtle forms of population stratification such as correlations between gene frequencies and neighborhood characteristics that are also correlated with SES and health outcomes (Abdellaoui et al., 2019; Haworth et al., 2019). When comparing our OLS estimates of the coefficient for income PGI with and without family fixed-effects, we observe that the within-family effects are typically halved (Figure S5.2). For instance, the estimated effect of a one standard deviation increase in the PGI for log occupational wage per hour decreases from 0.074 (95% CI: 0.07-0.08) to 0.046 (95% CI: 0.03-0.06) after controlling for family fixed-effects. Likewise, the estimate of a one standard deviation increase in the income PGI with family fixed effects implies a 0.29 reduction in BMI (95% CI: 0.16-0.41), while it is estimated to be a 0.52 reduction without family fixed effects (95% CI: 0.51-0.62). However, even with the smaller point estimates and the larger standard errors from within-family analyses, we still find statistically significant associations of the income PGI with all socioeconomic outcomes we investigated as well as with BMI, waist-to-hip ratio, and diseases of the musculoskeletal system and connective tissues. Thus, approximately one half of the observed associations between our income PGI, socioeconomic attainment, and health outcomes in late adulthood are due to random genetic differences between siblings.

Finally, combining the GIV regression with family fixed-effects allows us to estimate the combined linear causal effects of common SNPs while adjusting the PGI for measurement error. Despite substantially larger standard errors of the point estimates due to the two-stage least squares approach of the GIV regression, we find effects of the genetic lottery for a number of outcomes that are statistically distinguishable from zero, including occupational wages, household income, regional income, years of schooling, and having a college degree. For example, a one-standard-deviation increase in income PGI is estimated to increase the chance of obtaining a college degree by 14.5 percentage points (95% CI: 10.4-18.6) and an annual household income greater than £52,000 by 9.2 percentage points (95% CI: 4.3-14.1). Although none of the health and disease measures is statistically significant in GIV fixed-effects estimations due to lower estimation precision, the point estimates are very similar to the statistically significant OLS estimates in the first column of Table 5.2 and 5.3.

We repeated these analyses with a PGI for income that was not augmented by using MTAG (Table S5.13) and obtained qualitatively similar results, but with smaller point estimates in OLS regression due to the larger measurement error in the non-augmented PGI. We also conducted these analysis using a PGI for educational attainment (Table S5.13), with very similar results. Interesting, the PGI for educational attainment remains associated with health outcomes even after we add controls for actually achieved educational attainment, albeit with smaller effect sizes.

These results are inline with findings from Selzam et al. (2019) who compared PGI predictions within- and between-family for standardized test scores, IQ, and health-related outcomes using the Twins Early Development Study from the UK. They found that PGI are still predictive within-family while within-family estimate sizes for the PGI are typically smaller than between-family estimates. The differences are particularly large for standardized test scores, for which family background seems to play a more important role. These differences tend to disappear once parental socioeconomic variables are controlled for, suggesting that it is mainly the family's socioeconomic status that confounds the PGI. Similar findings for within-family estimates were also reported by Belsky et al. (2018).

5.6 Decomposition of the genetic lottery effects

The previous section demonstrated that the genetic lottery for income has incontrovertible consequences for a broad range of life-time outcomes. However, as mentioned in section 5.1.1, these genetic influences do not imply purely biological mechanisms, nor do they imply that policy interventions are doomed to be unsuccessful (Goldberger 1979; Jencks 1980; Harden and Koellinger 2020). To illustrate these important points, consider an intervenable pathway m_{ij} for individual i in family j through which the genetic lottery for income may affect an outcome such as health (e.g. access to favourable environmental conditions such as high-quality health care, healthy nutrition, or clean air and water). This intervenable pathway m_{ij} can be added to model (2) and an auxiliary regression can be conducted, where m_{ij} is the dependent variable:

$$y_{ij} = \tilde{\alpha}_j + \tilde{\delta}_1 s_{ij} + \tilde{\delta}_2 m_{ij} + z'_{ij}\tilde{\theta} \quad + \tilde{e}_{ij} \tag{5.3}$$

$$m_{ij} = \alpha^m{}_j + \gamma s_{ij} + z'_{ij}\theta^m + e^m{}_{ij} \tag{5.4}$$

Then, the coefficient of the PGI δ from the model (2) can be written as:

$$\delta = \tilde{\delta}_1 + \gamma \cdot \tilde{\delta}_2 \tag{5.5}$$

Therefore, the effect of genetic lottery δ can be decomposed into the effect working via pathway m_{ij} $(\gamma \cdot \tilde{\delta}_2)$ and the residual effect that does not work via that pathway $(\tilde{\delta}_1)$. Estimates of each parameter $(\tilde{\delta}_1, \tilde{\delta}_2, \gamma)$ can simply be obtained by estimating the equations (5.3) and (5.4) separately and the pathway effect $(\gamma \cdot \tilde{\delta}_2)$ can be estimated as the product of estimates of γ and $\tilde{\delta}_2$. The standard errors can be computed by the delta method.

As an empirical illustration, we focus on having a college degree as an example of m_{ij}. Colleges are social institutions that have admission policies, procedures, and graduation requirements that are shaped by their decision makers and that can be influenced by policy. In this sense, colleges are intervenable institutions. They create value by giving their attendees access to potentially valuable assets (e.g. knowledge and skills). They can also bestow advantages on their attendees by serving as a signalling mechanism for potential employers that have imperfect information about job applicants (Arcidiacono et al., 2010; Michael, 1973). Of note, colleges remain intervenable institutions independent from how heritable it is to have a college degree and to which extent the genetic architecture of having a college degree is shared with other lifetime outcomes such as income or health. In fact, policy interventions could change both the heritability of having a college degree as well as it's molecular genetic architecture dramatically. For example, a policy that randomly assigns people to college could lower the heritability of educational attainment substantially. Alternatively, a policy that forbids men to go to college would lead to a perfect correlation between having a college degree and whether an individual has one or two X chromosomes, without any meaningful biological mechanism that would stop men from going to college in a different environment. And yet, as long as colleges grant some advantages to their attendees that have health benefits, any genetic variant that is associated with college attendance would also have an indirect health benefit, but these health effects of genes could in principle be intervened upon.

To increase statistical power, we limit our empirical analyses to five lifetime outcomes that are continuously distributed and available for many UKB participants (occupational wages, BMI, waist-to-hip ratio, blood pressure, and lung function). The participants were at least aged 40, with the mean age of 57, when they were assessed for these measures. This limits concerns about potential reverse causality of these outcomes on college attendance.

While we can interpret the total effects of the genetic lottery as causal in the within-family model, this is not the case for the decomposed effects. In order for the intervenable pathway m_{ij} to be causal, it would be required that the PGI is exogenous with respect to both the late-adulthood outcomes and college education conditional on the covariates and, second, that having a college degree is exogenous with respect to the outcomes later in life conditional both on the PGI and the covariates.[18] Whereas the first part of these assumptions is plausibly satisfied given the random distribution of the PGI between siblings, the second part is likely to be violated in practice. In particular, this condition requires that there is no unobserved variable that affects both the late-adulthood outcomes and college education, which is clearly unrealistic. Having a college degree can be expected to affect many health-relevant circumstances, including income, neighborhood quality, and lifestyle-related choices that could influence health (e.g., smoking, alcohol consumption, diet, and physical activity) despite conditioning on family fixed effects. Therefore, the decomposed effects we estimate here do not illustrate the causal mechanism of the genetic effect. Instead, the results reported in Table 5.4 illustrate that the genetic lottery for income affects occupational wages and health partly via college education and its unobserved accompaniments — videlicet pathways that can be environmentally intervened upon (Barcellos et al., 2018).

For occupational wages and all the objective health outcomes that we examined, we observe that the effect of the MTAG income PGI that operates via college education and its accompaniments is statistically significant after Bonferroni correction for multiple testing. A one-standard-deviation increase in the PGI boosts the probability of attaining a college degree by up to 14.5 percentage points (Table 5.2), and having a college degree is in turn associated with lower waist-to-hip ratio, BMI, and blood pressure as well as better lung function and higher occupational wages. The intervenable pathway

[18] This is the same logic as the sequential ignorability assumption in causal mediation analysis (J. Heckman & Pinto, 2015; Imai et al., 2010)

that is approximated by having a college degree accounts for almost 35% of the total effect of the income PGI on occupational wages. For the health outcomes, 9% - 29% is accounted for by the indirect path, with the lowest indirect effect for BMI and the highest for lung function. Obviously, these are lower bound estimates for how much of the effect of the genetic lottery could be intervened upon because the residual effects of the PGI could include other m_{ij} that imperfectly correlated with having a college degree. While the estimated residual effects of the PGI on the health outcomes in Table 5.4 are often too noisy to draw a clear statistical inference, we find statistically significant effects of the m_{ij} pathway that is approximated by having a college degree in every case.

Thus, educational attainment and its accompaniments play a crucial role in the relationship between genetic fortune for income and health outcomes in later life. Thus, the genetic associations we report here clearly do not imply biological determinism.

5.7 Returns to schooling

The results above show a clear relationship between genetic predisposition (i.e., the results of genetic lottery), educational attainment, and income. This reinvigorates the much-debated question in economics of how sensitive estimates of the returns to schooling are to hitherto unobserved genetic confounds. Could it be that the strong, positive relationship between schooling and income is biased upwards by unobserved differences in family backgrounds and "ability"[19] that are at least partially rooted in genetic factors (Griliches, 1977; J. J. Heckman et al., 2006; Mincer, 1958)? We address this question for the first time with an explicit control for potential confounds from common genetic variants that may influence both education and income. Specifically, we use data from the HRS and our (nonaugmented) PGI for income and apply GIV regression to correct for measurement error in the PGI (DiPrete et al., 2018).

The coefficient we estimate is **not** the *ex ante* expected rate of return, which depends on psychic and financial costs of education, expected tax rates, expected number of working years after completing school, expected option values of additional years of education, and other information known to the economic agent at the time schooling decisions are being made (J. J. Heckman et al., 2006). The

[19] See footnote 5.

approach we take here is much more humble. It addresses the question of whether the *ex post* average growth rate of income with respect to schooling is potentially biased by hitherto unobserved linear effects of common genetic variants. Nevertheless, we use the more well-known phrase “returns to schooling” throughout the rest of the paper to improve understandability.

We pool individual observations in the HRS across the waves spanning from 1992 to 2014, which provides us with a weighted average of cross-sectional estimates, and we estimate a standard Mincer equation. We also consider a more flexible specification to capture potentially nonlinear returns to higher education by including a dummy variable for college education as well as an interaction term for having a college degree and years of schooling. As relevant proxies for family backgrounds, we also add controls for years of schooling for both parents.

As a measure of genetic confounds, we would ideally want to have a PGI that captures only directly pleiotropic effects on educational attainment and individual income (rather than genetic effects that are mediated by educational attainment). Thus, a PGI for educational attainment cannot be used as a control variable in this context because it would remove the covariation in years of schooling and income that we intend to identify. However, it is possible to obtain reasonable upper and lower bounds of the relationship between education and income conditional on genetic effects using GIV regression (DiPrete et al., 2018).

More specifically, the GIV regressions of the returns to schooling estimate the following equations with two-stage least squares:

$$y_i = {\beta_0}^c + {\beta_1}^c edu_i + {\beta_2}^c {s_{y|edu,i}}^{(1)} + z'_i \gamma^c + {e_i}^c \tag{5.6}$$

$${s_{y|edu,i}}^{(1)} = {\delta_1}^c {s_{y,i}}^{(2)} + {\delta_2}^c edu_i + z'_i \theta^c + {u_i}^c \tag{5.7}$$

$$y_i = {\beta_0}^u + {\beta_1}^u edu_i + {\beta_2}^u {s_{y,i}}^{(1)} + z'_i \gamma^u + {e_i}^u \tag{5.8}$$

$${s_{y,i}}^{(1)} = {\delta_1}^u {s_{y,i}}^{(2)} + {\delta_2}^u edu_i + z'_i \theta^u + {u_i}^u \tag{5.9}$$

where GIV-C and GIV-U are described by equations (5.6) and (5.7) as well as (5.8) and (5.9), respectively. y_i denotes log hourly wages and edu_i the years of schooling for individual *i*. ${s_{k,i}}^{(1)}$ is a PGI summarizing the GWAS effects of outcome *k* estimated with the first subsample, where outcome *k* is log hourly wage (*y*) for GIV-U while it is the log hourly wage conditional on years of schooling ($y|edu$) for GIV-C. ${s_{y,i}}^{(2)}$ is a PGI constructed from a GWAS on hourly wage estimated with the second subsample. $\boldsymbol{z_i}$ is a vector of control variables and e_i and u_i are error terms.

Extensive simulations under a wide variety of conditions found the GIV-U estimate to be downwardly biased and the GIV-C estimate to be upwardly biased as long as no environmental endogeneity was present (DiPrete et al., 2018). Thus, when taken together, the use of GIV-U and GIV-C will generally produce bounds on the true effect of T. Moreover, in the simulations performed by DiPrete, Burik, and Koellinger (2018), the upward bias of GIV-C was always smaller than the upward bias in OLS.

Intuitively, GIV-U provides the lower bound for the relationship between education and income conditional on the currently observed linear SNP effects because the PGI that is used as a control in this regression also captures genetic effects on income that work via education. On the other hand, GIV-C provides an upper bound because although it mimics a regression of income on education conditional on all SNPs, it does so only imperfectly (see Table 1 in DiPrete et al. (2018)) and some of the bias due to direct pleiotropic effects of SNPs on education and income may remain in the estimates.

When environmental sources of endogeneity are present, of course, the GIV-U + GIV-C bounding strategy may fail, just as all other methods fail. As a practical matter, therefore, accurate estimates of the effects of education on wages require strategies for identifying and reducing the impact of environmental endogeneity. Therefore, the bounds reported here only reflect the extent of confounds due to the linear effects of common genetic variants in the returns to schooling.

In addition to the two GIV models, we consider a baseline OLS model excluding PGI, as well as a naïve model, where the PGI is included as a control variable without accounting for attenuation bias due to estimation errors in the GWAS. Note that we do not use the MTAG income PGI here.

Table 5.5 presents our results. The estimate with the baseline controls for the pooled sample (Panel A, column 1) suggests that one additional year of schooling is associated with an average increase in hourly wages of 11% (95% CI: 9.7-12.4), which is slightly higher than earlier estimates from cross-sectional OLS in other US samples (Card, 1999; Harmon et al., 2003; J. J. Heckman et al., 2006). However, the HRS is a sample of elderly individuals who are approaching or who already are at the end of their professional careers, which could contribute to the slightly higher returns to schooling we find here. Previous attempts to uncover causal estimates of the returns to schooling have shown that the cross-sectional OLS estimates tend to be lower than instrumental variable based approaches (Harmon et al., 2003). The second column shows the results when the PGI is naïvely controlled for, i.e., by simply adding the income PGI as an additional control variable in an OLS regression. The estimated returns to schooling decreases slightly to 10.7% (95% CI: 9.4-12.1) for each additional year of schooling. Notably, a one-standard-deviation increase in the PGI in this model is associated with 3% higher hourly wages even after adjusting for educational attainment (95% CI: 1.3-4.8). Due to the measurement error in the PGI for income, this is a downward biased, lower-bound estimate of the relevance of genetic effects on income after controlling for education.

The coefficient estimates for the returns to schooling decrease marginally (~0.5 percentage points) after including controls for parental education, which is a proxy for both genetic and environmental advantages that parents pass on to their children. Interestingly, the coefficient estimates of income PGI are also slightly lower in models that include these controls (~0.2 percentage points), possibly because parental education captures some of the indirect genetic effects that work via favorable environmental conditions that highly educated parents tend to provide for their children (Kong et al., 2018).

Columns 3 and 4 in Panel 1 show the estimates that correct the measurement error in the income PGI with GIV-C and GIV-U regression, providing upper and lower bounds, respectively, of the coefficients for educational attainment conditional on observed genetic confounds. Our results suggest that the average return for an additional year of schooling is between 10.3% and 10.4% even after adjusting for the now observed linear common genetic confounds (95% CI: 8.7-11.8; 8.8-12.0). Furthermore, GIV yields substantially larger estimates of the genetic effects, with a one-standard-deviation increase in the PGI being associated with 8.4% to 15.8% higher hourly wages after adjusting for educational attainment (95% CI: 2.9-13.9; 5.2-26.4). These results decrease slightly when controls for parental education are included (7.9% and 14.8%).

Our sex-specific estimation results suggest that the returns to schooling are substantially higher for women than for men in the HRS, which is in line with previous studies. The gender differential in returns to schooling has been well documented and has previously been attributed to differences in discrimination, tastes, and circumstances of highly educated women compared to less educated women (Dougherty, 2005). In particular, the baseline OLS model estimates an average return of 7.8% (95% CI: 5.7-10) for an additional year for schooling for men (Panel B, column 1) but almost twice as much for women (13.3%; 95% CI: 11.5-15.1) (Panel C, column 1). The estimated returns decrease by almost the same small magnitude for both men and women when we adjust for potential genetic confounds (Panels B and C, columns 2-4). Furthermore, having a college degree seems to yield an additional 10% (95% CI:

1-18) income advantage for women over and above the 12% (95% CI: 9-15) higher hourly wages for an additional year of schooling in the GIV models (Panel C, column 3-4).

As a robustness check, the same analyses in the HRS are repeated with 3-year moving averages of wages, which reduces measurement error and transitory variance in the wage distribution. As reported in Table S5.10, the overall results are largely similar to the original results, while some statistical precision is lost due to a smaller sample size.

Our results are comparable to the results of studies that used differences between monozygotic twins to estimate the returns to schooling. For instance, Ashenfelter and Rouse (1998) report that including family fixed effects reduces the returns to schooling from 11% (95% CI: 0.09-0.13) to 7% (95% CI: 0.03-0.11) in the Princeton Twins survey data. Similarly, Behrman et al. (1994) show that the returns to schooling decreases from 7% (95% CI: 0.07-0.07) to 3.5% (95% CI: 0.03-0.04) in the National Academy of Science-National Research Council Twins and the Minnesota Twin Registry. Although some of these estimates are noisy, controlling for family fixed-effects seems to reduce the returns to schooling more sharply in MZ-twin designs than in our approach. This is not surprising given that our approach controls only for currently observed linear genetic confounding effects and parental education as a measure of family background, whereas the twin approach entirely eliminates the bias arising from all family-specific environments and all linear genetic confounds.

Oster (2019) notes that coefficient stability alone cannot provide evidence against omitted variable bias—it does so only if the additional controls are sufficiently important in explaining the outcome variation. There is only a marginal increase in R^2 when we use the naïve control strategy. However, while we cannot obtain R^2 from IV regression directly, the substantially larger coefficient estimate of the PGI in GIV regressions may imply a nonnegligible change in R^2 when the measurement error in the PGI is adequately corrected for.

In summary, controlling for now observable confounds from linear effects of common genetic variants slightly decreases the estimated returns to schooling, but not by more than 0.8 percentage points. At the same time, the estimated relationship between genetic predisposition and realized income remains substantial even after we control for educational attainment. Even in regressions that explicitly control for one’s own and one’s parents’ education, a one-standard-deviation increase in the PGI is associated with an 8-15% higher average wage in the pooled GIV-C and GIV-U models.

5.7 Discussion

Conceptually, genetic endowments are a form of luck — they are one-time, irreversible, exogenously given, individual-specific endowments that result from the natural experiment of meiosis that randomly mixes the genotypes of one's biological parents. We have shown here that genetic fortune for high income, in the form of random genetic differences between siblings, contributes to inequalities throughout the life course, influencing the education people attain, which occupations they pursue, how much they earn, the quality of the neighborhoods they live in, and the type of health outcomes they will tend to experience in late adulthood. Our results illustrate how tightly health, skills, work, achievements, and genetic luck are coupled: the idea that human agency in the form of choices and effort could be neatly separated from luck is unsubstantiated in light of the life-long consequences of the genetic lottery that influence behavior and achievements. The inequalities due to genetic luck that we showed here clearly violate the principle of equal opportunity. They also raise questions about how much credit and responsibilities society can or should attribute to individual's socio-economic and health-related outcomes in life (Rawls, 1999; Roemer, 1998). If inequalities partly result from a genetic lottery, the case in favor of a social contract that provides insurance against unfavorable outcomes is strong (Alesina et al., 2018; Alesina & La Ferrara, 2005; Cappelen et al., 2013; Gromet et al., 2015).

Specifically, our results show that the positive relationship between SES and health (Chetty et al., 2016; Stringhini et al., 2017a; Wilkinson & Marmot, 2003) is due partly to family-specific genetic and environmental endowments that affect both factors. Furthermore, siblings who “won” the genetic lottery for income are more likely to have favorable health outcomes later in life (e.g., lower BMI), but this genetic advantage is partly mediated by obtaining a college degree. Although our study design does not allow us to identify the causal effect of education on health, our results strongly suggest that high educational attainment and its accompaniments tend to bring about a lifestyle that has health benefits. Furthermore, we have shown that genetic fortune for income also causes differences in educational attainment. However, even when we control for the currently observed genetic confounds, the positive relationship between income and educational attainment remains strong, with an average of 8-11% higher hourly wages for each additional year of schooling. These results illustrate that the causal pathways from genes to behavior, achievements, and health involve environmental and behavioral pathways that can be intervened upon, such as education. Thus, genes contribute to inequality, but this does not imply biological determinism or an irrelevance of policy.

Genetic predispositions, such as those we studied here, have relevance for all branches of economics that are concerned with differences between individuals (Harden & Koellinger, 2020). The rapidly growing availability of genetic data and improvements in computing power and statistical methods now allow us to investigate links between genetic and environmental factors, human behaviour, and economic outcomes directly. This new type of data now permits economists to use genetically-informed study designs that enrich our empirical toolbox and that allow us to ask new questions and to gain new insights on core questions of our discipline. Our results here are illustrations of this.

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5.9 Tables

Table 5.1 Association between socioeconomic status (SES) measures and health outcomes in the UK Biobank

	log occupational wage per hour		College education	
	OLS	OLS-FE	OLS	OLS-FE
summary index	-0.126***	-0.049	-0.112***	-0.046***
(N = 13,862 | 26,550)	(0.009)	(0.018)	(0.005)	(0.011)
waist-to-hip ratio	-0.019***	-0.007	-0.017***	-0.007**
(N = 17,658 | 35,028)	(0.002)	(0.003)	(0.001)	(0.002)
BMI	-1.248***	-0.103	-1.298***	-0.415**
(N = 17,644 | 34,968)	(0.108)	(0.202)	(0.055)	(0.111)
blood pressure	-2.531***	-0.788	-1.885***	-1.185*
(N = 15,818 | 31,372)	(0.326)	(0.663)	(0.171)	(0.371)
lung function	0.279***	0.097	0.188***	0.082**
(N = 15,506 | 29,844)	(0.019)	(0.040)	(0.010)	(0.022)
ever hospitalized	-0.061***	-0.019	-0.047***	-0.007
(N = 17,692 | 35,132)	(0.009)	(0.021)	(0.005)	(0.011)
ever diagnosed with cancer	0.006	-0.008	0.002	0.004
(N = 17,692 | 35,132)	(0.008)	(0.018)	(0.004)	(0.011)
infectious and parasitic diseases	-0.030***	-0.017	-0.028***	-0.003
(N = 17,692 | 35,132)	(0.006)	(0.014)	(0.003)	(0.008)
neoplasms	0.013	-0.007	0.006	0.005
(N = 17,692 | 35,132)	(0.008)	(0.017)	(0.004)	(0.010)
diseases of blood organs and immune system	-0.028**	-0.006	-0.031***	-0.009
(N = 17,692 | 35,132)	(0.009)	(0.020)	(0.005)	(0.012)
endocrine, nutritional, and metabolic diseases	-0.054***	-0.011	-0.069***	-0.024
(N = 17,692 | 35,132)	(0.008)	(0.018)	(0.004)	(0.011)
mental, behavioral, nervous system disorders	-0.071***	-0.047	-0.059***	-0.026
(N = 17,692 | 35,132)	(0.008)	(0.019)	(0.004)	(0.010)
diseases of the eye and adnexa	-0.006	-0.009	-0.017***	-0.019
(N = 17,692 | 35,132)	(0.006)	(0.014)	(0.004)	(0.009)
diseases of the circulatory system	-0.081***	-0.017	-0.086***	-0.038*
(N = 17,692 | 35,132)	(0.010)	(0.022)	(0.005)	(0.012)
diseases of the respiratory system	-0.051***	-0.027	-0.047***	-0.018
(N = 17,692 | 35,132)	(0.008)	(0.017)	(0.004)	(0.010)
diseases of the digestive system	-0.090***	-0.026	-0.075***	-0.010
(N = 17,692 | 35,132)	(0.011)	(0.024)	(0.006)	(0.014)
diseases of the skin and subcutaneous tissue	-0.014	-0.011	-0.023***	-0.018

	log occupational wage per hour		College education	
	OLS	OLS-FE	OLS	OLS-FE
(N = 17,692 | 35,132)	(0.007)	(0.015)	(0.004)	(0.009)
diseases of musculoskeletal system and connective tissue	-0.065***	-0.026	-0.068***	-0.029
(N = 17,692 | 35,132)	(0.010)	(0.022)	(0.005)	(0.012)
diseases of genitourinary system	-0.063***	-0.014	-0.053***	-0.017
(N = 17,692 | 35,132)	(0.010)	(0.021)	(0.005)	(0.012)
symptoms and signs not elsewhere classified	-0.068***	-0.024	-0.066***	0.000
(N = 17,692 | 35,132)	(0.011)	(0.024)	(0.006)	(0.013)
injury, poisoning, and other consequences of external causes	-0.035***	-0.030	-0.015**	-0.002
(N = 17,692 | 35,132)	(0.008)	(0.018)	(0.004)	(0.011)
external causes of morbidity and mortality	-0.045***	-0.043	-0.023***	-0.007
(N = 17,692 | 35,132)	(0.008)	(0.019)	(0.004)	(0.011)
other health conditions	-0.052***	-0.025	-0.067***	-0.026
(N = 17,692 | 35,132)	(0.011)	(0.025)	(0.006)	(0.014)

Note: The table reports the coefficients from separate regressions of health outcomes on log occupational wages per hour and a dummy variable for college education, with or without family fixed effects (FE). Standard errors clustered by family are reported in parentheses. Significance at family-wise error rate 5% (*), 1% (**), 0.1% (***), where multiple hypothesis testing is corrected by Holm's method (Holm, 1979) for each set of analysis. For each outcome, the sample is restricted to sibling pairs for both of whom the outcome is observed. The summary index is a weighted average of all the health outcomes constructed according to Anderson (2008) such that lower values imply a better health. All regressions controlled for a sex dummy, year of birth, year of assessment, and the interaction terms between the sex dummy and all other covariates. Regressions on log hourly wages also included dummies for year and age of observation.

Table 5.1 Associations between the polygenic index for income and measures of socioeconomic achievement and health in UK Biobank siblings

	OLS	OLS-FE	GIV	GIV-FE
Socioeconomic outcomes				
log hourly wage	0.074***	0.046***	0.147***	0.084**
(N=17,692)	(0.002)	(0.007)	(0.008)	(0.022)
top household income	0.056***	0.034***	0.122***	0.092**
(N=27,412)	(0.003)	(0.007)	(0.008)	(0.025)
log regional income	0.041***	0.015***	0.080***	0.041*
(N=31,692)	(0.001)	(0.003)	(0.005)	(0.012)
neighborhood score	1.523***	0.643*	2.869***	1.598
(N=29,166)	(0.088)	(0.203)	(0.284)	(0.694)
years of education	1.394***	0.771***	2.774***	1.498***
(N=35,132)	(0.026)	(0.066)	(0.095)	(0.237)
college degree	0.131***	0.069***	0.258***	0.145***
(N=35,132)	(0.002)	(0.006)	(0.009)	(0.021)
health proxies				
waist-to-hip ratio	-0.007***	-0.004**	-0.015***	-0.009
(N=35,498)	(0.000)	(0.001)	(0.001)	(0.003)
BMI	-0.563***	-0.286***	-0.994***	-0.497
(N=35,432)	(0.027)	(0.063)	(0.086)	(0.223)
blood pressure	-0.847***	-0.608	-1.678***	-0.795
(N=31,770)	(0.078)	(0.208)	(0.250)	(0.735)
lung function	0.055***	0.017	0.112***	0.052
(N=30,240)	(0.005)	(0.013)	(0.015)	(0.047)

Note: The table reports the coefficient estimates for the standardized polygenic index for income (PGI). Standard errors clustered by family are reported in parentheses. Significance at family-wise error rate 5% (*), 1% (**), 0.1% (***), where multiple testing is controlled using Holm's method (Holm, 1979) for each set of analysis. For each outcome, the sample is restricted to sibling pairs for both of whom the outcome is observed. FE: family fixed effects included. OLS regressions use MTAG PGI for income (i.e. a PGI for income that also takes information from a GWAS on educational attainment into account). GIV regressions use two (non-MTAG) income PGI estimated from two independent samples, where one PGI instruments the other. All analyses included dummy variables for the year of birth, male, and being the younger sibling as well as the first 20 genetic PCs. For economic outcomes, we use age dummies instead of the year of birth and add dummies for the year of survey. For health outcomes we also control for the age dummies instead but not for the year of survey. In every case, we also include the interaction terms between the male dummy and the rest of covariates.

Table 5.2 Associations between the polygenic index for income and disease diagnosis outcomes in UK Biobank siblings

	OLS	OLS-FE	GIV	GIV-FE
ever hospitalized	-0.021***	-0.012	-0.036***	-0.028
(N=35,602)	(0.002)	(0.006)	(0.006)	(0.020)
ever diagnosed with cancer	-0.001	0.001	0.000	0.007
(N=35,602)	(0.002)	(0.006)	(0.006)	(0.021)
infectious and parasitic diseases	-0.013***	-0.005	-0.026***	0.004
(N=35,602)	(0.002)	(0.005)	(0.005)	(0.017)
neoplasms	0.000	0.001	0.002	0.007
(N=35,602)	(0.002)	(0.006)	(0.006)	(0.021)
diseases of blood organs and immune system	-0.012***	0.001	-0.024**	0.002
(N=35,602)	(0.002)	(0.007)	(0.007)	(0.023)
endocrine, nutritional, and metabolic diseases	-0.026***	-0.011	-0.030***	0.007
(N=35,602)	(0.002)	(0.006)	(0.007)	(0.022)
mental, behavioral, nervous system disorders	-0.027***	-0.009	-0.048***	0.002
(N=35,602)	(0.002)	(0.006)	(0.007)	(0.021)
diseases of the eye and adnexa	-0.006***	-0.005	-0.016*	-0.018
(N=35,602)	(0.002)	(0.005)	(0.005)	(0.017)
diseases of the circulatory system	-0.035***	-0.013	-0.066***	-0.035
(N=35,602)	(0.003)	(0.007)	(0.008)	(0.025)
diseases of the respiratory system	-0.022***	-0.010	-0.045***	-0.026
(N=35,602)	(0.002)	(0.006)	(0.007)	(0.021)
diseases of the digestive system	-0.033***	-0.013	-0.068***	-0.043
(N=35,602)	(0.003)	(0.008)	(0.008)	(0.027)
diseases of the skin and subcutaneous tissue	-0.008***	-0.005	-0.013*	-0.013
(N=35,602)	(0.002)	(0.005)	(0.006)	(0.018)
diseases of musculoskeletal system and connective tissue	-0.035***	-0.023*	-0.065***	-0.037

Table 5.2 Associations between the polygenic index for income and disease diagnosis outcomes in UK Biobank siblings

	OLS	OLS-FE	GIV	GIV-FE
(N=35,602)	(0.002)	(0.007)	(0.008)	(0.025)
diseases of genitourinary system	-0.022***	-0.011	-0.051***	-0.006
(N=35,602)	(0.002)	(0.007)	(0.008)	(0.024)
symptoms and signs not elsewhere classified	-0.033***	-0.016	-0.064***	-0.032
(N=35,602)	(0.003)	(0.008)	(0.008)	(0.027)
injury, poisoning, and other consequences of external causes	-0.009***	-0.004	-0.018*	-0.023
(N=35,602)	(0.002)	(0.006)	(0.006)	(0.021)
external causes of morbidity and mortality	-0.011***	-0.004	-0.020*	-0.027
(N=35,602)	(0.002)	(0.006)	(0.007)	(0.022)
other health conditions	-0.032***	-0.022	-0.056***	-0.039
(N=35,602)	(0.003)	(0.008)	(0.009)	(0.027)

Note: The table reports the coefficient estimates for the standardized polygenic indice for income (PGI). Standard errors clustered by family are reported in parentheses. Significance at family-wise error rate 5% (*), 1% (**), 0.1% (***), where multiple testing is controlled using Holm's method (Holm, 1979) for each set of analysis. For each outcome, the sample is restricted to sibling pairs for both of whom the outcome is observed. FE: family fixed effects included. OLS regressions use MTAG PGI for income (i.e. a PGI for income that also takes information from a GWAS on educational attainment into account). GIV regressions use two (non-MTAG) income PGI estimated from two independent samples, where one PGI instruments the other. All analyses included dummy variables for the year of birth, male, and being the younger sibling as well as the first 20 genetic PCs. For economic outcomes, we use age dummies instead of the year of birth and add dummies for the year of survey. For health outcomes we also control for the age dummies instead but not for the year of survey. In every case, we also include the interaction terms between the male dummy and the rest of covariates.

Table 5.3 Decomposition of the genetic lottery effects in the UK Biobank siblings

	estimation	effect via college education	residual effect	total effect	effect via college education %
log occupational wage per hour	OLS	0.014***	0.031***	0.046***	31.7
(N=17,578)		(0.002)	(0.006)	(0.007)	
	GIV	0.030***	0.057*	0.087***	34.7
		(0.006)	(0.021)	(0.022)	
waist-to-hip ratio	OLS	-0.0004**	-0.003**	-0.004***	11
(N=35,028)		(0.0001)	(0.001)	(0.001)	
	GIV	-0.001*	-0.008	-0.008	10.1
		(0.000)	(0.003)	(0.003)	
BMI	OLS	-0.025*	-0.256***	-0.281***	8.8
(N=34,968)		(0.008)	(0.064)	(0.064)	
	GIV	-0.052*	-0.415	-0.467	11.2
		(0.019)	(0.228)	(0.224)	
blood pressure	OLS	-0.077*	-0.546*	-0.622*	12.3
(N=31,372)		(0.027)	(0.210)	(0.209)	
	GIV	-0.159*	-0.596	-0.755	21
		(0.060)	(0.748)	(0.735)	
lung function	OLS	0.005**	0.013	0.018	29.4
(N=29,844)		(0.002)	(0.014)	(0.013)	
	GIV	0.011*	0.041	0.052	21.2
		(0.004)	(0.048)	(0.047)	

Note: * p<0.05, ** p<0.01, *** p<0.001 with Bonferroni correction for testing 5 outcomes. Standard errors clustered by family are reported in parentheses. The standard errors for the indirect effects are computed using the delta method. All regressions used family fixed effects. The table reports decomposition of the genetic lottery effects i for 4 health measures and occupational wages into the effect working via college education and the residual effect. "effect via college education %" reports the proportion of the effect via college education in the total effect. OLS regressions use MTAG PGI for income. GIV regressions use two income PGI estimated from two independent samples, where one PGI instruments the other. Covariates are the top 20 genetic PCs and dummy variables for the year of birth, male, the age at the time of assessment, and being a younger sibling, as well as the interaction terms between the male dummy and the rest of covariates. For occupational wages, we use age dummies instead of the year of birth and add dummies for the year of survey. For each outcome, the sample is restricted to sibling pairs for both of whom the outcome is observed.

Table 5.5 Estimates of income with respect to schooling and genetic factors in the Health and Retirement Study

	no PGI				naive control				GIV-C				GIV-U			
Panel A: Male+Female																
Educ	0.1105***	0.1051***	0.0901***	0.0839***	0.1073***	0.1023***	0.0878***	0.0820***	0.1040***	0.0992***	0.0864***	0.0805***	0.1026***	0.0980***	0.0850***	0.0795***
	(0.007)	(0.008)	(0.010)	(0.011)	(0.007)	(0.008)	(0.010)	(0.011)	(0.008)	(0.008)	(0.011)	(0.011)	(0.008)	(0.008)	(0.011)	(0.011)
Educ × College			0.0602	0.0595			0.0584	0.0579			0.0601	0.0593			0.0538	0.0536
			(0.031)	(0.031)			(0.031)	(0.031)			(0.032)	(0.032)			(0.031)	(0.031)
Income PGI					0.0304***	0.0287***	0.0292***	0.0274**	0.1577**	0.1484**	0.1534**	0.1437**	0.0836**	0.0792**	0.0813**	0.0767**
					(0.009)	(0.008)	(0.008)	(0.008)	(0.054)	(0.053)	(0.054)	(0.053)	(0.028)	(0.028)	(0.028)	(0.028)
Parental Educ		Y		Y		Y		Y		Y		Y		Y		Y
R²	0.181	0.183	0.183	0.184	0.183	0.184	0.184	0.185								
Obs.	20058	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Panel B: Male																
Educ	0.0784***	0.0706***	0.0372*	0.0294*	0.0762***	0.0688***	0.0365*	0.0290*	0.0734***	0.0671***	0.0398**	0.0330*	0.0713***	0.0645***	0.0361*	0.0291*
	(0.011)	(0.012)	(0.015)	(0.015)	(0.012)	(0.012)	(0.015)	(0.015)	(0.012)	(0.012)	(0.015)	(0.015)	(0.012)	(0.012)	(0.015)	(0.015)
Educ × College			0.0219	0.0221			0.0202	0.0206			0.0240	0.0240			0.0112	0.0119
			(0.045)	(0.045)			(0.045)	(0.045)			(0.047)	(0.046)			(0.046)	(0.045)
Income PGI					0.0271*	0.0242	0.0228	0.0199	0.2020*	0.1924*	0.1864*	0.1762	0.1057*	0.1008*	0.0970*	0.0918*
					(0.014)	(0.014)	(0.014)	(0.014)	(0.090)	(0.090)	(0.090)	(0.090)	(0.046)	(0.046)	(0.046)	(0.046)
Parental Educ		Y		Y		Y		Y		Y		Y		Y		Y
R²	0.105	0.108	0.111	0.114	0.106	0.109	0.111	0.114								
Obs.	8310	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Panel C: Female																
Educ	0.1330***	0.1295***	0.1273***	0.1230***	0.1291***	0.1259***	0.1238***	0.1198***	0.1263***	0.1229***	0.1209***	0.1166***	0.1253***	0.1224***	0.1208***	0.1170***
	(0.009)	(0.010)	(0.014)	(0.015)	(0.010)	(0.010)	(0.014)	(0.015)	(0.011)	(0.011)	(0.016)	(0.016)	(0.011)	(0.011)	(0.015)	(0.016)
Educ × College			0.1013*	0.0995*			0.0996*	0.0981*			0.0991*	0.0973*			0.0978*	0.0964*
			(0.043)	(0.043)			(0.043)	(0.042)			(0.043)	(0.043)			(0.043)	(0.043)
Income PGI					0.0315**	0.0303**	0.0311**	0.0299**	0.1263	0.1179	0.1220	0.1138	0.0675	0.0636	0.0652	0.0614
					(0.011)	(0.011)	(0.011)	(0.011)	(0.067)	(0.066)	(0.067)	(0.066)	(0.035)	(0.035)	(0.035)	(0.035)
Parental Educ		Y		Y		Y		Y		Y		Y		Y		Y
R²	0.151	0.152	0.152	0.153	0.152	0.153	0.153	0.154								
Obs.	11748	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Note: * $p<0.05$, ** $p<0.01$, *** $p<0.001$; regressions of log hourly wage on years of schooling, the income PGI, and baseline covariates. The sample is restricted to those aged between 30 and 64. As baseline covariates, we include experience (age – years of schooling – 6), experience^2, year of observation, birth cohorts, and genotyping batches, and 20 genetic principal components. The pooled *Male+Female* estimates also include a dummy variable for male, as well as interaction terms between the male dummy and all other covariates. The first column reports the result with the baseline covariates while the other columns report the baseline model with the PGI added using different approaches. In the parentheses, we report standard errors clustered by individuals.

Chapter 5

Supplementary Information

S5.1 Imputing occupational wages from standardized occupation codes

The UK Biobank (UKB) does not contain information about individual income. However, it provides rich information directly relevant to labor earnings such as 4-digit standardized occupation codes (SOCs) and working hours. We take advantage of this information to impute occupational wages in the UKB data. We use three datasets to develop our imputation algorithm: the Labour Force Survey (LFS) for the UK, the Annual Survey of Hours and Earnings (ASHE), and the British Household Panel Survey (BHPS), which was collected independently from the LFS. In short, we fit a regression model on wages in the LFS using mean and median wages for standardized job codes obtained from the ASHE. We then assess the accuracy of our imputation algorithm in the BHPS. As a final step, we apply the imputation algorithm in the UKB to obtain our measure of occupational wages.

S5.1.1 The Labour Force Survey (LFS)

The LFS data are collected by the Office for National Statistics (ONS) of the UK. With the intention to be representative of the whole UK population, the LFS has selected samples every quarter by randomly drawing residential addresses from the postcode database since 1973. The households of those drawn addresses are followed for five consecutive quarters, where information on earnings is collected in the first and last waves. Covering a long period of years, the LFS provides data with a large sample size along with various sets of individual information relevant to labor earnings. We pool samples of wage-earning individuals aged between 35 and 64 observed from 2002 to 2016, given that the UKB sample consists of those aged 40-64. We include those aged 35-39 to increase the sample size of the LFS because these individuals should not be too different from those aged over 40.

In addition to those with incomplete data, we excluded those who reported working hours less than one hour per week as well as those who reported working part-time (full-time) but working for more than or equal to (less than) 30 hours per week. We exclude these observations as they only introduce more noise in the estimation. As a result, we obtain a sample size of 464,192.

S5.1.2 The Annual Survey of Hours and Earnings (ASHE)

The ASHE, also collected by the ONS, provides detailed labor statistics of the UK working population. It is based on a 1% sample randomly drawn annually from employees recorded in the labor tax database of the UK. It is therefore the best source available from which high-quality wage information of each occupation can be obtained. The occupation groups are defined by the Standard Occupation Classification (SOC) constructed by the ONS. The classifications define four levels of occupation groups indexed by 4-digit codes. In the case of the 2000 version, the 4-digit SOC defines 353 occupation groups.

S5.1.3 The British Household Panel Survey (BHPS)

Conducted by the Institute for Social and Economic Research at the University of Essex, the BHPS is an annual survey that provides data on a nationally representative sample of more than 5,000 households and their adult members, who were followed from 1991 to 2009, with additional subsamples added in 1997 and 1999. Similar to the LFS, the household samples were drawn randomly from the postcode database. Despite its smaller sample size compared to that of the LFS, the BHPS has rich information on working individuals, which can suitably be used to test the accuracy of wage imputation based on LFS data. We pool working individuals aged 40-64 observed from 2002 to 2009, removing one extreme outlier with a peculiarly high wage. As it is done for the LFS, we also exclude those who reported working for less than one hour per week. A sample size of 32,947 is obtained as a result.

S5.1.4 Occupation composition

While the LFS and the BHPS consist of representative samples of the UK population, the participants of the UKB data were not recruited in such a way that they can exactly represent the UK population. This fact implies that using the BHPS to assess the imputation accuracy may lead to exceedingly optimistic results of the imputation accuracy to the extent that the imputation error occurs due to the sample difference between the LFS and the UKB. Therefore, it is important to first identify any distinctive differences between the data sets. Since it is practically impossible to discuss every summary statistic for all three data sets, we examine only the occupation composition of each data set.

Table S5.11 presents the mean wages of nine major occupation groups (defined by the 1-digit SOCs) obtained from the ASHE and averaged over 2006-2010, the period during which the UKB participants were surveyed. It shows that the top three major occupation groups are: “1. Managers and senior officials”, “2. Professional occupations” and “3. Associate professional and technical occupations”. On the other hand, the bottom three groups are: “7. Sales and customer service occupations”, “9. Elementary occupations”, and “6. Personal service occupations”

Figure S5.4 depicts the composition of these major occupation groups for each sample. Clearly, compared to the LFS and the BHPS, a larger share of the individuals in the UKB had a job classified in the top three occupation groups. It is also evident that there are relatively fewer individuals in the UKB who had a job that belongs to the bottom three occupation groups. In contrast, there is only a subtle difference between the LFS and the BHPS in their job composition, which is not a surprise as they are meant to represent the UK population. Hence, it is important to keep in mind that the UKB sample includes many individuals who had relatively high-paying jobs and their actual wage levels are likely to be higher on average than those in the LFS and the BHPS.

S5.1.5 Imputation approach

Our imputation approach is fully parametric and conducted in two steps. We first fit a regression of log wages in the LFS data. Based on the estimated coefficients, we then predict log-wages for samples in the UKB. We impute both weekly and hourly wages because the latter demands less information while the former can be imputed more precisely. This procedure requires that the two data sets contain the same predictor variables. Additionally, the available predictor variables must be sufficiently correlated with the wage distribution. Given these requirements, it is possible to use the following predictors: 4-digit standardized occupation code (SOC), working hours, full/part-time status, age, sex, square, cube, and interaction terms, as well as year-specific effects.

The pivotal information for predicting wages is the occupational information given by the 4-digit SOCs. However, simply including dummy variables for the 4-digit SOCs in the prediction model (353 occupation groups in total for the 2000 SOC) in combination with other categorical characteristics (*e.g.*, age, sex) can lead to cells with zero or too few observations, which in turn will result in failed or inaccurate imputations for some of the sample. Therefore, instead of dummy variables, we include mean and median wages for each individual's occupation group by sex and full/part-time status obtained from the ASHE.

This is the key feature of our imputation procedure that ensures both the efficiency and the accuracy of the imputation. In particular, using wage data from the ASHE is useful in that it allows us to include interaction terms between occupational profiles and other variables without substantially increasing the number of parameters, which can efficiently capture any heterogeneity across occupational groups. Another important reason is a change in the SOC system made in 2010, which updated the SOC from its 2000 version to the 2010 version. As the job codes in the two SOC systems cannot straightforwardly be converted into the other system, in essence, it is impossible to pool the LFS data for a long period that covers both before and after 2010 if one wishes to make use of detailed occupational information. Complementing the LFS with the ASHE data offers a convenient solution to this complication.

Specifically, the prediction model is specified as:

$$log(Y_i) \; = \alpha + X_i\beta + \; Z_i\gamma + interaction_i\delta + \epsilon_i \qquad \text{(S5.1)}$$

where $log\ (Y_i)$ are log weekly gross wages from employment, standardized to the 2015 currency value by the Consumer Price Index. X_i is a vector of predictors including working hours per week (and its square), and dummies for full/part-time status (full if working hours ≥30), age, sex, year of observation, and 2-digit SOCs.[1] Z_i is a vector that contains log mean and log median weekly wages as well as their interaction term for the 4-digit-level occupation group (by sex and full/part-time status) to which individual *i* belongs. "$interaction_i$" includes interaction terms between sex, full/part-time status, the remaining variables in X_i, and the Z_i term.

The prediction model for hourly wages is identical except that the hours worked variable is used only to construct hourly wages from the weekly wages and the dummy for full/part-time status as well as hours worked are not included as predictors. Furthermore, occupational hourly wages are collected from the ASHE only by sex.

The imputation is then conducted as follows: *(i)* estimate the prediction model in the LFS data using mean and median wages of each SOC obtained from the ASHE; *(ii)* predict log wages in the UKB sample based on the estimated coefficients from *(i).* To evaluate the imputation accuracy, we utilize the BHPS data by comparing the predicted log-wages from step *(i)* for samples in the BHPS with their actual log-wages. By regressing the imputed log-wages on the actual log wages of the BHPS, we obtain an R^2 of approximately 0.75 for weekly wages and 0.50 for hourly **wages. Figure S5.5** presents a scatter plot of the actual log wages against the imputed log wages, which demonstrates that the wages are imputed with

[1] While the variation over 4-digit level occupation groups is supposed to be captured by mean and median wages from the ASHE, including the dummies for occupational groups appears to still improve the model fit by correcting some group-level difference between the LHS and the ASHE data. The 2-digit level is chosen to have sufficient observations in each group. Additionally, the difference between the 2000 and 2010 SOC systems is not too problematic for the 2-digit level classifications.

reasonable accuracy. Note that the distribution of reported log wages may contain transitory variance; therefore, the reported imputation accuracy can be regarded as a conservative result.

S5.1.3 Imputing wages of the UKB

We impute both weekly and hourly wages for individuals in the UKB. For the former, only the current job information is used since the information on hours worked is available only for the current job. Additionally, only individuals younger than 65 are considered. For the latter, we use primarily information on the current job, while we instead use the information on the most recent job held before the age of 65 if it is not reported or if an individual is older than 64. Therefore, whereas we impute weekly wages with more reliable information, we can obtain a larger sample size for hourly wages. As a result, we impute weekly wages for 236,743 individuals and hourly wages for 282,963 individuals.

Since the two imputed wages are both available for 236,743 individuals, the first check is to compare the two imputed wages as follows: we subtract the log of hours worked from the imputed log weekly wages, which effectively produces the log hourly wage. R^2 between this computed term and the imputed hourly wage is 0.92, which implies that both of the wages are imputed with reasonable accuracy.

We ran GWAS on both weekly and hourly wages imputed for the UKB. For the former, hours worked and their polynomial terms are also controlled for. We then confirmed that the genetic correlation between the two wage measures is not statistically distinguishable from one (0.993 with $SE = 0.004$), which means that the distributions of the GWAS estimates are almost the same. Because imputing hourly wages requires less information and allows us to have a larger sample size, we utilize only log hourly wages in this paper.

S5.2 Estimating heritability from SNP data

S5.2.1 Heritability framework

Consider the following general framework for the outcome of interest, y, for some individual, i:

$$y_i = g_i + e_i \tag{S5.2}$$

where y_i is decomposed into a contribution from genes in the form of SNPs, denoted by g_i, and the environment, denoted by e_i. Genetic effects are modeled as $g_i = \mathbf{x}_i'\boldsymbol{\beta}$ where $\mathbf{x}_i$ is the vector that comprises data on J standardized SNPs for the given individual. Here, vector $\boldsymbol{\beta}$ represents the vector of causal SNP effects, which includes SNP effects that work indirectly e.g., via behavioral or environmental pathways. Finally, e is a residual that can be interpreted as the nongenetic component of environmental influences.

This linear model is a simplified version of how genetic factors can contribute to an outcome by making two important assumptions. First, it abstracts from alleles that have dominant or recessive effects.[2] Second, it does not include possible gene–gene or gene–environment interactions. However, the weighted average effects of the alleles can be estimated with this linear model, which is a useful starting point.

The challenge is that the true vector $\boldsymbol{\beta}$ is unknown, and any estimate of $\boldsymbol{\beta}$ is noisy and potentially biased in finite population samples, especially if the genetic architecture of y is complex and driven by many SNPs that each have very small effect sizes. However, one can still obtain an estimate of h_{SNP}^2 by considering whether two randomly drawn individuals who are genetically slightly more similar to each other than expected by chance, also tend to resemble each other slightly more in terms of the given outcome.

More specifically, if we are able to compute genetic similarities between people, we can model the covariance between individuals in terms of outcomes as a function of genetic similarity. This approach enables us to decompose the total variance in y into the variance from the genetic and environment components, denoted by σ_g^2 and σ_e^2 respectively, assuming that g and e are orthogonal (Visscher, 2010; Yang et al., 2010).

Such a model can be extended to control for confounding factors, such as population structure, and can thus be formulated as a so-called linear mixed model (LMM), where SNPs are assumed to have linear random effects and the covariates are assumed to have linear, fixed effects.

Importantly, the term “fixed effects” has different meanings in different fields. In complex trait genetics (i.e., the field that considers outcomes to which many genes contribute) fixed effects are simply conceptualized as nonstochastic effects—they are parameters that have a fixed value in a population. However, in panel econometrics, fixed effects often refer to firm-, country- or individual-specific means that do not change over time. In the context of family data, fixed effects can be considered as family-

[2] This assumption is often justified by pointing to existing data and theory that primarily suggest additive genetic effects for most genetically complex traits (W. G. Hill et al., 2008).

specific means that do not change from one family member to the next. Here, we use the term fixed effect interchangeably. That is to say, when we talk about fixed effects in an LMM, we simply mean non-stochastic effects, and when we talk about fixed effects in a family study, we mean family-specific effects.

Under the formal derivations involved in such a SNP LMM, one typically assumes that the elements of $\boldsymbol{\beta}$ (i.e., the vector of effects of the standardized SNPs) are independent and identically distributed draws from a normal distribution with mean zero, and a variance equal to σ_β^2. This assumption should be thought of as a mild prior on the SNP effects which implies that a trait is influenced by many, if not all, SNPs, where, in turn, the contribution of each SNP separately is very small. Under this model, the true h_{SNP}^2 is given by the total genetic variance, $\sigma_g^2 = J\sigma_\beta^2$, over the total phenotypic variance, after correcting for the covariates that are assumed to have fixed effects. That is, $h_{SNP}^2 = \sigma_g^2(\sigma_g^2 + \sigma_e^2)^{-1}$.

S5.2.2 Genomic-relatedness-based restricted maximum likelihood estimation

Under such an LMM, h_{SNP}^2 is typically estimated using restricted maximum likelihood estimation. This approach is referred to as genomic-relatedness-based restricted maximum likelihood (GREML) estimation (Daniel J. Benjamin et al., 2012).

A crucial and strong assumption of this framework is that the true linear combination of genetic effects towards the outcome, *g*, is orthogonal to *e*. As long as this assumption is satisfied, GREML tends to yield robust estimates of h_{SNP}^2under many different types of genetic architectures, even if the effect sizes of SNPs are not strictly drawn from a normal distribution. This result holds true as long as the set of SNPs that are analyzed represent the true genetic architecture of the trait in terms of *MAF*and *LD*(Evans et al., 2018; Lee & Chow, 2014).

GREML estimates of $h_{SNP}^2$from population samples can be influenced by indirect genetic influences of biological relatives (e.g., parents) that are not included in the sample, but that influence the observed outcomes through their behavior and the environment they create or provide (Young et al., 2018). Strictly speaking, such indirect genetic influences are not part of the standard definition of heritability. Nevertheless, the h_{SNP}^2 GREML estimate that can be obtained from population samples reflects true genetic effects that influence the outcomes of the observed individuals either via biological or environmental channels or a combination of both.

We estimate the heritability of occupation wages in the UKB sample using GREML. We first estimate h^2_{SNP} with a single genetic variance parameter that uses all available unrelated individuals with data on occupational wages (196,187 in total, including 93,666 males and 102,521 females). For this estimation, we used SNPs that were included in the HapMap3 reference panel (Altshuler et al., 2010) because this set of SNPs tends to be measured with high accuracy and provides good coverage of common genetic variation among humans of European ancestries. For SNPs that contain mostly redundant information (LD $R^2 > 0.9$), we keep only the SNP with the highest MAF.[3] Furthermore, we exclude rare SNPs with MAF<1% because they cannot be measured with high accuracy, and each of them contributes only a marginal share of the overall genetic variation in the sample (Auton et al., 2015). As covariates, we use dummies for age and the year of observation; dummies that account for differences in the income imputation procedure and genotyping and assessment processes; and the first 40 PCs from the genetic data (Marchini et al., 2015). We also include a male dummy and interact it with the whole set of covariates in the pooled analysis. To reduce the computational burden due to the large sample size, we take advantage of an efficient algorithm developed by (Loh et al., 2015).

An additional feature of GREML is that it allows us to decompose the total SNP-based heritability for different types of SNPs. Specifically, if the SNPs are partitioned into independent groups $k = 1, \ldots, K$, the total genetic variance σ^2_g equals $\sum_{k=1}^{K} \quad \sigma^2_{gk}$, where $\sigma^2_{gk} = J_k \sigma^2_{\beta k}$ denotes the variance accounted for by the J_k SNPs in group k. Thus, by parsing the total set of SNPs into categories of interest (e.g., by chromosome, MAF, or LD), one can learn about the molecular genetic architecture of y without needing to estimate the effects of each SNP directly.

Partitioning SNPs in this manner implicitly allows SNP effect sizes to be drawn from different distributions for the various categories considered (e.g., rare SNPs may on average have considerably larger effects than common SNPs), thereby reducing the scope for bias in GREML estimates (Evans et al., 2018). Furthermore, as we indicated, one can easily correct for covariates in GREML, enabling us to control for important sources of bias such as population structure.

[3] This procedure is called LD-pruning, which was performed using Plink software (Purcell et al., 2007). In principle, LD-pruning is not necessary for GREML to work properly, although it might increase the estimate slightly. See (Yang et al., 2017) for an additional discussion.

The multiple variance parameter models require the computation of many GRMs. Since this is the computationally most intensive step of the procedure, we further reduce computational costs by restricting the analyses to a subset of 24,000 randomly selected unrelated individuals. We explore two cases: First, we allow the variance to differ across different groups of SNPs with different genetic features. More specifically, we define four groups of SNPs depending on *i)* whether they are common (MAF ≥ 0.05) or rare (0.01 < MAF < 0.05)[4] and *ii)* whether they have a relatively high or low LD score, using the median LD score as the cutoff.[5] Since we are allowing for different variances of different genetic features, we use all available SNPs except for low-frequency ones (MAF < 0.01). Second, we let the variance differ across autosomes, which therefore gives 22 groups of SNPs. For computational reasons, we limited analysis to SNPs included in the HapMap3 reference panel.

S5.2.3 Result

Table S5.5 reports the results. The h^2_{SNP}estimates are 12.6% (*SE* = 0.5%) for females and 10.3% (*SE* = 0.5%) for males, suggesting a higher heritability of income for females. Thus, the heritability of occupational wages is somewhat higher for females than for males in our sample. When both male and female samples are analyzed together, the pooled h^2_{SNP} is estimated to be 10.3% (*SE* = 0.3%). Note that the estimate for the pooled sample is not necessarily the weighted average between the two estimates for males and females because additional covariates are included to control for male-female heterogeneity.

Figure S5.6 reports the heritability estimates of occupational wages from four different groups of SNPs, clustering them by their minor allele frequencies and LD. These estimates can shed light on the molecular genetic architecture of income by suggesting whether the observed heritability is primarily due to common genetic variants, which are most likely to have small effects, or due to relatively rare variants that may have stronger effects (Gibson, 2012). Furthermore, this “binning” of SNPs into groups avoids potential bias in the GREML estimates which could stem from violations of the assumption that the effect sizes of all SNPs in R2 are drawn from the same distribution, irrespective of their LD and MAF (Evans et al., 2018). Our results imply that relatively common SNPs (*MAF* ≥ 5%) with above-median

[4] Common SNPs mean that their minor alleles are frequently observed, which leads to larger variation at those SNP locations. If SNPs are rare, we do not find much variation at those locations across individuals of the given population.

[5] The degree of LD between two SNPs can be measured by the Pearson correlation coefficient while the degree of LD for a given SNP can be measured by the LD score, which is the sum of the Pearson correlation coefficients with other SNPs.

LD scores contribute most to the total heritability of occupational wages (h^2_{SNP} = 4.6%, *SE* = 0.9%), followed by relatively rare SNPs (1% < *MAF* < 5%) with below-median LD scores (h^2_{SNP} = 3.0%, *SE* = 1.9%). In contrast, rare SNPs with above-median LD scores seem to play at most a minor role. The sum of these four point estimates in Figure S5.6 is 10.2% (*SE* = 2.2%), which is very close to the pooled h^2_{SNP} estimate of 10.3% (*SE* = 0.3%). Notably, there are many rare genetic variants with low LD that are currently not included in genotyping arrays and that are difficult or impossible to impute (Auton et al., 2015; McCarthy et al., 2016). The effects of such rare, low-LD SNPs are unobserved here, which could contribute to the gap between our h2SNP estimates and heritability estimates for income from twin studies (Witte et al., 2014).

Figure S5.7 plots the heritability estimates of each chromosome against the number of effective loci per chromosome.[6] For a genetically highly complex trait that has a very large number of causal SNPs across the genome, one would expect that each chromosome's contribution to the total heritability is approximately proportional to the number of independent loci on the chromosome (i.e., the amount of information contained in the chromosome). Indeed, the results in Figure S5.7 show that chromosomes with more effective loci contribute more to the heritability of income than chromosomes with fewer effective loci. A naïve regression of the subheritability estimates of each chromosome on the number of effective loci yields a standardized coefficient of 0.72 (95% CI: 0.41-1.02) and R^2 = 0.5, suggesting a robust positive relationship between the number of effective loci and contributions to the heritability of occupational wage, which leaves room for some variation of the importance of each chromosome. Overall, these results are consistent with the idea that occupational wage is a genetically highly complex trait that is influenced by a large number of SNPs with small effects. Finally, the sum of h^2_{SNP} estimates across chromosomes is 9.5% (*SE* = 1.5%), which is slightly lower than the pooled h^2_{SNP} estimate reported in Table S5.5 (10.3%, *SE* = 0.3%), but the 95% confidence intervals of both point estimates overlap, assuming asymptotic normality.

Our SNP-based heritability estimate of ≈10% for occupational wages is considerably lower than most previously reported twin-study heritability estimates for income (Hyytinen et al., 2019; Taubman, 1976a, 1976b). While some of this divergence may be driven by imprecise point estimates, potential

[6] Effective loci refer to the set of SNPs that can be considered statistically independent of each other. We obtained the number of effective loci for each chromosome from (Lee, Wedow, et al., 2018).

upward bias in twin studies, or differences in the samples and measures of income used, our results are consistent with many studies on other traits that find lower heritability estimates with SNP-based methods compared to classic twin studies (Witte et al., 2014). Most likely, a part of the difference can be attributed to a downward bias in h2SNP estimates due to unobserved genetic markers such as very rare and structural genetic variants that are in low LD with the observed SNPs on current genotyping arrays. Indeed, studies on BMI and height showed that much of this so-called "missing heritability" can be recovered when rare and structural genetic variants are observed and taken into account (Auton et al., 2015; Wainschtein et al., 2019).

However, since **X** is the result of both the genetic and the social lottery, h^2_{SNP} estimates based on **X** in population samples such as the one we used here may also capture indirect genetics effects from unobserved family members (e.g., parents and siblings) that influence the outcomes of the study participants via their behavior and the environment they create (Kong et al., 2018; Young et al., 2018). These so-called genetic nurturing effects violate the assumption of our estimation method that genetic effects and exogenously given environmental effects are orthogonal to each other. Genetic nurture effects are likely to be particularly relevant for socioeconomic outcomes such as income, and they are an interesting source of inequality by themselves (Koellinger & Harden, 2018). Indirect genetic effects via relatives induce an upward bias in the h2SNP estimate. Our within-family analyses using PGI shed some light on whether such indirect effects exist and how important they are.

S5.3 Genome-wide association study (GWAS) on occupational wages

We follow a preregistered analysis plan (https://osf.io/rg8sh/) and conduct GWAS on occupational wages in the UKB. A GWAS systematically scans all measured genetic variations among people for associations with outcomes of interest. Thanks to rapid decreases in genotyping costs and a correspondingly rapid increase in the availability of genetic data, GWAS on thousands of traits have been conducted, enabling a remarkable range of discoveries in population and complex-trait genetics as well as epidemiology and the social sciences (Harden & Koellinger, 2020; Visscher et al., 2017).

Consider Equation S5.2 again. In medical research, interest in $\boldsymbol{\beta}$ stems primarily from the hope of gaining insights into the biological causes of diseases that could potentially be targeted by drugs or other treatments (King et al., 2019; Visscher et al., 2017). In the context of socioeconomic differences, however, estimates of $\boldsymbol{\beta}$ are not only a useful starting point for biological investigations, but also may help to better understand the influence of individual behavior and the environment (D. J. Benjamin et al., 2012; Harden & Koellinger, 2020).

The statistical challenge is that the true vector $\boldsymbol{\beta}$ is unknown and any estimate of $\boldsymbol{\beta}$ (denoted $\mathbf{b}$) is noisy and potentially biased in finite population samples, especially if the genetic architecture of y is complex and driven by many SNPs that each have very small effect sizes (Chabris et al., 2015). Moreover, the number of SNPs J is typically orders of magnitude greater than the number of individuals in the sample (N). Therefore, Equation S5.2 cannot be estimated by fitting all SNPs simultaneously in a multiple regression. Instead, the outcome is regressed on each SNP separately, resulting in J regressions in total. As a consequence, the LD-structure between SNPs (i.e., correlation between regressors) is ignored, and GWAS estimates should be considered as pointers to LD-linked regions in the genome (so-called loci) that are associated with the outcome rather than causal estimates.

More importantly, uncontrolled correlations between allele frequencies, environments, and ancestry backgrounds violate the assumption that $\mathbf{x}_i$ and e are orthogonal, making it challenging to interpret GWAS estimates of $\mathbf{b}$ from population samples (Hamer & Sirota, 2000; Young et al., 2019). The standard approach to tackle this challenge is (1) to restrict the sample to individuals of similar ancestries (due to data availability, this typically means European ancestries7) and (2) to control for leading principal components (PC) from genetic data in our GWAS. These lead PCs tend to capture differences in genotypes across geographic regions and ancestries, provided they are constructed using a large set of uncorrelated SNPs (Abdellaoui et al., 2013; Price et al., 2006). We follow this state-of-art approach here and conduct a GWAS on the log of occupational wages, including 40 genetic PCs as control variables to

[7] Between 2007 and 2017, 86% of GWAS discovery samples were of European ancestries (Mills & Rahal, 2019) partly because the interest and investments in genetic research vary dramatically across countries and more than 50% of all GWAS participants until 2017 were recruited in the UK and Iceland alone — two countries that are populated by a majority of people of European ancestries. However, factors such as distrust of the medical/scientific community, poor access to primary medical care, the failure of researchers to actively recruit non-Europeans, the alienation of minority health professionals, the lack of knowledge about clinical trials, as well as language and cultural barriers were also identified as important impediments to more diverse genotyped research samples (Shavers-Hornaday et al., 1997).

adjust for population stratification bias and modeling the error structure with random SNP effects to account for relatedness. Appendix 1.III describes our GWAS estimation procedure in detail. (See FAQ section "What is a GWAS? Are the genetic variants identified in a GWAS "causal"?)

It is crucial to understand that $\mathbf{b}$ is *not* a clean estimate of biological effects for two reasons. First, $\mathbf{b}$ includes indirect effects of $\mathbf{x}_i$ on y_i that work via behavioral or environmental pathways (e.g., self-selection of *i* into specific environments and feedback loops between the behavior of *i* and the responses from those environments). Thus, $\mathbf{b}$ partly reflects social facts that depend on environmental conditions and may vary across different environments and samples. In our context, technological progress, labor market conditions, and social factors such as discrimination or racism may influence the $\mathbf{b}$ for income. Thus, the effects of $\mathbf{x}_i$ on y_i that are captured by $\mathbf{b}$ are *not* universally true or simply "given by nature". Rather, $\mathbf{b}$ reflects social and economic realities that may be outside of the control of any given individual *i* but are subject to change over time and could be malleable by collective human action, policy reforms etc. Which specific environmental factors influence $\mathbf{b}$ is an empirical question of considerable interest for the social sciences and policy.

Second, $\mathbf{x}_i$ is the outcome of both the genetic and the social lottery in a population sample, which implies that $\mathbf{b}$ captures both genetic and family-specific effects. To isolate the effects of the genetic and the social lottery, it would be necessary to estimate $\mathbf{b}$ from random differences in $\mathbf{x}_i$ between biological relatives (e.g., siblings or parents and their children). However, doing so would sharply reduce the GWAS sample size N and the variance in $\mathbf{x}_i$ and y_i, which would lead to a substantial loss of statistical power to estimate $\mathbf{b}$. In the absence of extremely large genotyped family samples, the best strategy to estimate $\mathbf{b}$ is arguably to maximize the statistical power by maximizing N with population samples, followed by within-family analyses that make use of polygenic indices that have been constructed from estimates of b in independent samples (Chabris et al., 2015; Kong et al., 2018; Lee, Wedow, et al., 2018). We follow this strategy in the current study.

Specifically, we conduct GWAS on occupational wages in the UKB population sample using a linear mixed model (LMM). In our LMM, we assign a fixed effect to the SNP under consideration, while treating the effects of all other SNPs as random (Yang et al., 2014). In addition, we control for the 40 leading PCs from the genetic data in our LMM.

For each SNP $j = 1, \ldots, J$, we consider a leave-one-chromosome-out (LOCO) LMM for our sample of N individuals. That is, we examine

$$y = x_j\beta_j + Z\boldsymbol{\gamma} + X_{(j)}\boldsymbol{\beta}_{(j)} + e \tag{S5.3}$$

where y denotes the outcome vector and x_j the N-by-1 vector of data on SNP j. The main parameter of interest is β_j, the effect of SNP j. In this model, Z denotes the N-by-K matrix of covariates, with effects $\boldsymbol{\gamma}$, and $X_{(j)}$ denotes the matrix of SNP data, excluding the SNP at hand as well as all other SNPs on the same chromosome, with associated random effects $\boldsymbol{\beta}_{(j)}$.

Effectively, under this LOCO LMM, we have an error structure that captures contributions from the environment as well as SNPs located on other chromosomes. This error structure is fully characterized by the two parameters σ_g^2 and σ_ε^2. We estimate this LOCO LMM in two steps. First, the parameters σ_g^2 and σ_ε^2 are estimated using GREML (i.e., the same method that is also used for h_{SNP}^2 estimation). Second, the effects, β_j and $\boldsymbol{\gamma}$, are then estimated with generalized least squares. To reduce the computational burden, we use an efficient approximation algorithm that converges after a small number of iterations (Loh et al., 2015).

To account for the possibility that occupational wages are influenced by different sex-specific factors, we estimate GWAS according to Equation S5.3 separately for males (N= 133,689) and females (N= 149,274) using the same set of covariates as in the heritability estimation described above. Next, we combined the sex-specific results using a special case of the MTAG (multi-trait analysis of GWAS) method.[8] MTAG implements a generalized version of inverse-variance-weighted meta-analysis that takes into account the relatedness between the male and female samples as well as potential bias due to an uncontrolled population structure (Turley et al., 2018).[9]

Several quality control filters were applied to exclude SNPs that are problematic, implemented according to the commonly applied procedure developed by (Winkler et al. (2014)). The main steps include

[8] The similarity of the genetic architecture of income for males and females can be quantified by the genetic correlation coefficient. A robust estimate of this quantity can be obtained with bivariate LD score regression (Canela-Xandri et al., 2018; Lee, McGue, et al., 2018). Applying this method to our GWAS results on income in the UKB, we estimate a genetic correlation of 0.921 (SE=0.034) between males and females, which is very high but statistically indistinguishable from a perfect genetic correlation of 1 (Koellinger et al., 2018).

[9] A measure of bias due to population stratification can be obtained from the intercept, a so-called LD score regression, which regresses the LD scores of all SNPs on their observed Chi-squared test statistic in a GWAS (B. K. Bulik-Sullivan et al., 2015).

removing SNPs that have missing or incorrect numerical values for some variables (a *p*-value outside of [0,1], for instance); have a MAF below 0.1%; have imputation accuracy below 0.7; have the effect-coded allele or the other allele with values different from “A,” “C,” “G,” or “T”; are duplicate SNPs; and have an allele frequency different from the allele frequency in the HRC reference panel by more than 0.2.

A systematic scan of all observed SNPs in a GWAS imposes a high multiple-testing burden, which led to the adoption of a stringent *p*-value threshold of 5×10^{-8} for genome-wide significance, reflecting a Bonferroni correction for one million independent tests (Shah et al. (2008)). Although the actual number of SNPs in a GWAS is often higher than one million, many SNPs are correlated, and the *p*-value threshold of 5×10^{-8} is the accepted benchmark for GWAS in European ancestry samples that rely primarily on common SNPs.[10]

We follow this standard approach here. Of the 9,773,980 autosomal SNPs included in our GWAS on occupational wages in the UKB (N= 282,963), we identified 3,920 genome-wide significant SNPs. These 3,920 SNPs cluster across 45 approximately independent loci.[11] We found one novel locus that has never been reported for any other traits.[12]

The GWAS results are visually presented in a so-called Manhattan plot in Figure S5.8, where the *p*-values of all SNPs are plotted on a $-log_{10}$ scale against their chromosomal position. The SNPs with the lowest *p*-value per locus are referred to as lead SNPs and are reported in Table S5.6. The effect sizes of the lead SNPs in absolute terms range from 0.018 to 0.005 with a mean of 0.007, which corresponds to a 0.7% change in occupational wage per allele.[13] In terms of R^2, the variance explained by each lead SNP ranges from 0.011% to 0.037% with a mean of 0.014%, implying that each of the lead SNPs captures only a very

[10] More stringent thresholds may be necessary for non-European ancestries that observe a higher degree of genetic variation and datasets that include very rare or structural genetic variants that are not in strong LD with common SNPs (Auton et al., 2015).

[11] We define a locus using a clumping algorithm that begins by selecting the SNP with the lowest p-value as the lead SNP in the first clump and includes in the first clump all SNPs that have R^2 greater than 0.1 with the lead SNP. Next, the SNP with the second-lowest *p*-value outside the first clump becomes the lead SNP of the second clump, and the second clump is created analogously but using only the SNPs outside of the first clump. This process continues until every genome-wide-significant SNP is either designated a lead SNP or is clumped to another lead SNP. The genomic proximity is not considered when forming clumps. The LD between the SNPs is calculated from a reference panel of the Haplotype Reference Consortium (HRC; (McCarthy et al., 2016))

[12] We looked up the previous GWAS results by using the GWAS Catalog data obtained on February 21 2020 (Buniello et al., 2019).

[13] These effect size estimates are not LD-adjusted.

small proportion of the variation in occupational wages. Note that uncontrolled population structure (Price et al., 2006), indirect genetic effects (Kong et al., 2018), and the statistical winner's curse would tend to bias these effect size estimates away from zero (Palmer & Pe'er, 2017), which implies that the true causal effects may be even smaller. The genomic loci that are represented by our lead SNPs can be positionally mapped to 184 protein-coding genes. An analysis of the set of genes that are potentially tagged by our GWAS results shows that they are most strongly expressed in brain tissues.[14]

We compared our results to GWAS results for other SES measures by using the 45 lead SNPs as well as the SNPs that are highly correlated with them ($R^2 > 0.6$). Twenty-six of our loci were previously found to be significantly associated with household income (W. D. Hill et al., 2019) and 31 loci with educational attainment (Lee, Wedow, et al., 2018). The similarity of the distribution of SNP effects for two different traits ($\boldsymbol{\beta}1$, $\boldsymbol{\beta}2$) is given by the so-called genetic correlation coefficient (B. Bulik-Sullivan et al., 2015; Okbay et al., 2016). The genetic correlation of occupational wages with educational attainment is 0.923 (*SE* = 0.01) and 0.919 (*SE* = 0.02) with household income, which is statistically distinguishable from one.[15] Thus, the genetic architecture of these different measures of SES is very similar, but not exactly identical.

Most of the genome-wide significant loci identified here were previously found to be associated with health outcomes such as BMI, HDL cholesterol levels, diabetes, bipolar disorder, alcohol consumption, Parkinson's disease, and many others (Table S5.6). Thus, genetic factors linked to income also tend to have relevance for health and vice versa. Several different mechanisms could lead to this relevance (Hemani et al., 2018; Solovieff et al., 2013). First, it is possible that some genes affect both income and health directly via the same biological mechanism. Second, health and income may act as mediating variables for each other. For example, income could have causal downstream consequences on health or health conditions, with early onset conditions (e.g., ADHD) possibly having causal effects on income. Finally, the identified genes may also be associated with unobserved outcomes that influence both health and income (e.g., neighborhood quality during childhood). GWAS results by themselves do not

[14] Functional mapping and annotation of our GWAS results was conducted using the bioinformatic tool FUMA (Watanabe et al., 2017).

[15] The genetic correlation is the correlation between two sets of standardized GWAS effect sizes. We estimated this by using LD score regression (B. Bulik-Sullivan et al., 2015). Testing whether these estimates are different from one yields p-values of 5.03×10-13 and 3.78×10-8 respectively for educational attainment and household income, which indicates that the genetic correlation is not perfect.

illuminate causal pathways, but the identified genetic loci can serve as useful starting points for follow-up studies that aim at elucidating mechanisms (Harden & Koellinger, 2020; Visscher et al., 2017). Thus, although we do not know why our GWAS identifies these loci for income, it is clear that the genetic architectures of income and health are related and no clear boundaries can be drawn between socioeconomic and medical outcomes. This is not surprising, given the well-known relationships between SES and health (Chetty et al., 2016; Piotrowska et al., 2015; Stringhini et al., 2017; Wilkinson & Marmot, 2003).

Although previous GWAS on household income or neighborhood differences (W. D. Hill et al., 2016, 2019) uncovered many interesting findings, it is challenging to interpret genetic associations with such aggregate measures of prosperity. Our approach that maps individual differences in income to individual-specific genetic markers reduces this complexity to some extent and our results allow for the formation of new types of genetically informed study designs on income inequality (e.g., to estimate the returns to schooling while explicitly controlling for genetic confounds). Furthermore, although the most recent GWAS on educational attainment (Lee, Wedow, et al., 2018) of more than 1.1 million individuals was the largest GWAS on SES to date, a genetic risk score constructed from our results improves upon the variance in individual income that can be captured by a risk score for educational attainment (see *A.IV. Polygenic indices*).

Since our GWAS results are derived from a sample of elderly inhabitants of the UK who all have European ancestries, there will be limits to the transferability of our results to other populations: The genetic associations with income we report here are conditional on the social and economic context of the White, educated, industrialized, rich, and democratic (Weird) sample we studied. Different contexts (e.g. discrimination against some groups in society) may imply different genetic architectures that would limit the external validity of our results (de Vlaming et al., 2017; Mostafavi et al., 2020). In addition, genetic associations also depend on the frequencies of genetic variants and their correlations with each other in the samples studied. This dependence generally limits the transferability of GWAS results and polygenic indices across groups that differ in ancestries (Martin et al., 2019; Rosenberg et al., 2019) and implies that our results cannot be used for comparison across groups. Our results cannot be used for predicting individual outcomes for the same reasons and for the limited statistical accuracy of our polygenic indice. (See FAQ sections "Can your polygenic score be used to predict how well someone will do in life?" and "Can your polygenic score be used for research studies in non-European-ancestry populations?")

5.4 Polygenic indices

The tiny effect sizes of each individual SNP in our GWAS on occupational wages ($R^2 < 0.04\%$) prohibit a statistically well-powered SNP-level replication of our results in the two available hold-out samples.[16] As an alternative, holistic form of replication, we constructed PGI from our GWAS estimates on occupational wages in the HRS and the WLS samples to test the associations with measures of self-reported income.

Our PGI uses LDpred-adjusted GWAS estimates, based on the observed LD structure in the prediction sample (Vilhjálmsson et al., 2015). Specifically, we construct PGI using all directly genotyped SNPs and those included in the HapMap3 reference panel (Altshuler et al., 2010), yielding 2,547,062 SNPs in the HRS, 1,519,416 SNPs in the WLS, and 1,685,746 SNPs in the UKB. This focus on common, high-quality SNPs improves the signal-to-noise ratio in the PGI relative to methods that use all available SNPs or only a small subset of them (e.g., only the SNPs that are genome-wide significant).[17]

The EA PGI are constructed from a publicly available version of the GWAS results reported in (Lee, Wedow, et al., 2018), which are based on $N \approx 760{,}000$, after regenerating GWAS results excluding each prediction sample.[18]

All PGIs are standardized to have zero mean and unit variance and tested in linear regressions on log hourly wages. The main quantity of interest here is the contribution of the PGI to variation in log hourly wages in a regression model with baseline controls. This contribution is measured by an increase in R^2 (ΔR^2) in response to adding the PGI to a baseline model that controls e.g., for age, sex, the first 20 principal components of the genetic data. We also report partial R^2, the variance explained by the PGI

[16] The combined number of individuals in HRS and WLS that have genetic data, information on income, and standard control variables is N = 13,558 (Table S5.2). This would yield only ≈50% statistical power to replicate a SNP with R2 = 0.04% at $\alpha = 0.05$ and only ≈15% power for a SNP with R2 = 0.01%.

[17] It is difficult to accurately measure and impute rare SNPs. Furthermore, the standard error of the estimated effect of rare SNPs is larger because $SE(b) \approx 2 \cdot MAF(1-MAF)$;see (Rietveld et al., 2013).

[18] Note that whenever constructing a PGI the GWAS summary statistics are regenerated to exclude a prediction sample, which prevents overfitting. Therefore, the actual sample size of EA GWAS used for PGI is slightly different for each prediction sample.

when partialling out the control variables from both the log hourly wage and the PGI. For comparison, we also constructed a PGI for educational attainment (EA) in HRS and WLS using the results from a much larger GWAS sample (N ≈ 0.76 million) that excluded the prediction samples (Lee, Wedow, et al., 2018). This PGI for EA has previously been shown to be correlated with labor market outcomes and measures of financial wealth in the HRS (Barth et al., 2020; Papageorge & Thom, 2019). All PGIs are standardized to have zero mean and unit variance.

The polygenic prediction results for the HRS can be found in Panel A of Table S5.7. The pooled baseline model with all control variables but without the PGI captures 8.6% of the variance in log hourly wages. When the PGI for income is added to the model, R^2 increases by 0.91%, giving a partial R^2 of 0.99% (p=6.2× 10^{-50}). This finding is in line with theoretical expectations that take the imprecision of the SNP effect-size estimates due to the finite GWAS sample size into account.[19] The coefficient estimate for the income PGI implies that one-standard deviation-increase in the PGI is associated with an 8.0% increase in hourly wages (95% CI: 6.2-9.7%).

The EA PGI is also associated with income in the HRS (ΔR^2≈1.10% in the pooled model; p = 4.4× 10^{-60}). If both PGI are included simultaneously, both remain predictive and statistically highly significant, jointly accounting for 1.29% of the variation in the hourly wage in the pooled HRS sample (p = 2.8× 10^{-12}; p = 1.6× 10^{-22}). Thus, the income PGI contributes information over and above the information in the EA PGI, although income and EA are genetically very similar (W. D. Hill et al., 2019; Koellinger et al., 2018) and the EA GWAS sample is substantially larger. This result likely occurred because the estimation error for the SNP effects is still relatively large, but not identical for both GWAS samples. Thus, having GWAS results for multiple indicators is a way to increase the combined predictive accuracy that can be obtained from genetic data.[20] Since the EA and income PGI are correlated with each other ($\rho \approx 0.54$), the increase in the explanatory power in the combined model is smaller than the sum

[19] Using the MetaGAP calculator (de Vlaming et al., 2017) with a GWAS sample size of N = 282,963 (corresponding to the size of our UKB sample), 250,000 independent SNPs (a realistic number after GWAS quality control), and assuming h^2_{SNP} = 0.1 with 20,000 independent causal SNPs as well as a perfect genetic correlation between the GWAS and the prediction sample, the expected R^2 of a polygenic indice is 1%.

[20] (Turley et al., 2018) developed a multivariate method to combine GWAS results from genetically strongly correlated traits that builds on a similar intuition. Indeed, adding several PGI as predictors in a multiple regression is a naïve way to mimic the increase in polygenic R^2 that their approach yields.

of ΔR^{2}'s from the models in which each PGI is added separately. Finally, both polygenic indices capture similar shares in income variation for males and females in the HRS sample.

Panel B of Table S5.7 reports the results for self-reported wage rates observed in the WLS. While the results are consistent with the HRS in that we find statistically significant associations between the log hourly wage and the PGI in every case, the predictive power of the PGI is overall lower in the WLS.[21] The pooled baseline model explains 19.2% of the variance and adding the income PGI increases the R^2 by 0.57%. The coefficient estimate implies that an increase in the PGI of one standard deviation is associated with an increase of approximately 5.8% (95% CI: 4.3-7.4) in the hourly wage rate. When using the EA PGI instead, the increase in R^2 is again slightly higher compared to the income PGI (ΔR^2= 0.62% and partial R^2= 0.76%). Similar to what we observed in HRS, both PGI remain individually predictive and statistically highly significant (p= 1.6× 10^{-4}; p =1.9× 10^{-5}) in a multiple regression that includes both scores, whose correlation is again $\rho \approx 0.54$.

In contrast to the HRS sample, we observed considerable heterogeneity between males and females in the WLS in terms of ΔR^2 of the PGI. While the females' wages observed in the WLS are as well predicted by the PGI as those in the HRS, the predictive accuracy of both PGI is lower for males. This result may be due to a lower SNP-based heritability of income for males in the WLS, but it may also be due to technical effects such as differences in the genetic architecture of income between males and females within and across the samples we studied.

In a similar vein, the predictive power of the PGI can also be underestimated due to the measurement error and transitory variance in the cross-sectional distribution of income. Table S5.8 reports the same set of analyses for the HRS but with 3-year moving averages of wages, which can alleviate such issues to some extent. In the pooled sample, 14.83% of the variation can be additionally explained by the income PGI. The income and educational attainment PGI together explain more than 2% of the variation. As such, the predictive power of the PGI is expected to be higher for better measures of income or longer-term income.

[21] The lower delta R^2 of the PGI in the WLS could be due to several factors, including a potentially lower h^2 of income in the WLS sample, a lower genetic correlation for income between the WLS and the UKB than between HRS and the UKB (de Vlaming et al., 2017), or because of the sibling pairs included in the WLS (the OLS estimates in WLS reflect within-family estimates to some degree, which tend to be smaller than between-family estimates, as shown in the following section).

Although both our income PGI and the PGI for educational attainment capture a small share of the distribution of income in independent hold-out samples, they are not useful for individual-level predictions for statistical as well as conceptual reasons. The statistical limitations of individual predictions are illustrated in Figure S5.3. Even for PGI values that are relatively extreme outliers (e.g., those 2 standard deviations below or above the mean), an extremely wide range of incomes is observed. More generally, no single variable with an R^2 ≈1% is useful for individual-level prediction. The $R^2$of PGI will increase in the future as GWAS sample sizes increase (Daetwyler et al., 2008), with an upper bound given by h2SNP, which, according to our estimates, is in the range of approximately 10% with current SNP data. However, even a variable with R^2 ≈10% would not be sufficiently accurate to make reliable individual-level predictions (Harden & Koellinger, 2020). As we emphasized before, PGI should not be considered as “objective” or “purely biological” measures. The GWAS results that are used to construct PGI may capture many things that are associated with income, but are not due to directly causal effects of genes (Haworth et al., 2019; Kong et al., 2018). To the extent that the income PGI capture directly causal genetic effects, these effects will reflect the social realities of the samples used in the study. For example, the environmental circumstances that matter in the context of income include the relative supply of and demand for certain types of skills (Acemoglu, 2002); the presence or absence of discrimination (Bertrand & Mullainathan, 2004; Reimers, 1983); the extent to which problems of asymmetric information between employers, workers, and job candidates can or cannot be resolved (Autor, 2001); existing regulations (Siebert, 1997); the opportunity costs of labor market participation (Becker, 1965), labor market discrimination (Kaas & Manger, 2012) and many other features of economic reality that are neither universal nor necessarily optimal from a welfare perspective. Thus, aside from statistical considerations, the environmental context of the income distribution puts limits on the potential transferability of the income PGI across samples (Mostafavi et al., 2020). If PGI are used for individual prediction despite these limitations (e.g., in school entrance exams or job hires (Plomin, 2019)), it can exacerbate existing stigmas, discrimination, and inefficiencies, and create or amplify economic and ethical dilemmas. Thus, while the PGI we constructed here can be a very useful tool for research, its practical implications are very limited at best and feature many complications.

S5.5 Additional information on data

S5.5.1 Health and Retirement Study (HRS)

In 2006, the HRS started collecting biomarkers and DNA samples in a subset of the participants (Weir, 2013). Here we used the second release of the HRS genetic data,22 which covers genotyping phases 1 to 3. In phase 1, DNA samples were extracted from buccal swabs and in phase 2 and 3 this was done using saliva samples. The DNA samples were genotyped at the Center for Inherited Disease Research (CIDR). Phases 1 and 2 were genotyped together on the Illumina HumanOmni2.5-4v1 array and phase 3 was genotyped on the Illumina HumanOmni2.5-8v1 array.

The two arrays have 2,365,472 overlapping SNPs. Those SNPs were then subjected to CIDR technical filters and tests for duplicate sample discordance, Mendelian errors in trios, Hardy Weinberg equiibrium testing, and tests on sex differences. In total, 2,075,208 SNPs passed these QC filters (Weir, 2013).

Autosomal SNPs were imputed using the worldwide reference panel from phase I of the 1000 Genomes project (v3, released March 2012) (Consortium & The 1000 Genomes Project Consortium, 2012; HRS, 2013). 1,945,761 Genotyped SNPs were used as a basis for imputation. Imputation was performed using IMPUTE2 software. The imputation output contains 22,378,417 autosomal SNPs. Before our analyses, we filtered out SNPs that had an imputation quality below 0.7. SNPs were also removed if the SNP was missing in over 5% of the sample or the *MAF* was smaller than 1%. Due to computational restraints in constructing the PGI with LDpred, we further reduced the number of SNPs to those that were directly genotyped or present in the HapMap3 imputation panel, providing us with a high-resolution coverage of common genetic variants. This leaves 2,547,062 SNPs included in the construction of the PGI.

Our analyses were restricted to unrelated participants of European descent. Specifically, HRS filtered out parent-offspring pairs, siblings and half-siblings. For participants present in version 1 of the HRS genetic data, we selected European descent using a list provided by HRS that is based on self-reported race and principal component analysis. For participants who were added to version 2 of the HRS genetic data, we excluded those who self-identified as having non-European ancestry as well as those who fall outside of the European ancestry cluster in our principal component analysis. The principal component analysis was performed by plotting the first four principal components of HRS version 1, together with HRS

[22] See https://hrs.isr.umich.edu/data-products/genetic-data/products#gdv2, for more information.

version 2 and the 1000 Genomes project reference panel. We also excluded individuals who did not satisfy HRS internal genotype quality control criteria.

S5.5.2 Wisconsin Longitudinal Study (WLS)

The WLS (Herd et al., 2014) is a longitudinal study of individuals who graduated from Wisconsin high schools in 1957 as well as one randomly selected sibling. The original respondents and their selected siblings were surveyed six times over the years. The WLS collected extensive information on family backgrounds, schooling, and labor market experiences. In addition, genetic data was also collected for approximately 9,800 individuals including both the original respondents and their siblings. We use hourly wage rates surveyed in 1992-1994, which was the first wave during which information on wages was collected and the last wave before most respondents reached retirement age. The nominal wages are converted into real wages in the same way as in the HRS.

The WLS has two waves of genetic data, in our analyses we use the second wave of genetic data (Herd, 2016). Over the course of 2007 and 2008 the WLS began to collect saliva samples by mail. Additional samples were added in 2010 during home interviews. A total of 9,027 panel members contributed saliva samples for genetic analysis. The DNA was extracted and genotyped at the CIDR using the Illumina HumanOmniExpress array (713,014 SNPs).

Similar to the HRS genetic data the SNPs were subjected to CIDR technical filters and tests for duplicate sample discordance, Mendelian errors in trios, Hardy Weinberg Equiibrium testing, and tests on sex differences (Herd, 2016).

In WLS, the autosomal SNPs were imputed using phase 3 from the 1000 Genomes project reference panel and imputation was performed using IMPUTE2 software (WLS, 2016). This process resulted in 32,367,317 autosomal SNPs. In our PGI analyses, SNPs were selected in the same way as in the HRS data, resulting in 1,519,416 SNPs.

Our analyses were restricted to unrelated participants of European descent. Selection on European descent was done based on principal component analysis by plotting the first four principal components together with those of the 1000 Genomes project reference panel. Self-reported ethnicity was not considered here as it was surveyed only in a later wave, which led to too many missing outcomes.

S5.5.3 UK Biobank

The UK Biobank genetic data contain genotypes for 488,377 participants (Bycroft et al., 2018). DNA was extracted from blood samples that were collected at a UK Biobank assessment center. A subset of 49,950 participants were genotyped using the UK BiLEVE Axiom Array by Affymetrix (807,411 markers). The remaining 438,427 participants were genotyped using the custom UK Biobank Axiom Array (825,927 markers). The two arrays have a 95% overlap.

The markers were assessed on quality for batch, plate, array, or sex effects, tests on Hardy–Weinberg equilibrium and discordance across control replicates. Autosomal SNPs were imputed using a custom imputation panel based on the Haplotype Reference Consortium data and UK10K Panel using IMPUTE4 software. This resulted in an imputation output of 93,095,623 autosomal SNPs.

For the sibling sample used as a hold-out sample for PGI analyses, SNPs were selected in the same way as in the HRS data, resulting in 1,685,746 SNPs.

Our analyses were restricted to unrelated participants of European descent internally identified by the UKB. The UKB identified them based on principal component analysis with the 1000 Genomes project reference panel. The individuals were dropped if their reported ethnic background was not white.

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S5.7 Tables

Table S5.1 List of variables in the UK Biobank

Variables	Details
log hourly wage	Imputed from standard occupation codes. See Appendix
top household income	= 1 if the annual household income before tax is greater than £52,000.
log regional income	Computed by matching home locations to Middle-layer Super Output Areas. Data from Official National Statistics (England and Wales only)
neighborhood score	Negative of index of multiple deprivation for Lower-layer Super Output Areas derived by the UK's Ministry of Housing, Communities & Local Government (England only)
years of education	See Okbay et al. (2016)
college degree	= 1 if having a college degree
waist-to-hip ratio	Waist circumference divided by hip circumference
BMI	Body mass index
blood pressure	Average of systolic and diastolic measures
lung function	Average of forced expiratory volume in the first second, forced vital capacity, and peak expiratory flow weighted by their covariance matrix. See Barcellos et al. (2019).
ever hospitalized	= 1 if any record in in-patient data
ever diagnosed with cancer	= 1 if any record in cancer registry
infectious and parasitic diseases	= 1 if any record for disorders classified in ICD-10 chapter 1 and codes Z20-29
neoplasms	= 1 if any record for disorders classified in ICD-10 chapter 2
diseases of blood organs and immune system	= 1 if any record for disorders classified in ICD-10 chapter 3
endocrine, nutritional, and metabolic diseases	= 1 if any record for disorders classified in ICD-10 chapter 4
mental, behavioral, nervous system disorders	= 1 if any record for disorders classified in ICD-10 chapter 5 and 6
diseases of the eye and adnexa	= 1 if any record for disorders classified in ICD-10 chapter 7
diseases of the circulatory system	= 1 if any record for disorders classified in ICD-10 chapter 9

diseases of the respiratory system	= 1 if any record for disorders classified in ICD-10 chapter 10
diseases of the digestive system	= 1 if any record for disorders classified in ICD-10 chapter 11
diseases of the skin and subcutaneous tissue	= 1 if any record for disorders classified in ICD-10 chapter 12
diseases of musculoskeletal system and connective tissue	= 1 if any record for disorders classified in ICD-10 chapter 13
diseases of genitourinary system	= 1 if any record for disorders classified in ICD-10 chapter 14
symptoms and signs not elsewhere classified	= 1 if any record for disorders classified in ICD-10 chapter 18
injury, poisoning, and other consequences of external causes	= 1 if any record for disorders classified in ICD-10 chapter 19
external causes of morbidity and mortality	= 1 if any record for disorders classified in ICD-10 chapter 20
other health conditions	= 1 if any record for the rest of disorders classified in ICD-10

Table S5.2 Descriptive statistics

	N	Mean	S.D	Min	Max
UK Biobank					
year of birth	38697	1951.045	7.347	1937	1969
male	38697	0.421	0.494	0	1
log hourly wage	25292	2.6	0.349	1.833	3.881
top household income	33477	0.233	0.423	0	1
regional income	35393	739.482	193.387	300	1730
neighborhood score	33276	-17.646	13.937	-82	-0.61
years of education	38424	14.627	5.135	7	20
college degree	38424	0.291	0.454	0	1
waist-to-hip ratio	38638	0.866	0.089	0.581	1.342
BMI	38596	27.267	4.706	13.789	63.809
blood pressure	36099	110.879	13.898	65.5	179
lung function	35357	0	0.849	-3.922	20.781
ever hospitalized	38697	0.831	0.375	0	1
ever diagnosed with cancer	38697	0.183	0.387	0	1
infectious and parasitic diseases	38697	0.098	0.297	0	1
neoplasms	38697	0.176	0.381	0	1
diseases of blood organs and immune system	38697	0.222	0.416	0	1
endocrine, nutritional, and metabolic diseases	38697	0.216	0.412	0	1
mental, behavioral, nervous system disorders	38697	0.186	0.389	0	1
diseases of the eye and adnexa	38697	0.117	0.322	0	1
diseases of the circulatory system	38697	0.359	0.48	0	1
diseases of the respiratory system	38697	0.172	0.378	0	1
diseases of the digestive system	38697	0.426	0.494	0	1
diseases of the skin and subcutaneous tissue	38697	0.118	0.323	0	1
diseases of musculoskeletal system and connective tissue	38697	0.316	0.465	0	1
diseases of genitourinary system	38697	0.283	0.45	0	1
symptoms and signs not elsewhere classified	38697	0.389	0.487	0	1
injury, poisoning, and other consequences of external causes	38697	0.171	0.376	0	1
external causes of morbidity and mortality	38697	0.181	0.385	0	1
other health conditions	38697	0.494	0.5	0	1

Health and Retirement Study					
number of survey responses	6171	3.605	2.047	1	12
year of birth	6171	1944.487	8.431	1928	1968
male	6171	0.451	0.498	0	1
hourly earnings	22247	11.622	15.908	0.002	1244.848
job experience	22180	36.37	5.531	7	57
years of education	6152	13.588	2.414	0	17
college degree	6152	0.307	0.461	0	1
father's years of education	5635	10.667	3.538	0	17
mother's yeras of education	5862	11.06	2.918	0	17
Wisconsin Longitudinal Study					
year of birth	7387	39.742	3.747	29	64
male	7387	0.494	0.5	0	1
sibling respondent	7387	0.319	0.466	0	1
hourly earnings	7387	18.261	33.418	0.04	1282.051
years of education	6902	13.905	2.423	7	21

Table S5.3 Summary of the UK Biobank samples

Analysis	Sample	N	Note
Heritability	Single-variance-parameter model	196,187	unrelated, wage observed
	Multiple-variance-parameter model	24,000	randomly selected, unrelated, wage observed
GWAS	Baseline sample	282,963	occupational wage observed
	Two sub-samples	141,481 each	for GIV prediction, occupational wage observed, no relatives across the sub-samples
	Baseline sample without siblings and their relative	252,958	for prediction with the sibling sample, wage observed
	Two sub-samples without siblings and their relative	126,478 each	for GIV prediction with the sibling sample, wage observed, no relatives across the sub-samples
Prediction	Sibling sample	38,698	18,807 genetic sibling groups for within-family prediction analyses

Table S5.4 Weights used to construct the summary index of health in the UK Biobank sample

Health measure	Weight
waist-to-hip ratio	0.070
BMI	0.055
blood pressure	0.113
lung function	0.079
ever hospitalized	0.001
ever diagnosed with cancer	0.049
infectious and parasitic diseases	0.050
neoplasms	0.037
diseases of blood organs and immune system	0.062
endocrine, nutritional, and metabolic diseases	-0.003
mental, behavioral, nervous system disorders	0.050
diseases of the eye and adnexa	0.101
diseases of the circulatory system	-0.026
diseases of the respiratory system	0.041
diseases of the digestive system	0.044
diseases of the skin and subcutaneous tissue	0.080
diseases of musculoskeletal system and connective tissue	0.042
diseases of genitourinary system	0.077
symptoms and signs not elsewhere classified	0.019
injury, poisoning, and other consequences of external causes	0.065
external causes of morbidity and mortality	0.010
other health conditions	-0.016

Table S5.5 Heritability estimation of occupational wages in the UK Biobank using a single variance genetic relatedness matrix restricted maximum likelihood (GREML)

	Estimates	*N*
Male+Female	0.103 (0.003)	196,187
Male	0.103 (0.005)	93,666
Female	0.126 (0.005)	102,521

Note: Standard errors in parentheses.

Table S5.6 Lead single nucleotide polymorphisms (SNPs) from a genome-wide association study (GWAS) on log occupational wages in the UK Biobank and overlap with other traits.

SNP ID	Chromo-some	Effect-coded allele	Effect allele frequency	Beta	R^2(%)	Overlap with other traits
rs1487441	6	A	0.485	0.0097	0.037	Alcohol consumption (drinks per week), Autism and educational attainment, Bipolar disorder, Cognitive ability, Educational attainment, Extremely high intelligence, General risk tolerance, Highest math class taken, Household income, Intelligence, QT interval (drug interaction), Regular attendance at a pub or social club, Risk-taking tendency (4-domain principal component model), Self-reported math ability, Tourette syndrome
rs11130203	3	A	0.308	0.0100	0.033	Blood protein levels, Chronic inflammatory diseases (ankylosing spondylitis, Crohn's disease, psoriasis, primary sclerosing cholangitis, ulcerative colitis) (pleiotropy), Cognitive ability, Crohn's disease, Depressed affect, Educational attainment, Estimated glomerular filtration rate, Extremely high intelligence, Feeling fed-up, Glioblastoma, Glioma, Gut microbiota (functional units), Highest math class taken, Household income, Inflammatory bowel disease, Intelligence, Menarche (age at onset), Metabolite levels, Parental longevity (father's age at death or father's attained age), Pediatric autoimmune diseases, Primary sclerosing cholangitis, Regular attendance at a religious group, Self-reported math ability, Ulcerative colitis
rs7627910	3	C	0.462	-0.0078	0.024	BMI, Cognitive ability, Cognitive ability, years of educational attainment or schizophrenia (pleiotropy),

						Depressed affect, Educational attainment, Feeling miserable, Gastroesophageal reflux disease, HDL cholesterol, HDL cholesterol levels, HDL cholesterol levels in current drinkers, HDL cholesterol levels x alcohol consumption (drinkers vs non-drinkers) interaction (2df), HDL cholesterol levels x alcohol consumption (regular vs non-regular drinkers) interaction (2df), HDL cholesterol x physical activity interaction (2df test), Household income, Intelligence, Menarche (age at onset), Morning person, Morningness, Parental longevity (mother's age at death or mother's attained age), Predicted visceral adipose tissue, Regular attendance at a gym or sports club, White blood cell count
rs11678979	2	C	0.271	0.0078	0.019	Balding type 1, BMI, Cognitive ability, Household income, Intelligence, Male-pattern baldness
rs4977836	9	A	0.417	0.0069	0.018	Autism and educational attainment, Bipolar disorder, Cognitive ability, Depressed affect, Educational attainment, Extremely high intelligence, Feeling lonely, Highest math class taken, Household income, Insomnia symptoms (never/rarely vs. sometimes/usually), Insomnia symptoms (never/rarely vs. usually), Intelligence, Mental health study participation (completed survey), Remission after SSRI treatment in MDD or neuroticism, Self-reported math ability
rs185291	5	C	0.584	-0.0069	0.018	Cognitive ability, Depression, Educational attainment, Highest math class taken, Household income, Intelligence, Lung function (FVC), Major depressive disorder, Sedentary behaviour duration, Self-reported math ability
rs890546	18	T	0.638	0.0070	0.018	Cognitive ability, Cognitive ability, years of educational attainment or

						schizophrenia (pleiotropy), Depressed affect, Depression, Depression (broad), Educational attainment, Experiencing mood swings, Feeling fed-up, Feeling hurt, General factor of neuroticism, Highest math class taken, Household income, Lifetime smoking index, Mood instability, Neuroticism, Neuroticism, Remission after SSRI treatment in MDD or neuroticism, Response to amphetamines, Subjective well-being, Well-being spectrum (multivariate analysis), Worry
rs199441	17	G	0.783	0.0076	0.016	Alcohol consumption (drinks per week), Alzheimer's disease in APOE e4- carriers, Balding type 1, Brain region volumes, Breast cancer, Celiac disease, Cognitive ability, Depressed affect, Epithelial ovarian cancer, Experiencing mood swings, Feeling fed-up, Feeling guilty, Feeling hurt, Feeling miserable, Feeling nervous, Feeling worry, General factor of neuroticism, Handedness (Left-handed vs. non-left-handed), Handedness (left-handed vs. right-handed), Handedness (non-right-handed vs right-handed), Intelligence, Intracranial volume, Intraocular pressure, Irritable mood, Lung function (FEV1), Lung function (FVC), Macular thickness, Male-pattern baldness, Multiple system atrophy, Neuroticism, Neuroticism, Ovarian cancer in BRCA1 mutation carriers, Parkinson's disease, Parkinson's disease or first degree relation to individual with Parkinson's disease, Post bronchodilator FEV1, Sense of smell, White matter microstructure (axial diffusivities), White matter microstructure (fractional anisotropy), White matter microstructure (mean diffusivities), White matter microstructure (radial diffusivities), Worry

rs3911063	3	C	0.323	0.0067	0.016	BMI, General risk tolerance, Household income, Predicted visceral adipose tissue, Risk-taking tendency (4-domain principal component model), Smoking initiation (ever regular vs never regular), Smoking status, Smoking status (ever vs never smokers), Waist circumference, Waist-hip ratio
rs35175818	16	C	0.372	-0.0065	0.016	Albumin-globulin ratio, Alcohol consumption (drinks per week), Allergic disease (asthma, hay fever or eczema), Bipolar disorder or body mass index, Blood protein levels, BMI, BMI (joint analysis main effects and physical activity interaction), BMI in physically active individuals, Body fat percentage, Childhood obesity, Chronic inflammatory diseases (ankylosing spondylitis, Crohn's disease, psoriasis, primary sclerosing cholangitis, ulcerative colitis) (pleiotropy), Chronic obstructive pulmonary disease, Cognitive ability, Crohn's disease, Eczema, Educational attainment, Estimated glomerular filtration rate, Extremely high intelligence, Hand grip strength, Hip circumference, Hip circumference adjusted for BMI, Household income, Inflammatory bowel disease, Inflammatory bowel disease (early onset), Intelligence, Offspring birth weight, Pediatric autoimmune diseases, Red blood cell count, Red cell distribution width, Type 1 diabetes, Ulcerative colitis, Waist circumference, Weight
rs34305371	1	A	0.102	0.0100	0.014	Alcohol consumption (drinks per week), Cognitive ability, Cognitive ability, years of educational attainment or schizophrenia (pleiotropy), Educational attainment, Household income, Insomnia, Intelligence
rs78871889	5	T	0.299	-0.0066	0.014	Educational attainment, Height, Highest math class taken, Household income

rs10053567	5	C	0.218	0.0072	0.014	Educational attainment
rs619466	18	G	0.906	-0.0101	0.014	Automobile speeding propensity, Depressed affect, Depressive symptoms, General factor of neuroticism, Household income, Life satisfaction, Neuroticism, Positive affect, Well-being spectrum (multivariate analysis)
rs62183028	2	T	0.312	-0.0063	0.013	Cognitive ability, Depressed affect, Educational attainment, Highest math class taken, Household income, Intelligence, Self-reported math ability
rs3847223	9	T	0.523	0.0057	0.013	Educational attainment, Household income
rs6928545	6	G	0.317	-0.0061	0.013	Cognitive ability, Household income, Intelligence
rs113011189	3	T	0.091	-0.0097	0.012	Educational attainment
rs59971723	4	A	0.381	-0.0057	0.012	Cognitive ability, Cognitive ability, years of educational attainment or schizophrenia (pleiotropy), Educational attainment, Height, Highest math class taken, Household income, Intelligence
rs56211325	2	T	0.024	0.0182	0.012	Cognitive ability, Household income, Intelligence
rs13107325	4	T	0.074	-0.0104	0.012	Adventurousness, Alcohol consumption, Alcohol consumption (drinks per week), Alcohol use disorder, Alcohol use disorder (consumption score), Alcohol use disorder (dependence and problematic use scores), Alcohol use disorder (total score), Autism spectrum disorder or schizophrenia, Balding type 1, Bitter alcoholic beverage consumption, Blood pressure, BMI, BMI (adjusted for smoking behaviour), BMI (joint analysis main effects and physical activity interaction), BMI (joint analysis main effects and smoking interaction), BMI in non-smokers, BMI in physically active individuals, Body fat percentage, Brain imaging

	measurements, Brain region volumes, Childhood body mass index, Cognitive ability, Cognitive ability, years of educational attainment or schizophrenia (pleiotropy), Diastolic blood pressure, Diastolic blood pressure x alcohol consumption interaction (2df test), Eczema, Educational attainment, Hand grip strength, HDL cholesterol, HDL cholesterol levels, HDL cholesterol levels in current drinkers, HDL cholesterol levels x alcohol consumption (drinkers vs non-drinkers) interaction (2df), HDL cholesterol levels x alcohol consumption (regular vs non-regular drinkers) interaction (2df), HDL cholesterol x physical activity interaction (2df test), Height, High density lipoprotein cholesterol levels, Hypertension, Insomnia, Intelligence, Low density lipoprotein cholesterol levels, Lung function (FVC), Male-pattern baldness, Mean arterial pressure, Mean arterial pressure x alcohol consumption interaction (2df test), Medication use (agents acting on the renin-angiotensin system), Multisite chronic pain, NT-proBNP levels in acute coronary syndrome, Obese vs. thin, Osteoarthritis, Predicted visceral adipose tissue, Red blood cell count, Risk-taking tendency (4-domain principal component model), Schizophrenia, Self-reported math ability, Sleep duration (short sleep), Systolic blood pressure, Systolic blood pressure x alcohol consumption interaction (2df test), Total cholesterol levels, Voxel-wise structural brain imaging measurements, vWF levels, Waist-hip ratio, Waist-to-hip ratio adjusted for BMI, White blood cell count

rs10818605	9	T	0.556	0.0055	0.012	Cognitive ability, Educational attainment, Highest math class taken, Household income
rs7715147	5	A	0.242	0.0063	0.012	Household income, Multiple system atrophy
rs6935954	6	G	0.576	0.0055	0.012	Age of smoking initiation, Birth weight, Chronotype, Educational attainment, Height, Lifetime smoking index, Mosquito bite size, Offspring birth weight, Parental longevity (father's age at death or father's attained age), Smoking cessation
rs10515086	5	T	0.171	-0.0072	0.012	Educational attainment, Household income
rs1455351	2	G	0.418	-0.0055	0.011	Cognitive ability, Educational attainment, Experiencing mood swings, Highest math class taken, Household income, Inflammatory bowel disease, Intelligence, Mood instability, Self-reported math ability, Smoking initiation (ever regular vs never regular), Smoking status, Ulcerative colitis
rs7556782	2	C	0.634	-0.0056	0.011	Carpal tunnel syndrome, Risk-taking tendency (4-domain principal component model), Smoking cessation, Waist-hip ratio
rs1254319	14	A	0.294	0.0059	0.011	Chronotype, Educational attainment, Glaucoma, Glaucoma (high intraocular pressure), Glaucoma (primary open-angle), Heel bone mineral density, Height, Highest math class taken, Hip circumference adjusted for BMI, Medication use (antiglaucoma preparations and miotics), Menarche (age at onset), Optic cup area, Optic disc area, Optic disc size, Optic nerve measurement (rim area), Refractive error, Self-reported math ability, Vertical cup-disc ratio, Waist-hip ratio
rs2535911	14	T	0.357	0.0056	0.011	Cognitive ability

rs6561943	13	T	0.257	-0.0061	0.011	BMI, Cognitive ability, Cognitive ability, years of educational attainment or schizophrenia (pleiotropy), Educational attainment, Experiencing mood swings, Highest math class taken, Household income, Intelligence, Predicted visceral adipose tissue, Type 2 diabetes
rs10789336	1	A	0.597	0.0054	0.011	Allergic rhinitis, Asthma and major depressive disorder, BMI, BMI (adjusted for smoking behaviour), BMI (joint analysis main effects and physical activity interaction), BMI (joint analysis main effects and smoking interaction), BMI in non-smokers, BMI in physically active individuals, BMI in physically inactive individuals, BMI in smokers, Body fat percentage, Childhood body mass index, Cognitive ability, Depression, Depression (broad), Depressive symptoms, Hip circumference, Insomnia, Intelligence, Major depressive disorder, Menarche (age at onset), Obesity, Obesity (early onset extreme), Subcutaneous adipose tissue, Waist circumference, Weight
rs11168416	12	T	0.324	-0.0057	0.011	Educational attainment, Highest math class taken, Metabolite levels
rs7975227	12	G	0.371	-0.0055	0.011	Intelligence
rs4811076	20	G	0.511	0.0053	0.011	Cognitive ability, Educational attainment, Highest math class taken, Self-reported math ability, Vitiligo, White blood cell count
rs2726518	4	C	0.571	-0.0053	0.011	Adventurousness, Cognitive ability, Colorectal cancer or advanced adenoma, Educational attainment, Highest math class taken, Household income, Intelligence, Multiple sclerosis
rs9824386	3	A	0.865	0.0077	0.011	Chronotype, Cognitive ability, Educational attainment, Highest math class taken, Intelligence, Metabolite levels, Morningness
rs7940022	11	T	0.680	0.0056	0.011	Balding type 1, Cognitive ability, Cognitive ability, years of educational

						attainment or schizophrenia (pleiotropy), Educational attainment, Highest math class taken, Household income, Intelligence, Male-pattern baldness
rs12204714	6	T	0.632	0.0054	0.011	Age at first birth, Educational attainment
rs2494995	1	C	0.217	-0.0063	0.011	Adventurousness, Attention deficit hyperactivity disorder or cannabis use, Balding type 1, Coffee consumption, Cognitive ability, Educational attainment, Household income, Intelligence, Number of sexual partners, Perceived intensity of sweet substances
rs4953097	2	T	0.663	-0.0055	0.011	Age at first sexual intercourse, Chronotype, Educational attainment, General risk tolerance, Height, Morning person
rs9729959	1	T	0.226	0.0062	0.011	Cognitive ability, Cognitive ability, years of educational attainment or schizophrenia (pleiotropy), Educational attainment, Glioma, Highest math class taken, Household income, Intelligence, Non-glioblastoma glioma, Regular attendance at a religious group, Self-reported math ability, Urinary sodium excretion
rs13240401	7	C	0.224	-0.0062	0.011	Cognitive ability, Educational attainment, Highest math class taken, Self-reported math ability
rs2282760	3	G	0.132	-0.0076	0.011	Age at voice drop, Coffee consumption, Depressive symptom (appetite changes) (binary trait), Depressive symptom (fatigue) (ordinal trait), Depressive symptoms (binary sum-score), Depressive symptoms (sum-score), Diastolic blood pressure, Eosinophil counts, Lung function (FVC), Morningness, Systolic blood pressure, Waist-to-hip ratio adjusted for BMI (additive genetic model)

rs141349367	8	T	0.059	-0.0109	0.011	
rs4408596	17	G	0.623	0.0053	0.011	Cognitive ability, Intelligence, Morning person

Note: Summary statistics were downloaded from the NHGRI-EBI GWAS Catalog (Buniello et al., 2019) on 21/02/2020. The association overlaps are checked for the lead SNPs as well as the SNPs in high LD with them ($R^2 > 0.6$). The Beta estimates measure the effect sizes on log occupational wage per effective allele count, which are approximated as: $\sigma_Y Z[2N(MAF)(1 - MAF)]^{-0.5}$, where $N = 282{,}963$ is the sample size, MAF is a effectallele frequency, and $\sigma_Y = 0.351$ is the standard deviation measured from the pooled sample of men and women of the UKB. Similarly, R^2, the variance explained by the SNP alone, is approximated as Z^2/N.

Table S5.7 Associations between polygenic indices for income and self-reported wages in the Health and Retirement Study and the Wisconsin Longitudinal Study

	Male				Female				Male + Female			
Panel A: Health and Retirement Study												
Income PGI		0.083***		0.047**		0.078***		0.043**		0.080***		0.045***
		(0.014)		(0.017)		(0.011)		(0.014)		(0.009)		(0.011)
EA PGI			0.093***	0.065***			0.089***	0.065***			0.091***	0.065***
			(0.013)	(0.017)			(0.011)	(0.014)			(0.009)	(0.011)
R² (%)	2.201	3.192	3.368	3.585	4.152	5.086	5.304	5.509	8.625	9.531	9.720	9.919
ΔR² (%)		0.991	1.167	1.384		0.934	1.152	1.358		0.905	1.095	1.294
partial R² (%)		1.013	1.194	1.415		0.975	1.202	1.416		0.991	1.198	1.416
Obs.	9183				13064				22247			
Panel B: Wisconsin Longitudinal Study												
Income PGI		0.048***		0.024		0.068***		0.048***		0.058***		0.036***
		(0.012)		(0.014)		(0.011)		(0.014)		(0.008)		(0.010)
EA PGI			0.060***	0.047***			0.063***	0.035**			0.061***	0.041***
			(0.012)	(0.014)			(0.011)	(0.014)			(0.008)	(0.010)
R² (%)	2.082	2.560	2.785	2.873	1.915	2.859	2.704	3.035	19.172	19.743	19.787	19.943
ΔR² (%)		0.478	0.702	0.791		0.944	0.789	1.120		0.571	0.615	0.771
partial R² (%)		0.488	0.717	0.807		0.963	0.804	1.142		0.706	0.761	0.954
Obs.	3650				3737				7387			

Note: * $p<0.05$, ** $p<0.01$, *** $p<0.001$; The table reports the coefficient estimates for the PGI for income, derived from the GWAS in the UKB. Panel A reports the results for the HRS and Panel B for the WLS. Repeated individual observations are pooled in the HRS (N=6,171). The results are reported for male, female, and pooled samples. In each case, the first column is the result from the baseline model. The baseline model is a regression of the log hourly wage on the covariates, which include age (with square and cube), dummy variables for male in the pooled analyses, year of observation, part-time worker (HRS only), genotyping batches (HRS only), the first 20 genetic principal components, as well as an interaction terms between the male dummy and the rest of covariates for the pooled samples. ΔR^2 measures the increase in R^2 compared to the baseline. The partial R^2 measures the variance explained by the PGI when partialling out the control variables from both the log hourly wage and the PGI. The R^2 figures are reported in %. Standard errors are clustered by family (WLS) or by individuals (HRS) and reported in parentheses.

Table S5.8 Associations between polygenic indices for income and 3-year moving averages of self-reported wages in the Health and Retirement Study

	Male				Female				Male+Female			
Income PGI		0.078***		0.046*		0.071***		0.035*		0.074***		0.039**
		(0.016)		(0.020)		(0.013)		(0.015)		(0.010)		(0.012)
EA PGI			0.088***	0.061**			0.087***	0.067***			0.087***	0.065***
			(0.015)	(0.020)			(0.013)	(0.016)			(0.010)	(0.012)
R² (%)	4.087	5.675	5.900	6.263	5.981	7.409	7.992	8.243	13.476	14.834	15.239	15.506
ΔR² (%)		1.588	1.813	2.176		1.427	2.010	2.262		1.358	1.763	2.030
partial *R² (%)*		1.655	1.89	2.269		1.518	2.138	2.406		1.57	2.038	2.346
Obs.	4,144				6,768				10,912			

Note: * p<0.05, ** p<0.01, *** p<0.001; The table reports the coefficient estimates for the PGI for income, derived from the GWAS in the UKB. Repeated individual observations are averaged in the HRS (N=4,021). The results are reported for male, female, and pooled samples. In each case, the first column is the result from the baseline model. The baseline model is a regression of the log hourly wage on the covariates, which include age (with square and cube), dummy variables for male in the pooled analyses, year of observation, part-time worker, and genotyping batches, the first 20 genetic principal components, as well as an interaction terms between the male dummy and the rest of covariates for the pooled samples. ΔR^2 measures the increase in R^2 compared to the baseline. The partial R^2 measures the variance explained by the PGI when partialling out the control variables from both the log hourly wage and the PGI. The R^2 figures are reported in %. Standard errors are clustered by individuals and reported in parentheses.

Table S5.9 Comparison of predictive power of polygenic indices in UK Biobank sibling sample.

	Income PGI ΔR^2	MTAG PGI ΔR^2	N
Log occupational wage per hour	2.77%	4.47%	17,690
Years of education	4.18%	7.26%	35,128
BMI	0.66%	1.40%	35,428

Note: The table reports the change in R^2 when a polygenic index is added to the model. As covariates, all analyses include dummy variables for the year of birth, male, and being the younger sibling as well as the first 20 genetic PCs. For occupational wages, we use age dummies instead of the year of birth and add dummies for the year of survey. For BMI ratios we also control for the age dummies instead but not for the year of survey. In every case, we also include the interaction terms between the male dummy and the rest of covariates.

Table S5.10 Estimates of 3-year moving-average income with respect to schooling and genetic factors in the Health and Retirement Study

	no PGI				naive control				GIV-C				GIV-U			
Panel A: Male+Female																
Educ	0.1107***	0.1055***	0.0920***	0.0857***	0.1076***	0.1026***	0.0900***	0.0840***	0.1048***	0.0997***	0.0890***	0.0826***	0.1040***	0.0992***	0.0880***	0.0821***
	(0.008)	(0.008)	(0.012)	(0.012)	(0.008)	(0.008)	(0.012)	(0.012)	(0.009)	(0.009)	(0.013)	(0.013)	(0.009)	(0.009)	(0.012)	(0.013)
Educ × College			0.0615	0.0603			0.0594	0.0584			0.0582	0.0571			0.0548	0.0541
			(0.034)	(0.034)			(0.034)	(0.034)			(0.035)	(0.035)			(0.034)	(0.034)
Income PGI					0.0284**	0.0272**	0.0272**	0.0258**	0.1224*	0.1138*	0.1184*	0.1092*	0.0663*	0.0623*	0.0641*	0.0598*
					(0.009)	(0.009)	(0.009)	(0.009)	(0.056)	(0.055)	(0.056)	(0.054)	(0.030)	(0.029)	(0.029)	(0.029)
Parental Educ		Y		Y		Y		Y		Y		Y		Y		Y
R^2	0.299	0.301	0.301	0.303	0.301	0.303	0.303	0.305								
Obs.	9906	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Panel B: Male																
Educ	0.0880***	0.0813***	0.0437**	0.0378*	0.0859***	0.0795***	0.0434**	0.0376*	0.0821***	0.0763***	0.0483**	0.0427**	0.0805***	0.0743***	0.0437**	0.0380*
	(0.013)	(0.013)	(0.016)	(0.016)	(0.013)	(0.013)	(0.016)	(0.016)	(0.014)	(0.014)	(0.016)	(0.016)	(0.013)	(0.014)	(0.016)	(0.016)
Educ × College			0.0353	0.0343			0.0337	0.0329			0.0400	0.0390			0.0247	0.0240
			(0.050)	(0.050)			(0.050)	(0.050)			(0.053)	(0.053)			(0.051)	(0.051)
Income PGI					0.0261	0.0246	0.0208	0.0194	0.1986*	0.1934	0.1814	0.1758	0.1057*	0.1035*	0.0954	0.0930
					(0.016)	(0.015)	(0.015)	(0.015)	(0.100)	(0.100)	(0.102)	(0.101)	(0.051)	(0.051)	(0.052)	(0.052)
Parental Educ		Y		Y		Y		Y		Y		Y		Y		Y
R^2	0.194	0.198	0.203	0.207	0.196	0.199	0.204	0.208								
Obs.	3784	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Panel C: Female																
Educ	0.1248***	0.1205***	0.1208***	0.1152***	0.1211***	0.1171***	0.1176***	0.1124***	0.1201***	0.1160***	0.1166***	0.1110***	0.1197***	0.1159***	0.1167***	0.1115***
	(0.011)	(0.011)	(0.017)	(0.018)	(0.011)	(0.011)	(0.017)	(0.018)	(0.012)	(0.012)	(0.019)	(0.019)	(0.012)	(0.012)	(0.018)	(0.019)
Educ × College			0.0911	0.0893			0.0887	0.0871			0.0847	0.0835			0.0866	0.0854
			(0.046)	(0.046)			(0.046)	(0.046)			(0.046)	(0.046)			(0.046)	(0.046)
Income PGI					0.0290*	0.0278*	0.0285*	0.0274*	0.0786	0.0691	0.0752	0.0659	0.0430	0.0383	0.0410	0.0364
					(0.012)	(0.012)	(0.012)	(0.012)	(0.066)	(0.065)	(0.067)	(0.065)	(0.036)	(0.035)	(0.036)	(0.035)
Parental Educ		Y		Y		Y		Y		Y		Y		Y		Y
R^2	0.249	0.251	0.251	0.253	0.252	0.254	0.253	0.255								
Obs.	6122	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Note: * p<0.05, ** p<0.01, *** p<0.001; regressions of log hourly wage on years of schooling, the income PGI, and baseline covariates. The sample is restricted to those aged between 30 and 64. As baseline covariates, we include experience (age – years of schooling – 6), experience^2, year of observation, birth cohorts, and genotyping batches, and 20 genetic principal components. The pooled *Male+Female* estimates also include a dummy variable for male, as well as interaction terms between the male dummy and all other covariates. The first column reports the result with the baseline covariates while the other columns report the baseline model with the PGI added using different approaches. In the parentheses, we report standard errors clustered by individuals.

Table S5.11 Average wages of major occupation groups in the UK (listed in order of highest wages)

Major occupation group	Weekly wage averaged over 2006-2010 (£)
1. Managers and Senior Officials	807.74
2. Professional Occupations	688.72
3. Associate Professional and Technical Occupations	526.3
5. Skilled Trades Occupations	451.32
8. Process, Plant and Machine Operatives	412.68
4. Administrative and Secretarial Occupations	322.38
6. Personal Service Occupations	246.9
9. Elementary Occupations	232.38
7. Sales and Customer Service Occupations	202.32

Source: The Annual Survey of Hours and Earnings

Table S5.12 Associations of polygenic index for income (without MTAG) in UK Biobank sibling pairs

			Conditional on education	
	OLS	OLS-FE	OLS	OLS-FE
Socioeconomic outcomes				
log hourly wage	0.0581***	0.0325***	0.0158***	0.0161
(*N*= 17,692 | 17,578)	(0.003)	(0.006)	(0.002)	(0.006)
top household income	0.0459***	0.0280**	0.0167***	0.0181
(*N*= 27,412 | 27,296)	(0.003)	(0.007)	(0.003)	(0.007)
log regional income	0.0315***	0.0143***	0.0143***	0.0112*
(*N*= 31,692 | 31,266)	(0.001)	(0.003)	(0.001)	(0.003)
neighborhood score	1.1489***	0.7167**	0.3561***	0.5556
(*N*= 29,166 | 28,778)	(0.088)	(0.196)	(0.088)	(0.198)
years of education	1.0508***	0.5683***		
(*N*= 35,132 | NA)	(0.027)	(0.065)		
college degree	0.0986***	0.0500***		
(*N*= 35,132 | NA)	(0.002)	(0.006)		
health proxies				
waist-to-hip ratio	-0.0051***	-0.0029	-0.0028***	-0.0022
(*N*= 35,498 | 35,028)	(0.000)	(0.001)	(0.000)	(0.001)
BMI	-0.3844***	-0.1559	-0.2051***	-0.1132
(*N*= 35,432 | 34,968)	(0.027)	(0.062)	(0.027)	(0.062)
blood pressure	-0.6487***	-0.2545	-0.4445***	-0.1968
(*N*= 31,770 | 31,372)	(0.078)	(0.200)	(0.081)	(0.203)
lung function	0.0453***	0.0044	0.0168**	-0.0032
(*N*= 30,240 | 29,844)	(0.005)	(0.012)	(0.005)	(0.012)

Table S5.12 Associations of polygenic index for income (without MTAG) in UK Biobank sibling pairs

			Conditional on education	
	OLS	OLS-FE	OLS	OLS-FE
disease diagnoses				
ever hospitalized	-0.0141***	-0.0066	-0.0072**	-0.0053
(*N*= 35,602 | 35,132)	(0.002)	(0.006)	(0.002)	(0.006)
ever diagnosed with cancer	0.0001	0.0028	-0.0002	0.0017
(*N*= 35,602 | 35,132)	(0.002)	(0.006)	(0.002)	(0.006)
infectious and parasitic diseases	-0.0088***	0.0007	-0.0045	0.0012
(*N*= 35,602 | 35,132)	(0.002)	(0.005)	(0.002)	(0.005)
neoplasms	0.0004	0.0024	-0.0004	0.0014
(*N*= 35,602 | 35,132)	(0.002)	(0.006)	(0.002)	(0.006)
diseases of blood organs and immune system	-0.0088***	-0.0007	-0.0039	0.0004
(*N*= 35,602 | 35,132)	(0.002)	(0.006)	(0.002)	(0.006)
endocrine, nutritional, and metabolic diseases	-0.0152***	-0.0032	-0.0048	-0.0008
(*N*= 35,602 | 35,132)	(0.002)	(0.006)	(0.002)	(0.006)
mental, behavioral, nervous system disorders	-0.0189***	-0.0042	-0.0105***	-0.0023
(*N*= 35,602 | 35,132)	(0.002)	(0.006)	(0.002)	(0.006)
diseases of the eye and adnexa	-0.0059**	-0.0031	-0.0036	-0.0022
(*N*= 35,602 | 35,132)	(0.002)	(0.005)	(0.002)	(0.005)
diseases of the circulatory system	-0.0264***	-0.0128	-0.0149***	-0.0105
(*N*= 35,602 | 35,132)	(0.002)	(0.007)	(0.003)	(0.007)
diseases of the respiratory system	-0.0173***	-0.0075	-0.0109***	-0.0057
(*N*= 35,602 | 35,132)	(0.002)	(0.006)	(0.002)	(0.006)

Table S5.12 Associations of polygenic index for income (without MTAG) in UK Biobank sibling pairs

			Conditional on education	
	OLS	OLS-FE	OLS	OLS-FE
diseases of the digestive system	-0.0246***	-0.0076	-0.0133***	-0.0053
(*N*= 35,602 | 35,132)	(0.003)	(0.007)	(0.003)	(0.007)
diseases of the skin and subcutaneous tissue	-0.0047*	-0.0014	-0.0011	0.0000
(*N*= 35,602 | 35,132)	(0.002)	(0.005)	(0.002)	(0.005)
diseases of musculoskeletal system and connective tissue	-0.0237***	-0.0096	-0.0136***	-0.0070
(*N*= 35,602 | 35,132)	(0.002)	(0.007)	(0.003)	(0.007)
diseases of genitourinary system	-0.0162***	-0.0036	-0.0080*	-0.0017
(*N*= 35,602 | 35,132)	(0.002)	(0.007)	(0.002)	(0.007)
symptoms and signs not elsewhere classified	-0.0252***	-0.0116	-0.0151***	-0.0107
(*N*= 35,602 | 35,132)	(0.003)	(0.007)	(0.003)	(0.007)
injury, poisoning, and other consequences of external causes	-0.0073**	-0.0027	-0.0042	-0.0028
(*N*= 35,602 | 35,132)	(0.002)	(0.006)	(0.002)	(0.006)
external causes of morbidity and mortality	-0.0082***	-0.0031	-0.0044	-0.0032
(*N*= 35,602 | 35,132)	(0.002)	(0.006)	(0.002)	(0.006)
other health conditions	-0.0222***	-0.0145	-0.0126***	-0.0129
(*N*= 35,602 | 35,132)	(0.003)	(0.008)	(0.003)	(0.008)

Note: Significance at family-wise error rate 5% (*), 1% (**), 0.1% (***), where multiple hypothesis testing is corrected using Holm's method (Holm, 1979) for each set of analysis. Standard errors clustered by family are reported in parentheses. The table reports the coefficient estimates for the standardized PGI for income (non-augmented). For each outcome, the sample is restricted to sibling pairs for both of whom the outcome is observed. FE indicates the models with family fixed effects included. The second column set reports the results where education is controlled for by including dummies for each qualification. As covariates we include dummy variables for the year of birth, male, and being a younger sibling as well as the top 20 genetic PCs. For the economic outcomes we control for the age dummies instead of the year of birth and add dummies for the year of survey. For BMI and waist-to-hip ratio we also control for the age dummies instead but not for the year of survey. In every case we also include the interaction terms between the male dummy and the rest of covariates.

Table S5.13 Associations of polygenic index for educational attainment in UK Biobank sibling pairs

			Conditional on education	
	OLS	OLS-FE	OLS	OLS-FE
Socioeconomic outcomes				
log hourly wage	0.0717***	0.0443***	0.0174***	0.0235**
(*N* = 17,692 | 17,578)	(0.002)	(0.007)	(0.002)	(0.006)
top household income	0.0547***	0.0339***	0.0171***	0.0203*
(*N* = 27,412 | 27,296)	(0.003)	(0.007)	(0.003)	(0.007)
log regional income	0.0397***	0.0132**	0.0185***	0.0093*
(*N* = 31,692 | 31,266)	(0.001)	(0.003)	(0.002)	(0.003)
neighborhood score	1.5003***	0.5229	0.5085***	0.3163
(*N* = 29,166 | 28,778)	(0.088)	(0.200)	(0.091)	(0.203)
years of education	1.3486***	0.7235***		
(*N* = 35,132 | NA)	(0.026)	(0.066)		
college degree	0.1281***	0.0662***		
(*N* = 35,132 | NA)	(0.002)	(0.006)		
health proxies				
waist-to-hip ratio	-0.0063***	-0.0038**	-0.0033***	-0.0029*
(*N* = 35,498 | 35,028)	(0.000)	(0.001)	(0.000)	(0.001)
BMI	-0.5545***	-0.2903***	-0.3452***	-0.2425**
(*N* = 35,432 | 34,968)	(0.027)	(0.063)	(0.028)	(0.064)
blood pressure	-0.8190***	-0.6570*	-0.5865***	-0.5989*
(*N* = 31,770 | 31,372)	(0.078)	(0.208)	(0.083)	(0.212)
lung function	0.0521***	0.0192	0.0156**	0.0102
(*N* = 30,240 | 29,844)	(0.005)	(0.013)	(0.005)	(0.013)
disease diagnoses				
ever hospitalized	-0.0206***	-0.0112	-0.0129***	-0.0102

Table S5.13 Associations of polygenic index for educational attainment in UK Biobank sibling pairs

			Conditional on education	
	OLS	OLS-FE	OLS	OLS-FE
(*N*= 35,602 | 35,132)	(0.002)	(0.006)	(0.002)	(0.006)
ever diagnosed with cancer	-0.0007	-0.0004	-0.0009**	-0.0011
(*N*= 35,602 | 35,132)	(0.002)	(0.006)	(0.002)	(0.006)
infectious and parasitic diseases	-0.0125***	-0.0067	-0.0068***	-0.0057
(*N*= 35,602 | 35,132)	(0.002)	(0.005)	(0.002)	(0.005)
neoplasms	0.0006	-0.0001	-0.0004	-0.0006
(*N*= 35,602 | 35,132)	(0.002)	(0.006)	(0.002)	(0.006)
diseases of blood organs and immune system	-0.0118***	0.0001	-0.0062**	0.0008
(*N*= 35,602 | 35,132)	(0.002)	(0.007)	(0.002)	(0.007)
endocrine, nutritional, and metabolic diseases	-0.0270***	-0.0136	-0.0152***	-0.0114
(*N*= 35,602 | 35,132)	(0.002)	(0.006)	(0.002)	(0.006)
mental, behavioral, nervous system disorders	-0.0275***	-0.0084	-0.0174***	-0.0055
(*N*= 35,602 | 35,132)	(0.002)	(0.006)	(0.002)	(0.006)
diseases of the eye and adnexa	-0.0060**	-0.0062	-0.0031**	-0.0053
(*N*= 35,602 | 35,132)	(0.002)	(0.005)	(0.002)	(0.005)
diseases of the circulatory system	-0.0348***	-0.0119	-0.0211***	-0.0098
(*N*= 35,602 | 35,132)	(0.003)	(0.007)	(0.003)	(0.007)
diseases of the respiratory system	-0.0209***	-0.0079	-0.0131***	-0.0062
(*N*= 35,602 | 35,132)	(0.002)	(0.006)	(0.002)	(0.006)
diseases of the digestive system	-0.0335***	-0.0143	-0.0202***	-0.0118
(*N*= 35,602 | 35,132)	(0.003)	(0.008)	(0.003)	(0.008)
diseases of the skin and subcutaneous tissue	-0.0082***	-0.0040	-0.0048**	-0.0024

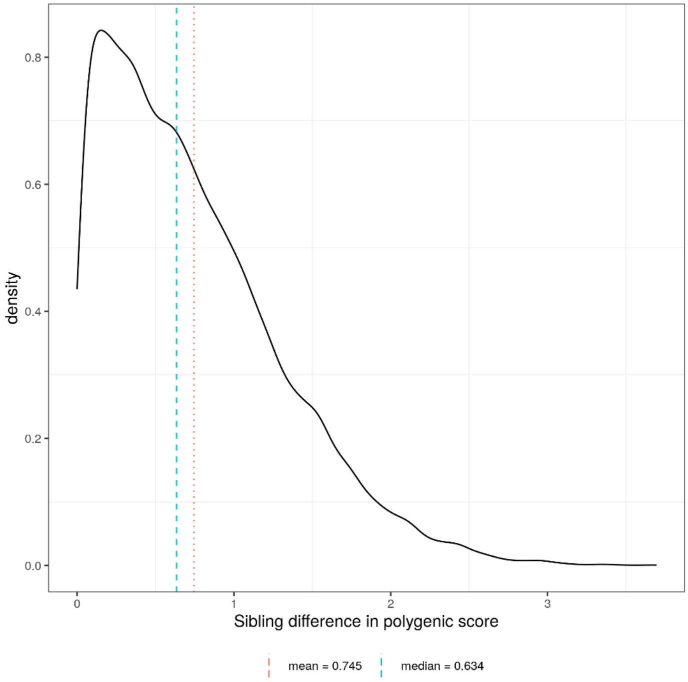
Table S5.13 Associations of polygenic index for educational attainment in UK Biobank sibling pairs

			Conditional on education	
	OLS	**OLS-FE**	**OLS**	**OLS-FE**
(*N*= 35,602 | 35,132)	(0.002)	(0.005)	(0.002)	(0.005)
diseases of musculoskeletal system and connective tissue	-0.0354***	-0.0256**	-0.0241***	-0.0229*
(*N*= 35,602 | 35,132)	(0.002)	(0.007)	(0.003)	(0.007)
diseases of genitourinary system	-0.0220***	-0.0111	-0.0128***	-0.0099
(*N*= 35,602 | 35,132)	(0.002)	(0.007)	(0.003)	(0.007)
symptoms and signs not elsewhere classified	-0.0317***	-0.0136	-0.0200***	-0.0127
(*N*= 35,602 | 35,132)	(0.003)	(0.008)	(0.003)	(0.008)
injury, poisoning, and other consequences of external causes	-0.0088***	-0.0035	-0.0051**	-0.0023
(*N*= 35,602 | 35,132)	(0.002)	(0.006)	(0.002)	(0.006)
external causes of morbidity and mortality	-0.0106***	-0.0038	-0.0061**	-0.0028
(*N*= 35,602 | 35,132)	(0.002)	(0.006)	(0.002)	(0.006)
other health conditions	-0.0325***	-0.0243*	-0.0219***	-0.0224*
(*N*= 35,602 | 35,132)	(0.003)	(0.008)	(0.003)	(0.008)

Note: Significance at family-wise error rate 5% (*), 1% (**), 0.1% (***), where multiple hypothesis testing is corrected using Holm's method (Holm, 1979) for each set of analysis. Standard errors clustered by family are reported in parentheses. The table reports the coefficient estimates for the standardized PGI for educational attainment. For each outcome, the sample is restricted to sibling pairs for both of whom the outcome is observed. FE indicates the models with family fixed effects included. The second column set reports the results where education is controlled for by including dummies for each qualification. As covariates we include dummy variables for the year of birth, male, and being a younger sibling as well as the top 20 genetic PCs. For the economic outcomes we control for the age dummies instead of the year of birth and add dummies for the year of survey. For BMI and waist-to-hip ratio we also control for the age dummies instead but not for the year of survey. In every case we also include the interaction terms between the male dummy and the rest of covariates.

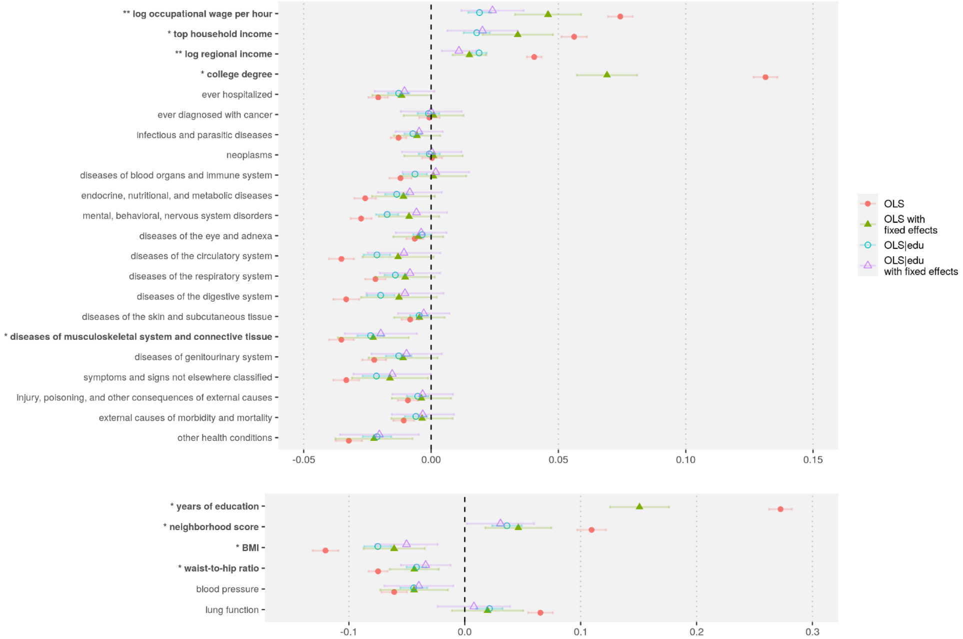
S5.8 Figures

Figure S5.1 Distribution of the differences in MTAG polygenic indices (PGI) for income between siblings in the UK Biobank



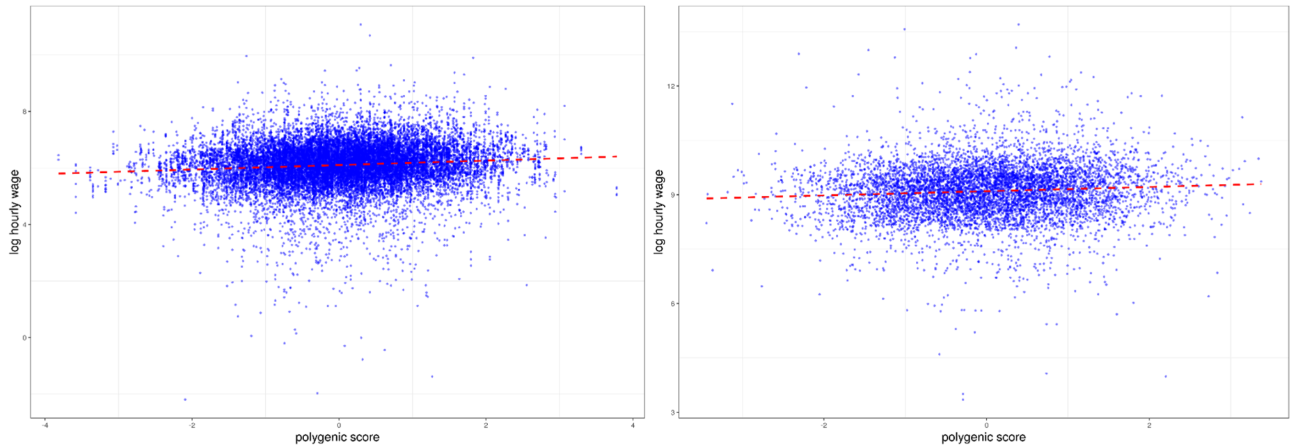
Note: The figure plots the density distribution of the absolute difference in the standardized PGI between siblings with Gaussian kernel.

Figure S5.1 Associations of MTAG polygenic index (PGI) for income in UK Biobank sibling pairs (OLS)



Note: The figure plots the regression coefficients for the standardized MTAG income PGI estimated by OLS with or without education controlled for. Error bars are 95% confidence intervals. The upper panel shows the estimates measured on percentage scale. The lower panel plots the standardized estimates (i.e., the outcomes and the PGI are both standardized). One asterisk indicates significance at the 5% family-wise error rate for the estimate with family fixed effects while two asterisks indicate the significance conditional on education. Multiple testing is corrected for using Holm's method (Holm, 1979). See Table 5 and 6 for more details.

Figure S5.3 Scatter plots of log hourly wages and polygenic indices for income

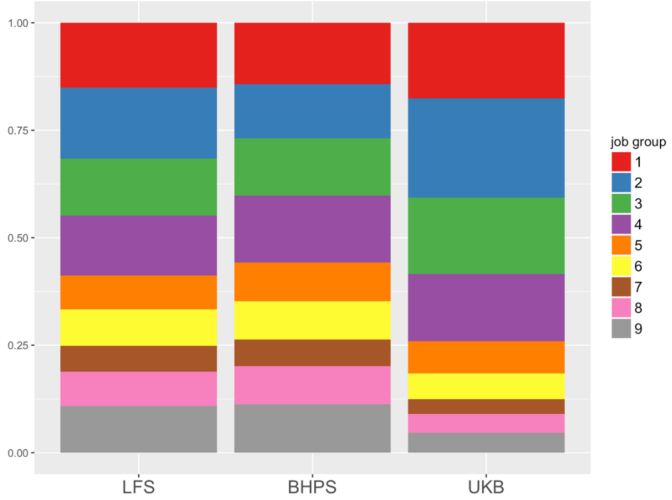


a. HRS

b. WLS

Note: The left figure presents a scatter plot for the sample from the Health and Retirement Study (*N*=22,247), while the right for the sample from the Wisconsin Longitudinal Study (*N*=7,387). The dotted lines are regression lines.

Figure S5.2 The composition of major occupation groups in the UK



Note: see Table for the major occupation group reference.

Figure S5.5 Scatter plots of imputed and observed log-wages in the BHPS (*N*=32,947)

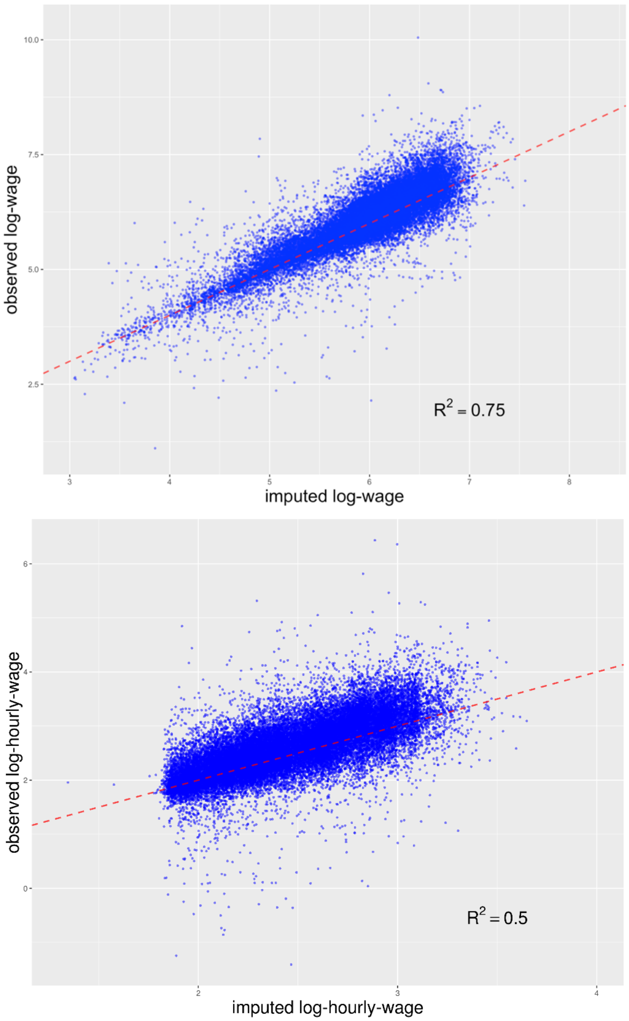
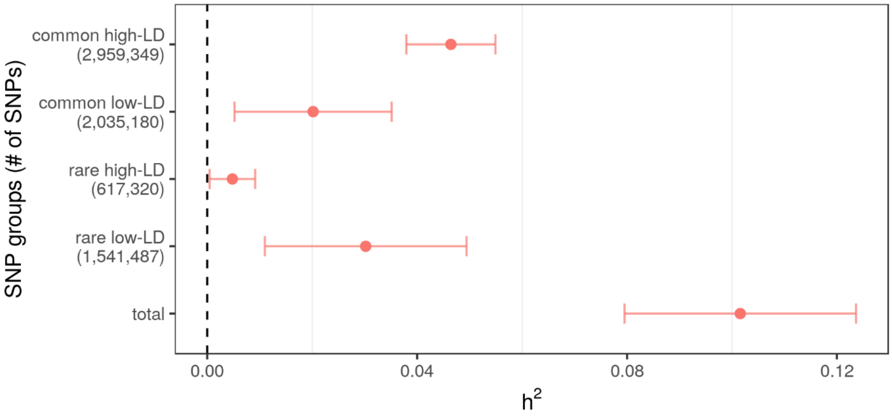
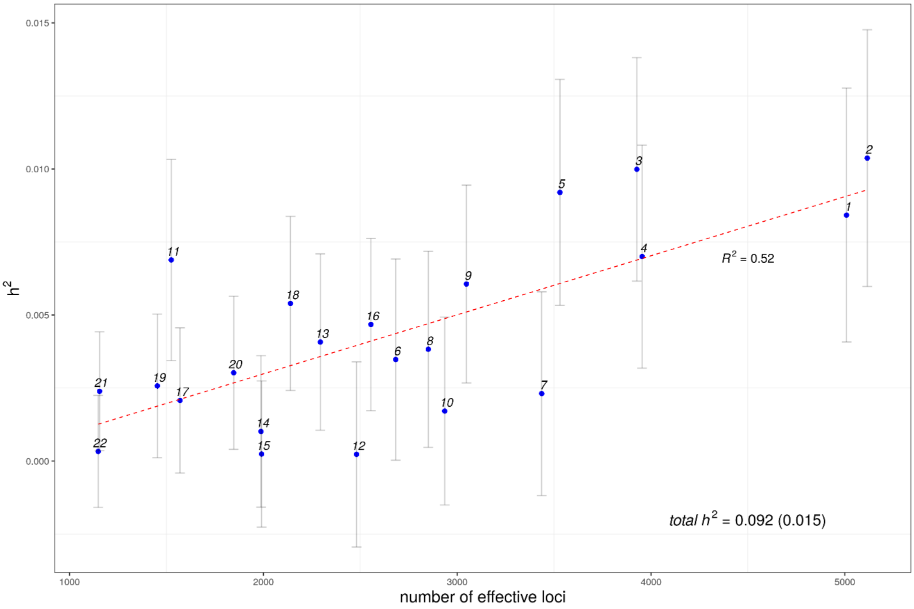


Figure S5.6 Decomposition of the total heritability of occupational wages by different groups of single nucleotide polymorphisms (SNPs)



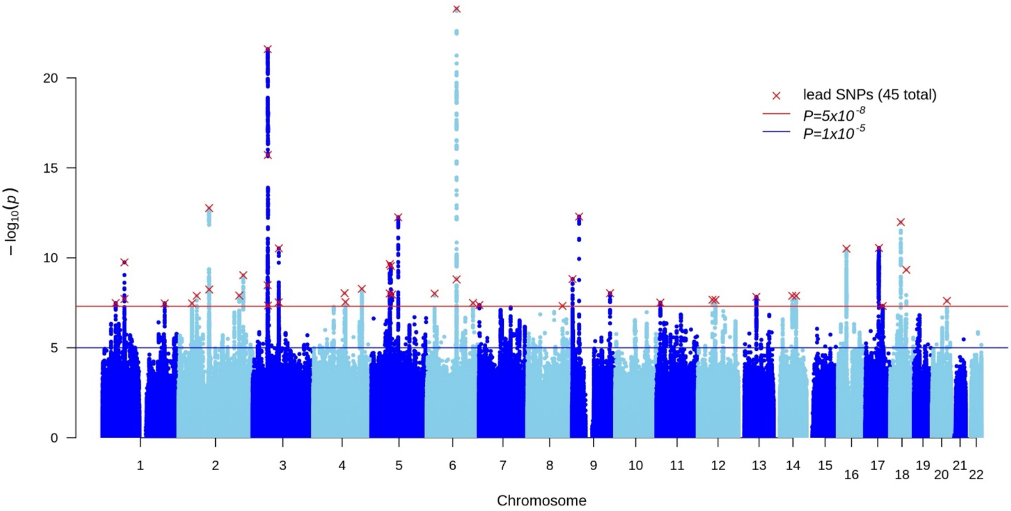
Note: GREML estimation in 24,000 unrelated individuals from the UK Biobank. Error bars are standard errors. SNPs are sorted into four groups by different genetic features. LD - linkage disequilibrium scores.

Figure S5.7 Decomposition of the total heritability of occupational wages by chromosomes



Note: GREML estimation in 24,000 unrelated individuals from the UK Biobank. Error bars are standard errors from GREML estimation. The standardized coefficient of a regression of chromosomal h^2_{SNP} on the effective number of loci per chromosome is 0.72 (95% *CI*: 0.41 - 1.02).

Figure S5.8 Manhattan plot for a genome-wide association study (GWAS) of occupational wages in the UK Biobank



Note: The GWAS is run on 282,963 individuals from the UK Biobank. The p-values are plotted on the -log_{10} scale on the vertical axis. Chromosomal positions of each of 9,773,981 single nucleotide polymorphisms (SNPs) are plotted on the horizontal axis.

Chapter 6

Disparities in socio-economic status and BMI in the UK are partly due to genetic and environmental luck

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Abstract

Two family-specific lotteries take place during conception— a social lottery that determines who our parents are and which environment we grow up in, and a genetic lottery that determines which part of their genomes our parents pass on to us. The outcomes of these lotteries create inequalities of opportunity that can translate into disparities in health and socioeconomic status. Here, we estimate a lower bound for the relevance of these two lotteries for differences in education, income and body mass index in a sample of 38,698 siblings in the UK who were born between 1937 and 1970. Our estimates are based on models that combine family-specific effects with gene-by-environment interactions. We find that the random differences between siblings in their genetic endowments clearly contribute towards inequalities in the outcomes we study. Our rough proxy of the environment people grew up in, which we derived from their place of birth, are also predictive of the studied outcomes, but not beyond the relevance of family environment. Our estimates suggest that at least 13 to 17 percent of the inequalities in education, wages and BMI in the UK are due to inequalities in opportunity that arise from the outcomes of the social and the genetic lottery.

6.1 Introduction

It has long been recognized that parent's health and socio-economic status (SES) are strong predictors for their children's health, educational attainment and income later in life. Furthermore, health, educational attainment, and income are all heritable to some degree (Benjamin et al., 2012; de Vlaming et al., 2017; Polderman et al., 2015; Taubman, 1976). Thus, parents do not only influence their children via the rearing environment they provide for them, but also by the random combination of the genes they pass on to their offspring. This creates two major sources of differences in opportunities at conception in the form of exogenously determined environmental and genetic endowments. Disparities in important life outcomes that arise from differences in opportunity are often viewed as unfair and less desirable than inequality that is created by active choices and agency (e.g. due to hard work). This may have policy implications because people tend to favour redistribution policies more when inequalities in opportunity and luck are major drivers of inequality (Alesina & La Ferrara, 2005; Alesina, Stantcheva, & Teso, 2018; Almås, Cappelen, Sørensen, & Tungodden, 2010; Cappelen, Konow, Sørensen, & Tungodden, 2013; Clark & D'Ambrosio, 2015; Gromet, Hartson, & Sherman, 2015). Thus, studying the relative importance of inequalities of opportunity for important life outcomes is of fundamental importance to discussions about fairness and policy.

Genetic factors that are linked to socio-economic status are a reflection of social realities. For example, societies that value high cognitive performance in schools and labour markets will tend to exhibit that genetic factors that are linked with cognitive health are also related to socio-economic outcomes such as educational attainment or income. Thus, genes do not operate in a vacuum – their effects are partially contingent on environmental factors. Furthermore, specific environments and genes may also interact with each other (Barcellos, Carvalho, & Turley, 2018, 2020; Schmitz & Conley, 2017a, 2017b), potentially further exacerbating the importance of the genetic and the social lottery as a source of inequality.

Recent advances in genetics have made it possible to measure genetic differences between people comprehensively, providing researchers with new opportunities to study the potential relevance of genetic luck and to investigate how exogenously given genetic and environmental endowments can interact to cause inequalities (Harden & Koellinger, 2020). Moreover, increases in sample size have led to publicly available summary statistics from large-scale genome-wide association studies (GWAS) for many outcomes related to SES and health, such as educational attainment (Lee et al., 2018), household income (Hill et al., 2019), occupational wages (Kweon et al., 2020), body fat percentage (Lu et al., 2016), and body mass index (BMI) (Locke et al., 2015). The estimated effects of these GWAS can be summarized in linear indices that are called polygenic indices (PGI[a]) (Daetwyler, Villanueva, & Woolliams, 2008; Dudbridge, 2013). Although PGI capture only a part of the heritability of a trait because they are measured with error (Daetwyler et al., 2008; DiPrete, Burik, & Koellinger, 2018; Dudbridge, 2013), they nevertheless provide a valuable new tool to analyse genetic contributions to inequality and to study potential interactions between genetic endowments and specific environmental conditions (Barcellos et al., 2018; Harden & Koellinger, 2020).

The goal of this study is to estimate a lower bound for the relevance of environmental and genetic luck and their interactions for important life outcomes. We employ data from the UK Biobank, which is currently the largest publicly available sample of genotyped siblings in the world (38,698 individuals). Genetic differences between biological siblings are due to the natural experiment of meiosis. During

[a] Here we follow the recent change proposed in Becker et al., (2021) from polygenic (risk) score to polygenic index to make it less likely to be wrongly interpreted as a value judgement.

meiosis, the two copies of each parental chromosome are randomly combined and then separated to create a set of two gametes (e.g., two eggs or two sperm), each of which contains only one new, resampled copy of each chromosome. The resulting genetic differences between full siblings are therefore random and independent from family-specific ancestry and environmental factors that vary between families.

Our choice of outcome variables was specified in a pre-registered analysis plan[b] and driven by considerations about data availability and statistical power. In the socioeconomic domain, we focus on educational attainment (EA) and hourly wages. Both are key components of socio-economic status, and both are linked to happiness (Boyce, Brown, & Moore, 2010; Frijters, Haisken-DeNew, & Shields, 2004), health, and longevity (Adler & Rehkopf, 2008; Stringhini et al., 2017; Wilkinson & Marmot, 2003). In the health domain, we focus on BMI as a proxy for morbidity that is also linked to mortality (Mokdad et al., 2003) and many other health outcomes. Importantly, for all three outcomes, large-scale GWAS results are available that allow constructing PGI that capture a substantial part of the heritability of these traits (Kweon et al., 2020; Lee et al., 2018; Locke et al., 2015).

We extracted measures of potentially relevant environmental factors during early childhood from available information about place of birth. Chetty and Hendren (2018a, 2018b) show childhood neighbourhood affects later-life outcomes like educational attainment and income. Amongst other factors, they find that school quality has a positive effect. Furthermore, neighbourhood SES has been shown to be related to infant health and infant mortality rate in the UK (Weightman et al., 2012). In this study, we used the local average school leaving age and the district mortality rate at the place of birth as measures of childhood environment.

Importantly, our genetic and environmental variables only capture a part of the ways in which the outcomes of the genetic and the social lottery may influence outcomes later in life, and all our variables are subject to substantial measurement error, which attenuates the estimated effects of these two lotteries towards zero. Thus, our study estimates a conservative lower bound for the potential relevance of these two sources of luck on lifetime outcomes.

In addition to the linear effects of PGI and childhood environments, we also investigate potential interaction effects between them. Numerous studies have begun identifying relevant gene-by-

[b] Our pre-registered analysis plan can be accessed here: https://osf.io/wf56h/

environment interactions both on SES and health outcomes. One example of a study on inequality and gene-by-environment interaction is Belsky et al. (2018), who study social mobility in several cohorts using a PGI based on GWAS results for educational attainment (EA) from Lee et al. (2018). They find that both parental SES and the genetic endowment of the child contribute to social mobility. In analyses that control for family fixed effects, the sibling with the higher PGI for EA is found to be more likely to have higher SES later in life, suggesting that random genetic differences between siblings contribute towards social mobility. While Belsky et al. also investigate gene-by-environment interactions and conduct analyses within-families, they do not combine the two approaches. This makes their results of the gene-by-environment analyses more difficult to interpret because they may be confounded by unobserved family-specific environments that correlated with genetic endowments (Harden & Koellinger, 2020; Schmitz & Conley, 2017a).

Similar to the study of Belsky et al. (2018), many gene-by-environment studies are difficult to interpret due to sensitivity to confounding from unobserved family-specific environments and population structure that are correlated with both the environmental measure and the underlying genetic factors (Harden & Koellinger, 2020; Schmitz & Conley, 2017a).

One of the solutions proposed in the literature is the use of natural experiments (Schmitz & Conley, 2017a), for instance using policy interventions (Schmitz & Conley, 2017b). Barcellos et al. (2018) take this approach and study the effects of genes and education on health outcomes in the UK Biobank. They make use of a well-known compulsory schooling age reform in the United Kingdom in in 1972 as a quasi-experiment and find that an increase in education can reduce health differences related to genetic risk of obesity. Furthermore, Barcellos et al. (2020) use a similar approach to Barcellos et al. (2018) to investigate the effects of the same schooling reform on education and wages later in life as well as the interaction between birth place effects and PGI. They found that the schooling reform reduced differences in educational attainment across birth places, but benefitting those with high PGI for EA the most. The effect of education on wage was twice as high in the top tercile of the PGI, compared to the bottom and middle terciles. While policy reforms that induce as-good-as-random variation in education are a common method to identify causal effects, the results are often specific to the policy and context that is being studied (Rosenzweig & Wolpin, 2000).

Our study investigates the effects of environmental and genetic luck and their possible interactions for important life outcomes using a novel approach. We combine measures of early childhood environment with random genetic differences between siblings in a within-family design. The random genetic differences between siblings are by definition independent from shared environments that are not captured by our early life exposures of interest, thereby circumventing the endogeneity problem that most gene-environment studies suffer from. Furthermore, we investigate different gene-environment interactions than those investigated in earlier work.

6.2 Materials

6.2.1 Sample

The UK Biobank is a large population-based longitudinal study, designed to study health in middle aged and older UK citizens (Fry et al., 2017; Sudlow et al., 2015). The participants were between 40 and 69 years old when they entered the study between 2006 and 2010. Participants answered a wide array of survey questions about their life and health and various physical measurements and biological samples (saliva, blood and urine) were taken during an assessment centre visit. Almost all participants were genotyped and all participants gave broad consent for research related to health and well-being. We restrict our analyses to individuals of European descent to limit possible confounding due to population structure. Identification of European ancestry was done by the UK Biobank based on principal component analysis with the 1000 Genomes project reference panel (1000 Genomes Project Consortium et al., 2015).

6.2.2 Early Childhood Environment

The UK Biobank does not contain direct measures of early childhood environment that are pertinent to our research question. To obtain proxies of socio-economic environment during childhood, we used birth place coordinates. We matched these coordinates to district-level early-childhood exposures that we obtained from historical data made available by Vision of Britain (Southall, 2011)[c]. Specifically, we use the local average school leaving age and the infant mortality rate at the district level (see Supplementary Information (SI) Section S6.2 for details).

[c] www.visionofbritain.org.uk

6.2.3 Outcomes

Following prior literature, we measured educational attainment in years of schooling (see SI S6.5). To obtain a proxy for individual income, we imputed occupational wages from standardized occupation codes using an algorithm developed by Kweon et al. (2020). The imputed values reflect the logarithm of the typical wage per hour for each occupation, adjusted for demographic characteristics such as sex and age. The imputation algorithm utilizes wage data provided by the UK Office of National Statistics, using the British Household Panel Survey to estimate model parameters and the Labour Force Survey for external validation. This procedure primarily captures wage differences between occupations and captures $R^2 \approx 0.50$ of the total variance of hourly wages. Finally, body mass index (BMI) -- our proxy for health -- is based on physical measures taken in the UK Biobank assessment centre.

6.2.4 Polygenic Indices

We constructed PGI using the results of the largest GWAS publicly available for educational attainment, occupational wages, and BMI, which are Lee et al. (2018), Kweon et al. (2020), and Locke et al. (2015) respectively. Furthermore, we used multi-trait analysis of genome-wide association summary statistics (MTAG; Turley et al., 2018) to increase the accuracy of the PGI by including summary statistics of genetically correlated traits. To account for linkage-disequilibrium, we constructed PGI using LDpred (Vilhjálmsson et al., 2015). SI Section S6.3 provides further detail.

6.3 Methods

First, we mapped the relationships of the outcomes in adulthood with early childhood environment and genetic endowments. We divided the sample into different terciles of the early childhood environment and PGI distributions. We then compared the means of our outcome variables across terciles to visualize how SES and BMI differ based on place of birth and genetic endowments.

We then regressed our outcomes on the PGI, dummy variables for the district terciles, and interaction terms between the two as well as other control variables:

$$y_i = \beta_0 + \beta_1 G_i + \boldsymbol{D_i \beta_2} + (G_i \times \boldsymbol{D_i})\boldsymbol{\beta_3} + \boldsymbol{PC_i \gamma} + \boldsymbol{Z_i \delta} + \epsilon_i \tag{6.1}$$

where y_i is the outcome of individual i (educational attainment, imputed log hourly wage or BMI), G_i is the PGI for the respective outcome, $\boldsymbol{D_i}$ is a vector with two dummy variables for the middle and top terciles of the distribution of our environmental variable (local average school leaving age or local infant mortality rate), $\boldsymbol{PC_i}$ is a vector of principle components of the genetic data to control for population stratification, $\boldsymbol{Z_i}$ is a vector of other control variables (including year of birth, year of birth squared, year of birth cubed, gender, gender interacted with the year of birth variables and genotyping batch), and ϵ_i is the error term. It should be noted that while our primary interest lies in the estimates for β_1, $\boldsymbol{\beta_2}$ and $\boldsymbol{\beta_3}$, the covariates included in $\boldsymbol{Z_i}$ are also the result of luck in the sense that nobody has an influence of their time and place of birth or their biological sex, either. Thus, all of the variance explained by model (6.1) can be attributed to luck defined as exogenously given resources that are outside of one's control.

Next, we re-estimate Equation (6.1) adding family fixed effects. By using family fixed effects, we utilize the random genetic differences between siblings that are by definition independent from shared environments that are not captured by our early life exposures of interest, thereby circumventing endogeneity problems caused by inadequately controlling for unobserved gene-environment correlations. Since our environmental exposures are local-level measures at the birth location, it is plausible that these exposures are not dependent on own genetic effects but only on parental genetic effects and pre-birth family characteristics, which are captured by the family fixed effects. Therefore, these family fixed effects also adjust for potential biases in the estimates of β_1 that result from indirect genetic effects such as genetic nurture (Kong et al., 2018) or any population stratification that is not captured by the principal components of the genetic data.

While the family fixed effects capture many possible biases, it can fail to deliver a within-family estimator for the interaction term, as the interaction term is not guaranteed to be independent of between-family variation (Giesselmann & Schmidt-Catran, 2018, 2020). Therefore, we extend our analyses to control for those sources of between-family variation by adding additional control variables for between-family variation to a random effects model based on Mundlak's work (Mundlak, 1978), extended to account for interaction terms:

$$y_{ij} = \beta_1 G_{ij} + \beta_2 E_{ij} + \beta_3 (G_{ij} \times E_{ij}) + \theta_1 \overline{G}_j + \theta_2 \overline{E}_j + \theta_3 \left(\overline{G}_j \times E_{ij}\right) + \theta_4 \left(G_{ij} \times \overline{E}_j\right) + \boldsymbol{Z}'_{ij} \boldsymbol{\delta_1} \\ + \overline{\boldsymbol{Z}}'_j \boldsymbol{\delta_2} + (u_j + \varepsilon_{ij}) \qquad (6.2)$$

where $\overline{X_j}$ indicates the family-specific mean of the variable X_{ij} and $(u_j + \varepsilon_{ij})$ is the error component, with u_j as the family-level random effect. All other variables are defined as above. Every variable in this regression was mean-centred, so that the estimated coefficients of the model provide the effect size at the means of all variables.

Estimating this model as a random-effects framework gives within-family estimate for β_1 , β_2, and β_3. The key components of this model are $\overline{G_j}$, $\overline{E_j}$, $(\overline{G_j} \times E_{ij})$, and $(G_{ij} \times \overline{E_j})$ which control for the unobserved between-family differences in the PGI, the environment measure, and the gene-environment interaction; thereby yielding within-family estimates for β_1 , β_2, and β_3. The within-family means are designed to capture more dimensions of the between family variation than the family fixed effects model. Therefore, a within-family estimate for the gene-environment interaction of this model will not represent a spurious gene-environment interaction (Giesselmann & Schmidt-Catran, 2018, 2020). While the model accounts for many possible sources of bias by including family specific effects and other control variables, it cannot control for all possible sources of omitted variable bias, especially those due to potential indirect genetic effects from siblings on each other, which may limit the causal interpretation of our estimates. However, indirect genetic effects from siblings would lead to a bias towards zero for the estimated effect of the PGI and the interaction term due to possible spill-over effects from the sibling with the higher PGI to the sibling with the lower PGI, decreasing the within-sibling differences in outcomes. Therefore, if sibling effects are present, our estimates are likely to underestimate the direct genetic effects.

6.4 Results

Figure 6.1 shows the mean educational attainment of the UK Biobank participants, divided into terciles of the distribution of mean local school leaving age in their neighborhood of birth (left panel) and the terciles of the EA PGI distribution (right panel). Participants born in neighborhoods in the top educational attainment terciles have on average 1.7 years more education compared to those in the bottom tercile. Inequality reflected by genetic differences are even larger, with those in the top tercile of the PGI distribution having on average 3.5 years more education than those in the bottom tercile.

Figure 6.2 shows the results for imputed log hourly wages. Participants in the top local schooling terciles have 1.07 pounds per hour higher wages than those in the bottom, and those born with a genetic endowment in the top tercile have 2.49 pounds per hour higher wages than those in the bottom.

Finally, Figure 6.3 shows the results for BMI. Participants in the top local schooling tercile have a mean BMI that is 0.53 lower than those in the bottom. The difference between the top and bottom BMI PGI terciles is 3.58 BMI points. For a person that is 180 cm tall, a difference of 3.58 BMI points would be equivalent to 11.6 kilograms.

SI Figure 6.1 shows the mean educational attainment, hourly wage and BMI by terciles of the infant mortality rate distribution. Those results show a similar pattern where persons born in the top tercile have more favorable outcomes than those in the bottom.

We illustrate the regression results from model (6.1) for EA in Figure 6.4. The panels show the scatterplots of EA and the EA PGI for the bottom, middle, and top terciles of the local school leaving age distribution, after residualizing both axis on control variables. The mean of both EA and the EA PGI vary across environments, an ANOVA mean comparison test shows that they significantly differ from each other ($p \leq 0.0001$). The difference in means show that being born in a district in the top tercile of the local school leaving age distribution is associated with approximately 1.1 years more education compared to being born in the bottom tercile. There is also difference in the effect of the EA PGI on EA between the three local school leaving age terciles, as indicated by a difference in slopes of the regression line. The slope indicates that that a 1 standard deviation (SD) increase in the PGI is associated with an increase in education of approximately 1.4 years in the bottom tercile and 1.51 or 1.74 for the middle or top tercile. The effect of the PGI is stronger for individuals from districts with a higher average school leaving age. Thus, the interaction between the PGI and the district of birth exacerbates the inequalities from each of the two sources of luck. Finally, the mean PGI also varies by the district terciles and its mean is 0.26 higher in the in the top tercile compared to the bottom ($p \leq 0.0001$). Thus, the social and genetic sources of luck that we investigated are positively correlated with each other, which further increases inequalities that arise from them. The results of this regression are also reported in column (1) of Table 6.1. Here, the effects of the EA PGI, the tercile dummies, as well as their interactions are all statistically significant with p-values below 0.05.

Column (2) of Table 6.1 reports regression results including family fixed effects. The family fixed effects absorb a substantial part of the signal from the other variables. The district terciles are designed to capture early childhood environmental effects, but the results show that they are not predictive beyond the family environment. It should be noted that the family-fixed effects may capture most of the variation in the terciles and the variation in the local average school leaving age between siblings is typically small, which decreases power. The coefficient for the PGI remains statistically significant ($p \leq 0.001$), but with a lower coefficient. This is in line with previous findings, and may be attributed to genetic nurture effects (Kong et al., 2018; Lee et al., 2018), which are indirect effects from parental genotypes on the offspring through the environment they provide. Parental genotypes are correlated with the genotypes of their offspring, and may also be correlated to environment they provide for their offspring. This induces an unobserved variable bias in the estimated effect of the PGI when there are no controls for parental genotype or family fixed effects. Another possibility is that the PGI also captures some population stratification (Hamer & Sirota, 2000), which is a term that describes the systematic differences in allele frequencies between subpopulations. This could cause an inflation of the coefficient for the PGI the coefficient before controlling for family-fixed effects, if there are environmental differences between the subpopulations that are correlated with the PGI and the outcome, even though twenty principal components of the genetic data were added as control variables (Price et al., 2006). While these two potential sources of the decrease in PGI are not indicative of luck due to direct genetic effects, both still refer to luck due to exogenously given endowments that our outside of one's control (i.e. parental environment and population effects). Nevertheless, our results indicate that direct genetic luck still plays an important role in educational attainment, even when family fixed effects are controlled for: A one standard deviation increase in the PGI implies an increase of 0.8 years of education.

Figure 6.5 shows the results for imputed log hourly wage and its respective PGI. The regression coefficients are reported in column (3) of Table 6.1. When comparing the bottom to the middle tercile, we see that being born into a middle tercile SES district does not affect hourly wages compared to the bottom tercile. Being born in the top tercile does have an impact on hourly wages and the coefficient in column (3) of Table 6.1 shows that it is associated with 5.0% higher wages. The coefficient for the PGI in column (3) is significant ($p \leq 0.001$) and indicates an increase in wages of approximately 7.2% per SD of the PGI, which is in line with previous findings (Kweon et al., 2020). The relationship between the PGI and mean log hourly wages is identical across terciles, which can be seen from the identical slope of the regression line across terciles in Figure 6.5 and interaction coefficients in column (3). Again, the mean PGI is higher in the highest tercile ($p \leq 0.0001$), indicating a positive correlation between genetic and social luck.

When adding family-fixed effects to the model in column (4), the coefficient of the PGI decreases compared to the model without family-fixed effects, but remains an important predictor of hourly wages. A one standard deviation increase in the PGI is associated with a 5.1% increase in hourly wages. Similar to the effects for EA, the district terciles are not predictive when controlling for family-fixed effects.

The regression results for BMI are visualized in a similar fashion in Figure 6.6. The top tercile of the local school leaving age distribution exhibits a substantially lower average BMI of 0.41 points ($p \leq 0.001$). Furthermore, the BMI PGI is associated with a 1.5 point increase in BMI per standard deviation of the PGI ($p \leq 0.001$). Similar to the results for hourly wages, the relationship between the PGI and BMI does not vary by district tercile.

Comparing the results of column (5) to column (6) in Table 6.1, the coefficient of the BMI PGI barely changes when family fixed-effects are controlled for, which indicates that genetic nurture is less important for BMI than for socio-economic outcomes. This is consistent with the findings reported by Kong et al. (2018) However, controlling for family-fixed effects again absorbs the effects of the local school leaving age on BMI.

We obtained qualitatively similar results when we used the local infant mortality rate terciles as proxies of early childhood environment (SI Table S6.3). One notable difference is that we observe an interaction effect between the BMI PGI and the local infant mortality rate on BMI in adulthood: The BMI PGI is more strongly associated with BMI in districts with low infant mortality rate. This interaction effect remains even after family-fixed effects are controlled for, indicating that the infant mortality rate may capture health-relevant environmental effects that are not captured by the local average schooling leaving age.

Finally, the results of our random effects models (Equation 6.2) are shown in Table 6.2. The estimates for EA, log hourly wage and BMI are shown in columns (1), (2), and (3), respectively. The results are very similar to the models with family fixed effects in Table 6.1. We see that genetic luck, measured by the respective PGI, remains an important factor even after controlling for non-genetic confounds such as population stratification and environmentally mediated indirect genetic effects from parents on their children. Thus, we find that genetic luck in the form of random genetic differences between siblings is an important factor that contributes to inequalities in socio-economic outcomes and BMI. Specifically, a one standard deviation increase in the PGI for EA is associated with a 0.8 year increase in EA. Similarly, a one standard deviation increase in the PGI for hourly wage is associated with a 4.7% wage increase. Finally, a one standard deviation increase in the PGI for BMI is associated with a 1.6 point increase in BMI. Similar to the family-fixed effects models in Table 6.1, the local school leaving age and the interaction terms lose their predictiveness when all the controls for between-family differences are added.

The overall variance explained in outcomes by our models in Table 6.2 can be interpreted as a lower bound of the effects of luck because all covariates measure exogenously given endowments that are out of the control of the individual. This includes the outcomes of the social lottery (i.e. the identity of one's parents, the family one is born into, the neighborhood the family lives in) as well the outcomes of the genetic lottery (i.e. one's biological sex and values of the polygenic indices).

Although one does not have any control over their year of birth, it could be argued that year of birth effects should not be counted as luck, as our outcomes may partly be determined by the process of aging. For instance, older employees may have more experience, which may increase their wages. Furthermore, biological processes in our body change due to aging which may affect our BMI. As everyone will go through the process of aging in their life, it could be argued that this should not be attributed to luck. However, it should be noted that the UK Biobank participants are past the typical schooling age, as the participants were between 40 and 69 when they entered the study. Thus, if birth year has an effect on educational attainment, it could very well be due to the luck of the social circumstances one is born in, as different schooling regulations were in place depending on the exact age of the participants.

To re-evaluate the amount of variance explained in our outcomes that can be attributed to sources of luck, we re-estimate our models from Table 6.2 by first removing all birthyear effects. Here, we first regress our outcomes and all covariates on birth year, birth year squared and birth year cubed and take the residuals. In these models approximately 14 percent of educational attainment can be attributed to luck, 17 percent of occupational wages and 13 percent of BMI. When comparing these numbers to the overall R^2 measures in Table 6.2, we see that the change in the share of variation that can be attributed to luck does not change much. The largest change is for educational attainment, where the share of luck drops by approximately 2 percent.

SI Table 6.4 shows the results of the random effects models using the local infant mortality rate as an early life exposure. The results are very similar to those reported in Table 6.2. For each of the outcomes, the PGI has a similar effect size to those reported in Table 6.2, and the local infant mortality rate and interaction terms are not predictive of the outcomes.

6.5 Discussion

We investigated the effects of inequalities in opportunity that are due to social and genetic luck on educational attainment, occupational wages and BMI. We tested potential interaction effects between genes and environment in a novel within-family study design that uses the random genetic differences between siblings to break the link between family-environments and genes. This approach allowed us to obtain estimates of gene-environment interactions that do not suffer from endogeneity bias, which is a common concern in gene-environment studies (Harden & Koellinger, 2020; Schmitz & Conley, 2017a).

Our results illustrate that both social and genetic luck contribute towards inequalities in socio-economic status and BMI. Our estimates suggest that at least 13 to 17 percent of the inequalities in education, wages and BMI in the UK are due to inequalities in opportunity that arise from the outcomes of the social and the genetic lottery. This estimate is likely to be strongly attenuated by measure error both in the polygenic indices and the proxies of childhood environment that we had available. Thus, the true influence of social and genetic luck on inequalities in the UK is likely to be substantially higher in reality. Future investigations on this would benefit from more precise polygenic indices as well as better measures of relevant environments during childhood.

Our results also showed that social and genetic luck are correlated, which exacerbates their influence on disparities on socioeconomic and health outcomes. This type of Matthew effect had previously been identified in large-scale, genetically informed study designs. For example, children who grew up in high-SES households also tended to have higher polygenic indices for educational attainment in Belsky et al. (2018). In Abdellaoui et al. (2019), polygenic index values for educational attainment where on average lower in regions of the UK that had overall lower SES (e.g. former coal mining areas). Furthermore, the indirect genetic effects for educational attainment reported by Kong et al. (2018) are another example for how tightly intertwined genetic and environmental factors are that contribute towards SES.

Our results further emphasize the importance of both social and genetic luck as drivers of inequalities in socio-economic status and BMI. In particular, we found that genetic luck is a strong predictor for our outcomes in all our model specifications, including those that rely on the random genetic differences between siblings for identification (e.g. models in which genetic effects have a causal interpretation). In contrast, we find that the early childhood environmental exposures lose their predictiveness when we control for family-fixed effects. Similarly, we find some evidence for gene-by-environment interactions, but not when controlling for family-specific effects.

However, this does not imply that social luck is less important than genetic luck. Rather, the environmental exposures we studied are based on noisy neighbourhood proxies that are unlikely to capture all facets of the environment that are relevant. Moreover, siblings are typically born in similar socio-economic environments and are on average 50% genetically identical. This implies that the differences between siblings tend to be smaller than differences between unrelated individuals, which decreases statistical power to detect true effects in study designs such as ours that use the random differences between siblings for identification. Even larger samples of genotyped siblings would be desirable to identify relevant environment and gene-by-environment interactions in such study designs. Thus, our study illustrates some of the challenges for identifying robust, non-endogenous gene-environment interactions.

The relative importance of social and genetic luck that we studied here has policy relevance because the extent to which people are willing to tolerate or endorse inequality partially depends on whether they perceive that disparity originates from differences in effort and choice (e.g., working hard) or from differences in circumstances that are outside of one's control (e.g., luck in the social or genetic lotteries). The existing empirical evidence suggests that inequality that can ultimately be traced back to luck may be perceived as unfair and people may favor redistributive policies more strongly if inequality is the result of luck rather than agency (Alesina & La Ferrara, 2005; Alesina et al., 2018; Almås et al., 2010; Cappelen et al., 2013; Clark & D'Ambrosio, 2015; Gromet et al., 2015). Furthermore, policies that aim at providing broad access to education and health care are desirable if policies aim at providing people with equal opportunities. However, more equal opportunities do not necessarily translate into equalities in outcomes. For example, previous studies have indicated that schooling reforms can reduce disparities in education and health that are rooted in genetic effects, but these reforms may not decrease inequalities in wages (Barcellos et al., 2018, 2020). Thus, it is important for science and policy to better understand the extent to which genetic and social luck contribute to inequality, the mechanisms that are at work, and whether and how the consequences of exogenously given endowments can be altered.

6.6 Author Contributions

Conceived and designed the study: CAPB, HK, PDK. Prepared data: CAPB, HK. Analysed the data: CAPB. Wrote and edited the manuscript: CAPB, PDK, HK.

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6.8 Data reporting

Access to the UK Biobank resource can be requested https://bbams.ndph.ox.ac.uk/ams/. We will share the polygenic indices we created and the district information we obtained via the standard data sharing mechanism of the UK Biobank.

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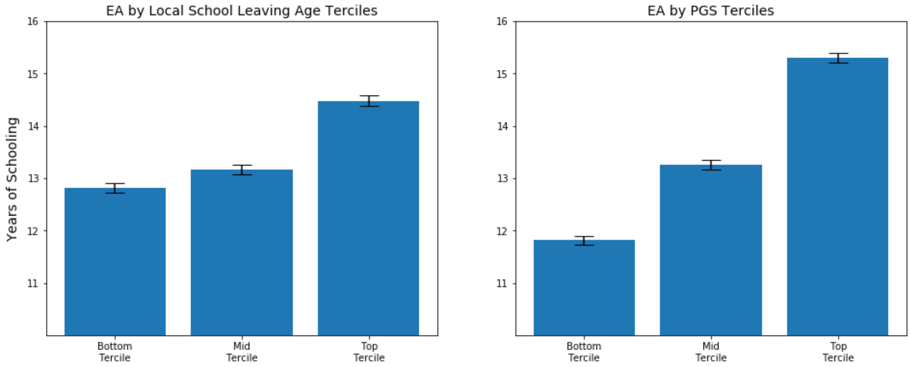
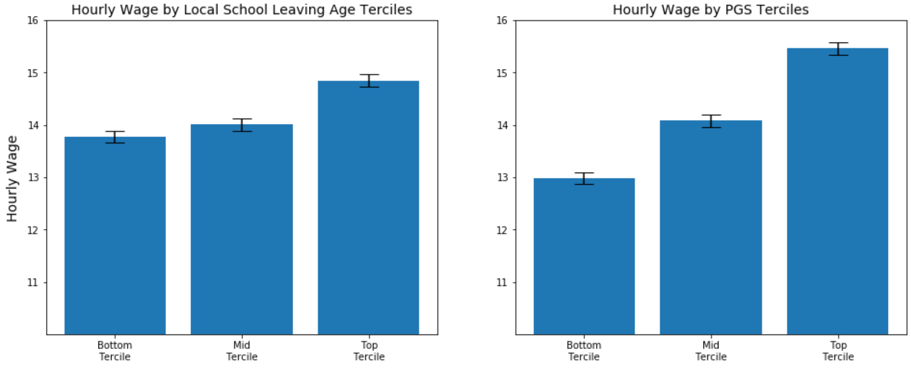
6.10 Figures

Figure 6.1 Mean of educational attainment for different terciles of the local school leaving age and PGI distribution



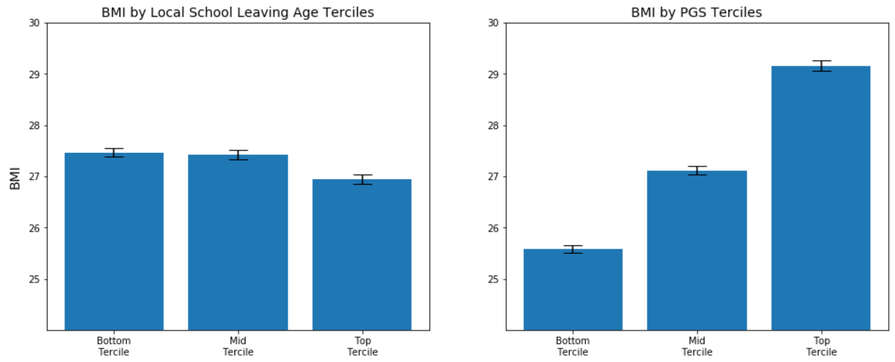
This figure shows the mean of educational attainment (EA), measured in years of schooling, by the different terciles of the average local school leaving age distribution (left panel) and the PGI for EA (right panel).

Figure 6.2 Mean hourly wage for different terciles of the local school leaving age and PGI distribution



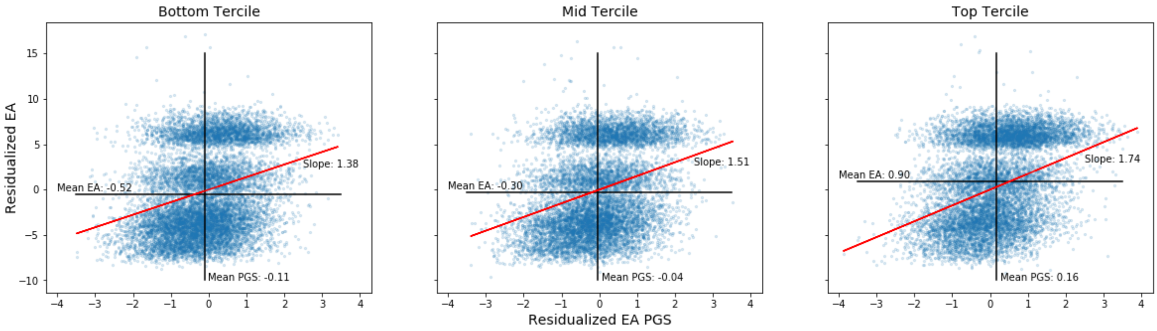
This figure shows the mean of imputed occupational wages, measured in pounds per hour, by the different terciles of the average local school leaving age distribution (left panel) and the PGI for occupational wages (right panel).

Figure 6.3 Mean BMI for different terciles of the local school leaving age and PGI distribution



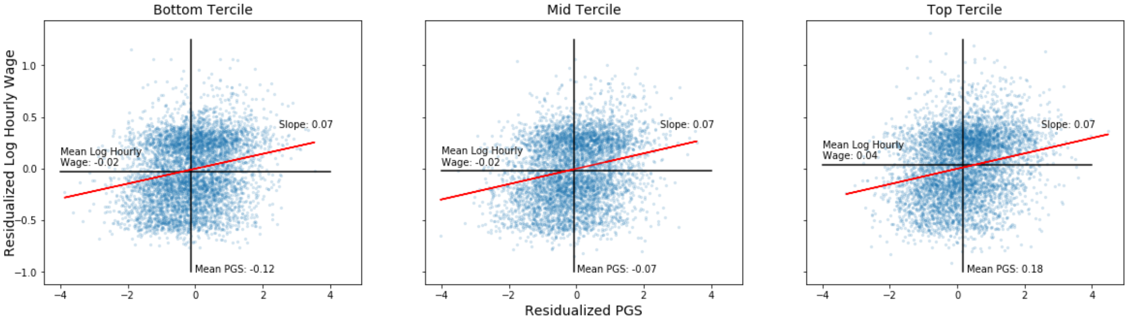
This figure shows the mean body mass index (BMI), by the different terciles of the average local school leaving age distribution (left panel) and the PGI for BMI (right panel).

Figure 6.4 Educational attainment by terciles of the local school leaving age



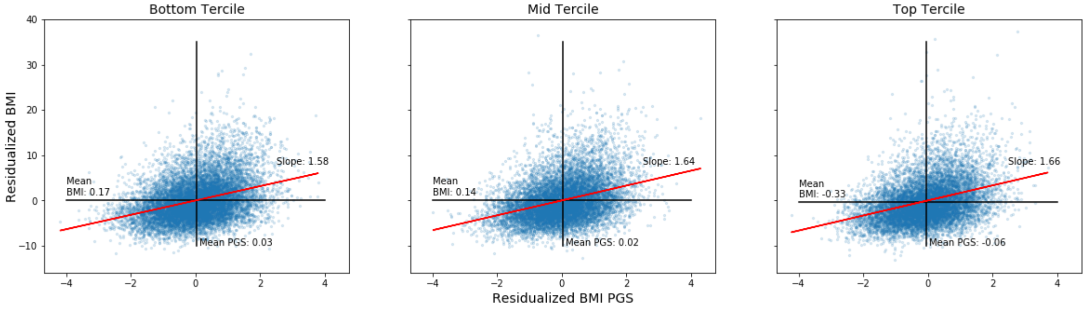
This figure shows the effect of the EA PGI on educational attainment for different terciles of the local school leaving age distribution. We residualized educational attainment and the EA PGI by regressing them on year of birth, year of birth squared, year of birth cubed, gender, gender interacted with the year of birth variables, twenty principal components and genotyping batch.

Figure 6.5 Log hourly wage by terciles of the local school leaving age



This figure shows the effect of the PGI for log hourly wage on imputed log hourly wage for different terciles of the local school leaving age distribution. We residualized log hourly wages and the income PGI by regressing them on year of birth, year of birth squared, year of birth cubed, gender, gender interacted with the year of birth variables, twenty principal components and genotyping batch.

Figure 6.6 BMI by terciles of the local school leaving age



This figure shows the effect of the PGI for BMI on BMI for different terciles of the local school leaving age distribution. We residualized BMI and the BMI PGI by regressing them on year of birth, year of birth squared, year of birth cubed, gender, gender interacted with the year of birth variables, twenty principal components and genotyping batch.

6.11 Tables

Table 6.1 Regression of the outcomes on PGI, local school leaving age terciles and interactions

	EA		Log Hourly Wage		BMI	
	(1)	(2)	(3)	(4)	(5)	(6)
Family Fixed Effects	No	Yes	No	Yes	No	Yes
PGI	1.384	0.799	0.072	0.051	1.584	1.561
S.E.	0.043	0.068	0.004	0.008	0.040	0.066
p-value	0.000	0.000	0.000	0.000	0.000	0.000
Middle Tercile	0.190	-0.072	0.006	-0.018	-0.045	0.173
S.E.	0.062	0.139	0.006	0.016	0.060	0.154
p-value	0.002	0.606	0.375	0.272	0.453	0.261
Top Tercile	1.123	-0.139	0.050	-0.003	-0.412	0.074
S.E.	0.065	0.144	0.007	0.016	0.063	0.150
p-value	0.000	0.334	0.000	0.838	0.000	0.619
PGI x Middle Tercile	0.124	0.033	0.002	-0.009	0.057	0.126
S.E.	0.061	0.092	0.006	0.011	0.059	0.095
p-value	0.043	0.719	0.713	0.409	0.328	0.185
PGI x Top Tercile	0.360	0.060	0.003	-0.005	0.077	0.033
S.E.	0.061	0.092	0.006	0.010	0.059	0.091
p-value	0.000	0.511	0.573	0.654	0.191	0.717
R^2 (Overall)	0.161	0.107	0.175	0.144	0.137	0.126
R^2 (Between)		0.136		0.145		0.146
R^2 (Within)		0.039		0.143		0.092
N	32474	32474	16175	16175	32942	32942
Sibling Groups		15787		7894		16013

This table shows Ordinary Least Squares (OLS) regression results for regressing each of the outcomes (Educational Attainment (EA), Imputed log hourly wages and Body Mass Index (BMI)), on their respective polygenic indices (PGI), local school leaving age terciles and interactions. Columns 1 and 2 show results for EA, columns 3 and 4 for log hourly wage, and columns 5 and 6 for BMI. Columns 2, 4 and 6 include family fixed effects. All regressions included the following control variables: age, age squared, age cubed, gender, gender interacted with age variables, twenty principal components of the genetic data and dummies for genotyping batches. In the family fixed effects models some control variables had to be dropped due to multi-collinearity.

Table 6.2 Random Effects Models

	EA	Log Hourly Wage	BMI
	(1)	(2)	(3)
PGI	0.823	0.047	1.612
S.E.	0.043	0.005	0.042
p-value	0.000	0.000	0.000
Local School Leaving Age	-0.031	0.010	-0.065
S.E.	0.085	0.009	0.087
p-value	0.712	0.260	0.454
PGI x Local School Leaving Age	-0.133	0.012	-0.018
S.E.	0.112	0.029	0.112
p-value	0.238	0.684	0.872
R^2 (Overall)	0.163	0.168	0.132
R^2 (Between)	0.216	0.188	0.156
R^2 (Within)	0.036	0.140	0.090
N	32474	16175	32942
Sibling Groups	15787	7894	16013

This table shows the results of the random effects models based on a Mundlak formulation. Column (1) shows results for educational attainment (EA), column (2) for imputed log hourly wages, column (3) for body mass index (BMI). The outcomes were regressed on the PGI, Local School Leaving age, their interaction and control variables (gender, year of birth and year of birth squared). For each variable within-family means were added to control for between family variation. See equation 6.2 for the full model.

Chapter 6

Supplementary Information

S6.1 Measures of early-childhood environment

As early-childhood environmental exposures, we derived the local average school leaving age and the infant mortality rate at the district level by exploiting the birth locations provided by the UKB. We obtained the historical local-level data from Vision of Britain (www.visionofbritain.org.uk), which covers the period from the early 20th century to the 1970s. Using boundary data for local government districts as of 1931, 1951, 1961, and 1971, we first coded the birth locations in terms of local government district. Based on this information, we constructed childhood local environment measures by matching the birth places to the local-level data.

We derived the local average school leaving age as of 1961 by using district-level data provided as fractions of pupils in the district who left school at the age of under-15, 15, 16, 17 to 19, and above-20. To these fractions, we multiplied the values of 10, 15, 16, 18, and 20, respectively, to compute the average school leaving age of the district. This data was only available for 1961.[1] We used the boundary data for local government districts as of 1961 to match the local average school leaving age to each participant.

The local infant mortality rates were available at the district level annually. To reduce the noise in the data, we smoothed the infant mortality rate time series for each district by using the Hodrick-Prescott filter with the smoothing parameter of 100 (Hodrick & Prescott, 1997). We also dropped observations if the number of births in the district was fewer than 50 in that year. The boundary data was only available for 1931, 1951, 1961, and 1971 while the local infant mortality data was available annually. Therefore, we used the boundary data from the year nearest to the birth year for each participant.

S6.2 Polygenic indices

We constructed polygenic indices (PGI) using the results of the largest GWAS that are currently publicly available for educational attainment (Lee et al., 2018), occupational wages (Kweon et al., 2020), and BMI (Locke et al., 2015). We further improved the accuracy of these PGI with MTAG (Turley et al., 2018), which is a multivariate statistical method that increases the statistical power of GWAS by including GWAS summary statistics from genetically correlated phenotypes.

[1] In 1951, this data was only available for men. Therefore, we only used the 1961 data.

MTAG analyses included GWAS summary statistics of phenotypes that pass the following criteria:

1. The phenotype belongs to the same scientific domain as the outcome variable of interest. This limits the possibilities of spurious associations when covariates are genetically correlated to the outcome.
2. The phenotype has been included in a previously published GWAS, as GWAS for novel phenotypes would go beyond the scope of this paper.
3. Genetic correlation (r(G)) between the phenotypes is at least 0.6 Here we follow the genetic correlation threshold of Becker et al. (2020) Where the authors conduct many MTAG analyses to construct a repository of PGI.
4. The heritability of the trait is significantly different from 0. Adding traits with little genetic signal would only add noise to our PGI.
5. The GWAS had a sample size of at least 20,000. So that the phenotype contributes significantly to the predictiveness of the PGI.

SI Table 1 gives an overview of all included GWAS summary statistics that meet these criteria. These studies were found via a systematic literature review and genetic correlations provided by LD Hub (Zheng et al., 2017) and Becker et al. (2020) If the phenotype was available in the UK Biobank, we conducted GWAS on a subsample of the UK Biobank that excluded siblings and their genetic relatives (see section 3). Genetic relatives were identified using relatedness coefficients provided by the UK Biobank. We meta-analysed these results with the publicly available GWAS summary statistics that excluded the UK Biobank. SI Table 1 provides an overview of the GWASs run in the UK Biobank.

SI Table 2 gives an overview of phenotypes that meet the above criteria, but had to be dropped during our preliminary analyses. The table also provides the reason for their dismissal.

To adjust for linkage-disequilibrium, we constructed PGI using LDpred (Vilhjálmsson et al., 2015). The Haplotype Reference Consortium (McCarthy et al., 2016) panel was used as LD reference and we employed the recommended LD window, (number of SNPs divided by 3000) and set the fraction of causal markers to 1. We limited the number of SNPs that we included in the PGI to those that are directly genotyped or are present in the HapMap3 reference panel (International HapMap 3 Consortium et al., 2010). This set of SNPs provides a good coverage of common genetic variants and it tends to yield PGI that perform well empirically (Lee et al., 2018). The number of SNPs included in each PGI is further limited by the fact that MTAG only considers SNPs that are present in all summary statistics. The remaining number of SNPs are 1,209,700; 1,209,700; and 1,188,098 for EA, Occupational wages and BMI respectively.

S6.3 GWAS in the UKB

For the phenotypes indicated with the UKB as the source in Table 1, we conducted GWAS on the UKB participants of European ancestry excluding those in the sibling sample and their close relatives (up to the third degree).

We followed the standard phenotype definitions in the literature except for the income outcomes. We coded household income as the natural log of the midpoint income of each income bracket, where 3/4 times the upper bound and 4/3 times the lower bound were used as the midpoint respectively for the lowest and highest brackets, which are open-ended. Regional income (local average weekly household income in 2011) was derived from home locations coded in Middle-layer Super Output Areas. We obtained the income data from the UK's Office for National Statistics, which was available for England and Wales only.

For the non-income outcomes, the control variables included dummy variables for sex, age, year of observation, and assessment centre, and their interaction with sex dummy as well as genotyping arrays and batches and 40 top genetic principal components. For the income outcomes, we conducted GWAS on male and female samples separately and meta-analysed the male and female results of each measure by relying on the meta-analysis version of MTAG to address possible sex heterogeneity in economic outcomes. In the GWAS of the income outcomes, dummy variables for employment status were additionally included.

Each GWAS was run based on a linear mixed model, estimated with BOLT-LMM (Loh et al., 2015). We then applied standard quality control filters to exclude SNPs that are problematic, which we implemented with EasyQC (Winkler et al., 2014). These filters removed SNPs that had missing or incorrect numerical values for output statistics (a p-value outside of [0,1], for example); duplicate SNPs; imputation accuracy below 0.7; a minor allele frequency lower than 0.1%; an allele other than "A," "C," "G," or "T"; or had an allele frequency that deviates 0.2 or more from the allele frequency in the reference panel (Haplotype Reference Consortium v1.1 (McCarthy et al., 2016)).

S6.4 Measuring educational attainment

We measured educational attainment in years of schooling, using a transformation from the highest achieved diploma to a set number of years such that it retains the rank order of lowest to highest degree as much as possible (see SI Table 3). Because the participants could report more than one qualifications, each reported qualification was converted to years of schooling and the maximum value was retained.

S6.5 Results for infant mortality rate

This section shows the results when using infant mortality rate as early childhood environmental exposure. SI Figure 1 shows the mean of EA, hourly wages and BMI of the UK Biobank participants when divided into terciles of the infant mortality rate distribution. Infant mortality rate was reverse coded such that higher numbers are better to ease the comparison to the results using local school leaving age, as discussed in the main text. The results for EA and BMI are similar to the results using local school leaving age. For hourly wages, we note the differences in sample sizes for the different terciles of the distribution. There are many more missing observations for hourly wages in the bottom tercile of the distribution, indicating attrition in our sample. Thus, the results for hourly wages cannot be interpreted in any meaningful way.

SI Table 3 shows the equivalent results of table 1 in the main text using local infant mortality rate terciles instead of local school leaving age. The results are in line with those of table 1. One notable difference is the interaction effects for BMI. There we do find that the PGI is more strongly associated with BMI in neighbourhoods with low infant mortality rate. The interaction effect remains for the middle tercile, even when controlling for family fixed effects. Again, due to attrition in the sample the results for hourly wages cannot be interpreted in any meaningful way.

SI table 4 shows the results for the random effects models using the local infant mortality rate as an early life exposure. The results are very similar to that of table 2 in the main text.

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S6.7 Tables

Table S6.1 Overview of GWAS Summary Statistics

Phenotype	Target	r(G)	N	Source
Hardest Math Class	EA, Occ. Wages	0.81, 0.78	430,439	(Lee et al., 2018)
Cognitive Performance	EA, Occ. Wages	0.63, 0.67	35,298	(Trampush et al., 2017)
Cognitive Performance	EA, Occ. Wages	0.63, 0.67	129,048	UKB Data Field: 20016
Cognitive Performance	EA, Occ. Wages	0.63, 0.67	101,205	UKB Data Field: 20191
Household Income	EA, Occ. Wages	0.74, 0.91	340,935	(Kweon et al., 2020)
Regional Income	EA, Occ. Wages	0.81, 0.83	359,437	(Kweon et al., 2020)
Body fat percentage	BMI	0.84	390,601	UKB Data Field: 23099
Hip Circumference	BMI	0.87	224,459	(Shungin et al., 2015)
Hip Circumference	BMI	0.87	397,156	UKB Data Field: 49
Waist Circumference	BMI	0.90	224,459	(Shungin et al., 2015)
Waist Circumference	BMI	0.90	397,197	UKB Data Field: 48

This table gives an overview of GWAS summary statistics from previous studies used to improve the accuracy of the PGI. The first column states the phenotype of the GWAS. The second column indicates for which outcome the summary statistics were used. The third column gives the genetic correlation between the phenotype and target outcome. The genetic correlation was calculated using the meta-analysed results if there were multiple sources for that phenotype. The reported correlation was calculated during our preliminary MTAG analyses. The fourth column gives the size of the GWAS. The fifth column gives a reference to the study where the GWAS was published or the UKB Data-Field.

Table S6.2 Overview of Dismissed GWAS Summary Statistics

Phenotype	Target	Source	Reason for dismissal
College Completion	EA, Occ. Wages	(Rietveld et al., 2013)	A
Body fat percentage	BMI	(Lu et al., 2016)	B
Obesity Class 1	BMI	(Berndt et al., 2013)	A
Obesity Class 2	BMI	(Berndt et al., 2013)	A
Obesity Class 3	BMI	(Berndt et al., 2013)	A
Overweight	BMI	(Berndt et al., 2013)	A
Leptin	BMI	(Kilpeläinen et al., 2016)	C
HOMA-IR	BMI	(Dupuis et al., 2010)	D

This table gives an overview of GWAS summary statistics but were dropped in preliminary analyses. The first column states the phenotype of the GWAS. The second column indicates for which outcome the summary statistics were used. The third column gives a reference to the study where the GWAS was published. The fourth column gives the reason code for the dismissal. Where the codes are as follows: A: the phenotype is a binary measure of another included phenotype and the sample is completely overlapping with it. B: the results are from mixed ancestry. C: The phenotype greatly reduced the number of overlapping SNPs used by MTAG. D: the phenotype had no reported number of samples per SNP.

Table S6.3 Transformation Qualification to Years of Schooling

Qualification	Years of schooling
College or University degree	20
A levels/AS levels or equivalent	13
O levels/GCSEs or equivalent	10
CSEs or equivalent	10
NVQ or HND or HNC or equivalent	Age when left full-time education – 5
Other professional qualifications e.g.: nursing, teaching	15
None of the above	7

This table shows the conversion for each type of diploma to a set years of schooling

Table S6.4 Regression of the outcomes on PGI, infant mortality rate terciles and interactions

	EA		Log Hourly Wage		BMI	
	(1)	(2)	(3)	(4)	(5)	(6)
Family Fixed Effects	No	Yes	No	Yes	No	Yes
PGI	1.483	0789	0.082	0.071	1.461	1.512
S.E.	0.049	0.071	0.008	0.012	0.046	0.068
p-value	0.000	0.000	0.000	0.000	0.000	0.000
Middle Tercile	0.644	0.034	0.016	0.014	-0.082	0.122
S.E.	0.087	0.113	0.011	0.015	0.084	0.115
p-value	0.002	0.003	0.138	0.346	0.330	0.286
Top Tercile	0.706	-0.026	0.025	0.007	-0.504	0.029
S.E.	0.124	0.177	0.014	0.020	0.120	0.181
p-value	0.000	0.883	0.069	0.714	0.000	0.875
PGI x Middle Tercile	0.107	0.136	-0.014	-0.025	0.242	0.171
S.E.	0.067	0.084	0.009	0.013	0.065	0.087
p-value	0.117	0.105	0.121	0.042	0.000	0.049
PGI x Top Tercile	0.065	0.007	-0.006	-0.028	0.271	0.151
S.E.	0.068	0.092	0.009	0.013	0.065	0.095
p-value	0.340	0.936	0.468	0.028	0.000	0.113
R^2 (Overall)	0.147	0.103	0.166	0.136	0.133	0.122
R^2 (Between)		0.129		0.126		0.138
R^2 (Within)		0.042		0.151		0.093
N	26612	26612	13102	13102	26898	27034
Sibling Groups		12933		6395		13136

This table shows Ordinary Least Squares (OLS) regression results for regressing each of the outcomes (Educational Attainment (EA), Imputed log hourly wages and Body Mass Index (BMI)), on their respective polygenic indices (PGI), infant mortality terciles and interactions. Infant mortality is reverse coded such that higher numbers are good. Columns 1 and 2 show results for EA, columns 3 and 4 for log hourly wage, and columns 5 and 6 for BMI. Columns 2, 4 and 6 include family fixed effects. All regressions included the following control variables: age, age squared, age cubed, gender, gender interacted with age variables, twenty principal components of the genetic data and dummies for genotyping batches. In the family fixed effects models some control variables had to be dropped due to multi-collinearity.

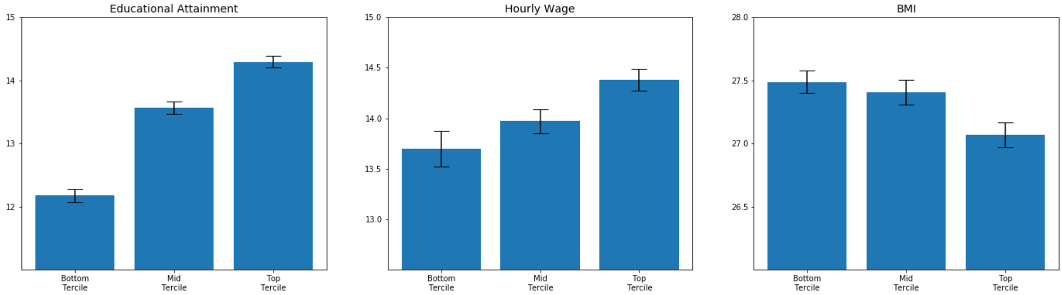
Table S6.5 Random Effects Models

	EA	Log Hourly Wage	BMI
	(1)	(2)	(3)
PGI	0.833	0.048	1.612
S.E.	0.048	0.005	0.046
p-value	0.000	0.000	0.000
Infant mortality rate	6.413	-0.148	-6.207
S.E.	7.675	1.088	7.972
p-value	0.403	0.892	0.436
PGI x Infant mortality rate	1.267	-0.693	-8.231
S.E.	5.474	0.740	5.218
p-value	0.817	0.349	0.115
R^2 (Overall)	0.147	0.157	0.132
R^2 (Between)	0.194	0.165	0.157
R^2 (Within)	0.037	0.145	0.090
N	26612	13102	27034
Sibling Groups	12933	6395	13136

This table shows the results of the random effects models based on a Mundlak formulation. Column (1) shows results for educational attainment (EA), column (2) for imputed log hourly wages, column (3) for body mass index (BMI). The outcomes were regressed on the PGI, infant mortality rate, their interaction and control variables (gender, year of birth and year of birth squared). Infant mortality rate is reverse coded such that higher numbers are good. For each variable within-family means were added to control for between family variation. See equation 6.2 for the full model.

S6.8 Figures

Figure S6.1 Outcomes by infant mortality rate terciles



This figure shows each of the outcomes plotted by the district infant mortality rate terciles. Infant mortality rate is reverse coded such that higher numbers are good. The left panel shows educational attainment, the middle hourly wages and the right BMI.

Chapter 7

A large-scale meta-analysis of genome-wide association studies on income

Based on forthcoming work by C.A.P. Burik, H. Kweon, A. Okbay, R. Karlsson Linnér, R. de Vlaming, P.D. Koellinger and many more. This work is part of an ongoing research effort with many collaborators. The work presented here also includes work done by many researchers affiliated with individual cohorts. Due to space constrains they are not mentioned here, but they will be credited in the eventual publication

Abstract

We present results of a large-scale GWAS meta-analysis of 1,161,574 observations from approximately 756,000 individuals using four different measures of income: personal income, household income, occupational wages and parental income. We identified 160 independent loci associated with income in an MTAG meta-analysis of all four of these methods. We find 67 independent loci associated with occupational wages, 48 for household income and 1 for parental income. We find no genome-wide significant SNPs for individual income. Overall, 4.3 to 7.6 percent of the variance in the income measures may be attributed to genetic factors. The four income measures show high genetic correlation with each other, a high genetic correlation with educational attainment, a moderate genetic correlation with cognitive performance and a moderate to high negative genetic correlation with the Townsend index. Furthermore, we find evidence for genetic heterogeneity between men and women.

7.1 Introduction

We conducted a large-scale GWAS meta-analysis of 1,161,574 observations from approximately 756,000 individuals using four different measures of income: personal income, household income, occupational wages and parental income. We meta-analyse GWAS results from 31 cohorts (Table 7.1 gives an overview of all cohorts and the sample size contribution of each cohort). This study is the first part of an ongoing research effort to generate a set of publicly available genome-wide association study (GWAS) results on income that will provide researchers from various disciplines with new, better ways to study the causes and consequences of inequality and social mobility – two matters that are of fundamental importance for science and policy (Piketty, 1995). Differences in wealth and income are not only robust predictors of subjective well-being (Sacks, Stevenson, & Wolfers, 2012; Stevenson & Wolfers, 2013), but low socio-economic status (SES, i.e. the combination of education, occupation, and income) is also a major risk factors for mental and physical diseases (Wilkinson & Marmot, 2003) as well as lower life expectancy (Stringhini et al., 2017). Paying attention to these robust health-related consequences of SES is particularly important and timely now because the income and wealth gap between the richest and poorest people has been steadily rising in the past few decades in the US and many other countries (Acemoglu, 2002; Piketty, 2014). Thus, understanding the structural causes of inequality, social mobility, and their links with health is of fundamental importance both as a matter of science and for interventions aiming to improve health outcomes, well-being, and longevity (Piketty, 1995).

In the last few years several large-scale GWAS related to socioeconomic outcomes have produced publicly available summary statistics, such as educational attainment (Lee et al., 2018; Okbay, et al., 2016; Rietveld et al., 2013), household income (Hill et al., 2019, 2016) and occupational wages (Kweon et al., 2020). These publicly available summary statistics provide many research opportunities in economics and other social sciences (Beauchamp et al., 2011; Benjamin et al., 2012; Freese, 2018; Harden & Koellinger, 2020).

While publicly available summary statistics for income exist, many of the potential follow-up analyses will benefit from GWAS results based on larger sample sizes than currently available. For instance, the increases in sample sizes of GWAS on educational attainment has led to a tremendous increase in predictiveness of polygenic indexes (PGI) for educational attainment. Where a sample size of 101,069 yielded a PGI that predicts approximately 2 percent of the variation in educational attainment (Rietveld et al., 2013), the latest GWAS on educational attainment of 1.1 million individuals lead to the PGI predicting up to approximately 13 percent (Lee et al., 2018).

While it is possible to use a PGI for educational attainment to predict income due to the high genetic correlation between the two (Hill et al., 2019; Kweon et al., 2020), Kweon et al. (2020) show that a PGI for occupational wages, can predict wages beyond the PGI for educational attainment, even with a much lower sample size. Furthermore, some analyses require separate GWAS summary statistics for income and educational attainment (e.g. GIV regression (DiPrete, Burik, & Koellinger, 2018)).

Finally, by employing multivariate methods (e.g. MTAG (Turley et al., 2018) or GenomicSEM (Grotzinger et al., 2019)) new GWAS results for income may further boost the statistical power of GWAS results across the socioeconomic spectrum. Therefore, it is key to generate a set of publicly available large-scale GWAS results for income that will provide researchers the necessary tools to conduct genetically informed analyses on income and inequality.

7.1.1 Phenotype description

We think of individual income, household income, educational attainment, and occupation as related, but not identical measures that capture different aspects an individual's socioeconomic circumstances. In this study, we use several measures of income and occupation to maximize the possible sample size. These measures may be combined using various multivariate approaches (e.g. MTAG (Turley et al.,

2018) or GenomicSEM (Grotzinger et al., 2019)). Furthermore, this allows for exploration of any potential genetic heterogeneity between different income measures.

Preferably, income is measured using official registry data to obtain high-accuracy measures of income. When official registry data is not available, self-reported income measures are used. We consider all sources of income that are “earned” as income (e.g. salaries, income from self-employment, profits from running one’s own business, bonuses, vacation benefits), but exclude non-earned monetary transfers such as rental income, capital gains, dividends, and transfers from the government, family, or former spouses.

Individual Income

Individual income is the most direct measure of the consumption and savings opportunities that a person has. Individual income is the result of various factors including achieved qualifications (e.g. education, learnt occupation, experience), personal characteristics (e.g. leadership, cognitive skills, consciousness), the demand and supply for these qualifications and characteristics in the labour market, and personal choices about labour supply (e.g. due to personal preferences, decisions about division of labour among household members).

Household income

We consider household income as an alternative measure, when personal income is not available. Household income shares many of the characteristics of individual income and shares some of the underlying factors contributing to it. However, household income aggregates the individual incomes of all household members (e.g. spouses and possibly even children or other relatives). Therefore, household income captures not only factors that contribute towards individual income, but also other factors such as the ability and desire to attract a spouse and the characteristics of that spouse

Occupational wages

A number of cohorts do not have any income data. Instead, those cohorts may use the available information on the occupations of participants. Occupation encompasses income potential and typically also reflects educational attainment, personal interests, social prestige and labour market opportunities. Here, we follow the example of Kweon et al. (2020) by measuring the income potential of occupations by imputing the expected wages for each occupation. The details on the imputation algorithms for each of the cohorts are described in Appendix 1.

Parental income

In one cohort we ran a GWAS on parental income using their offspring's genotype. In this cohort, iPSYCH (Pedersen et al., 2018), the participants are too young and therefore their current income does not accurately reflect their life-time earnings potential. Therefore, we opted to use the income of their parents instead. We consider this a valid approach as parental income is typically predictive for their offspring's income. More importantly, through biological inheritance the offspring's genotype is a draw of their parental genotypes. Therefore the offspring's genotype is also highly correlated with each of the parental genotypes.

Pensioners

While pensioners typically do not have any directly "earned" income, their pension income is usually reflective of their lifetime earnings. Cohorts can include pensioners when this is the case, with added control variables for pension income. Alternatively, the last earned income before retirement may be used, if available.

Categorical income

Many cohorts opt to use categorical responses to measure individual or household income. In these cases we convert these categories to a semi-continuous measure by taking the natural logarithm of the midpoint of the category. As the top and bottom category are often open-ended and do not have a midpoint, we convert the top category by taking the logarithm of 4/3 times the lower bound of that category. For the bottom category we take the logarithm of 3/4 times the upper bound of that category.

Table 7.2 gives an overview of the income measures for each cohort, as well as the survey question or a short description of the measure.

7.2 Data and Methods

Cohorts were asked to carefully follow our preregistered analysis plan[1] when conducting any analyses. Cohorts were instructed to only include individuals of European ancestry to limit the possibility of spurious findings. They were instructed to exclude individuals with missing covariates, individuals with a call rate lower than 0.95, ancestry outliers and to follow their usual internal quality control for their participants and genotypes. Cohorts were advised to exclude individuals that had not finished education,

[1] The analysis plan can be accessed here: https://osf.io/rg8sh/

or when education enrolment was not observed, to exclude individuals under the age of 30. Finally, we asked cohorts to remove individuals with unusual answers for self-reported income measures (e.g. a negative yearly income or a yearly income above 10 million euro's). Imputation was conducted using a reference panel from either the 1000 Genomes Project (Abecasis et al., 2012) or the Haplotype Reference Consortium (HRC) (McCarthy et al., 2016). Some cohorts made use of a combined reference panel using one of the two aforementioned reference panels in combination with a reference panel representative of the local population (e.g. UK10K (Walter et al., 2015), GoNL (Deelen et al., 2014) or an Estonian specific reference panel (Mitt et al., 2017)).

An overview of the genotyping platforms, cohort specific quality control thresholds and imputation procedure is provided in Table 7.3.

7.2.1 GWAS models

Cohorts were encouraged to run analyses using mixed linear models that account for (cryptic) relatedness (e.g. BOLT-LMM (Loh et al., 2015) or GCTA-MLMA (Yang, Zaitlen, Goddard, Visscher, & Price, 2014)). This allows cohorts to included related individuals, which yields larger sample sizes and greater statistical power. Therefore, it was especially recommended for family-based studies. Furthermore, mixed linear models are more effective in dealing with potential confounds due to subtle population structure than only using genetic PCs as control variables (Yang et al., 2014). As control variables each cohort was asked to include the following covariates: at least 15 principal components associated with the 15 (or more) largest eigenvalues of the variance-covariance matrix of the genotypic data; dummy variables for year of observation (if this varied in the sample); dummy variables for each age group, or age, age squared and age cubed if the sample is too small and there are too few observations in each age group; cohort specific dummy variables related to genotyping (e.g. genotyping batch or genotyping array); dummy variables for sources of income (e.g. self-employment), where wage employment is the reference category; hours worked, hours worked squared and hours worked cubed, unless the phenotype is household income; and if the phenotype is household income, the number of adults in the household, when possible.

When multiple observations of the income measure per individual are available (i.e. panel data), cohorts were advised to first regress the income measure on all control variables including time-fixed effects. Then, the mean of the residuals for each person should be taken as the phenotype.

Analyses were run on male and female subsets of each cohort separately. Table 7.4 gives a detailed overview of the specific analysis run by each cohort.

7.2.2 Meta-Analysis

Meta-analyses were carried out on the sets of cleaned summary statistics of each cohort after stringent quality control (see Appendix 2). For each phenotype a sample weighted meta-analysis was carried out for each gender using METAL (Willer, Li, & Abecasis, 2010). All meta-analyses were conducted using a unique SNP ID format as the identifier of each SNP (e.g. 1:123456:C:T). All meta-analyses were restricted to SNPs that were available in 80 percent of the maximum available sample size across all SNPs for each phenotype. As parental income was only available in iPSYCH, these meta-analyses includes all available SNPs that passed quality control filters.

After the meta-analysis for each phenotype for each gender, we meta-analysed the results for men and women using MTAG (Turley et al., 2018). MTAG accounts for possible (cryptic) relatedness and family-overlap between the male and female subsets of each cohort. For this analysis, we used meta-analysis equivalent settings for MTAG where we assumed perfect genetic correlation and equal heritability across gender.

Finally, we meta-analysed the MTAG output for each phenotype to conduct a meta-analysis across the different measures of income. Here we consider a MTAG model where each of the phenotypes are measuring the same underlying trait (i.e. perfect genetic correlation), with a different heritability for each phenotype.

MTAG does not provide the output summary statistics with a sample size. For each of the output files, we approximate a GWAS sample size equivalent for each SNP, which would be lower than the total number of observations per SNP due to family overlap. We use the following formula:

$$N_j \approx \frac{1}{SE_j^2 \times MAF_j\,(1 - MAF_j)} \tag{7.1}$$

Where N_j is the GWAS equivalent sample size for SNP j, SE_j^2 is the standard error of the coefficient found for that SNP and MAF_j is the minor allele frequency of that SNP.

7.2.3 LD Score regression

Using the LDSC software package (Bulik-Sullivan, Finucane, et al., 2015; Bulik-Sullivan, Loh, et al., 2015), we calculate the heritability of each phenotype after each meta-analysis. Thus, we estimate the heritability for male and female subsets as well as for their meta-analysed results. Furthermore, we calculated the genetic correlations between our main phenotypes to assess whether the genetic variants associated with our phenotypes tend to be the same and tend to have similar effect sizes as each other. We also calculated genetic correlations other traits in the socioeconomic spectrum that are possibly related and genetic correlations between the male and female subsamples for each phenotype. To calculate the genetic correlation we used bi-variate LD-score regression to estimate pairwise correlations. For both the heritability estimates and the genetic correlation estimates, we use the LD scores included in the LDSC software package, which are valid for European populations.

7.2.4 Approximately independent lead SNPs

We apply the clumping algorithm from the PLINK software package (Chang et al., 2015; Purcell et al., 2007) to identify approximately independent genome-wide significant "lead SNPs" (SNPs with a *p*-value below 5×10^{-8} are considered genome-wide significant). A lead SNP is a genome-wide significant SNP with lowest *p*-value in an approximately independent clump of SNPs. The clumping algorithm uses four input parameters: a primary *p*-value cut-off (set to 5×10^{-8}), a secondary *p*-value cut-off (set to 1×10^{-4}), an r^2 threshold (set to 0.1), and a SNP window (set to 1,000,000 kilobases). The clumping algorithm starts by selecting the smallest p-value SNP as the lead SNP. Then all SNPs within the SNP window (i.e. all SNPs within 1,000,000 kilobases of the lead SNP, which is effectively the entire chromosome) with an r^2 with the lead SNP above the threshold and with a *p*-value below the secondary cut-off are then assigned to belong in the same clump as the lead SNP. Afterwards, the next lead SNP is selected by taking the SNP with the lowest p-value that does not belong to any clump yet. The algorithm continues until all SNPs with a *p*-value below the primary cut-off are either selected as lead SNP or assigned to belong to the same clump as a lead SNP. We use the same parameter settings as previous studies in the field (Karlsson Linnér et al., 2019; Lee et al., 2018).

7.3 Results

Table 7.8 shows the results of the LDSC heritability estimates. Panel A shows the heritability estimates of the pooled male and female results. The heritability estimates of our different income measures vary between 4.3 percent (for individual income) 7.6 percent (for occupational wages). Many factors may contribute to the differences in heritability between our phenotypes. First, there is the issue of misreporting when self-reported income is used, which is the case with all the individual income and household income cohorts. It could be the case that people are less likely to misreport their occupation than their income. Second, aggregate income measures like household income are less sensitive to income shocks as they are averaged out between household members. As occupational wages is an imputed measure, it is not sensitive to temporary income shocks. Third, as occupational wages is imputed per occupation code, it does not contain any within occupation variation. It could be that within occupation variation of income, is less heritable than the between occupation variation of income. Finally, in the case of parental income, an additional level of noise is added due to using parental phenotypes and the offspring's genotypes. Overall our heritability estimates are lower than what has been found in some previous studies, where Kweon et al. (2020) found a heritability of 10.3 percent for occupational wages in the UK Biobank and Hill et al. (2016) found a heritability of 11 percent for household income in the UK Biobank. One possible explanation for this difference is the methods used in these analyses. Here we present results from LDSC, while both Kweon et al. (2020) and Hill et al. (2016) present results from GREML (Yang et al., 2010). Hill et al. (2019) find a heritability of 7.6 percent for household income in the UK Biobank using LDSC, which is closer to our estimates. Furthermore, while these previous studies present heritability estimates for a single cohort, our estimates come from a meta-analysis from several cohorts. These cohorts are samples from several different countries where individuals and households face may face different environments. Therefore, our meta-analysis can be seen as an average effect across these environments, which could result in a lower heritability.

Panels B and C of Table 7.8 show the heritability estimates for men and women separately. We note that there is a difference in the heritability for men and women most of the measures. The last column of panel A of Table 7.8 shows the *p*-value for a test of equal heritability using the following Z-test:

$$Z = \frac{h_{men}^2 - h_{women}^2}{\sqrt{(SE_{men}^2 + SE_{women}^2)}} \tag{7.2}$$

Where Z is the test statistic, considered to follow a normal distribution, h_i^2 is the heritability estimate for gender i, and SE_i is the standard error of that heritability estimate.

The heritability for individual income and household income are significantly higher for men than for women. The opposite holds true for occupational wages and for parental income the difference is not statistically significant. Furthermore, Table 7.9 shows the genetic correlation between men and women. While the genetic correlation is high for all our measures, it is significantly different from 1 for all of our measures, except individual income. We note that the standard error of our estimate for individual income is a lot higher than for the other measures due to the difference in sample size. The deviation from unity for the genetic correlation implies there is some genetic heterogeneity between men and women. This genetic heterogeneity may be attributed to the difference in environments men and women face. There is an extensive literature on for differences in wages and occupations between men and women and the factors that attribute to these difference, such as discrimination and differences in preferences and circumstances (See for instance Blau & Kahn (2017) for a discussion). All these factors may also play a role in the difference in genetic heterogeneity between and women, as genes do not operate in a vacuum, but can act through differences in environments. Similar genetic heterogeneity between men and women has been found in traits that may be related to income like risk tolerance (Karlsson Linnér et al., 2019).

In Table 7.10 we present the genetic correlations between our different measures, with the meta-analysed combination measure, as well as their genetic correlation with other socioeconomic traits to assess the similarity in genetic architecture between them. The different measures are all highly correlated with each other and the meta-analysed combination measure, with genetic correlation estimates varying between 0.81 and 1.11. Thus, the different measures mostly share their genetic architecture. However, as the genetic correlation between some of the measures significantly differ from 1, there is some genetic heterogeneity between the different measures. Furthermore, we find that all measures have a high genetic correlation with educational attainment; a moderate genetic correlation with cognitive performance; and a moderate to high negative genetic correlation with the Townsend index. As educational attainment has a direct effect on income (Card, 2001; Harmon, Oosterbeek, & Walker, 2003), this high correlation is expected and it is similar to which has been found in previous studies (Hill et al., 2019; Kweon et al., 2020). A similar argument can be made for the relation between cognitive performance and our different measures of income. Hill et al. (2019) explore the potential link between cognitive performance and income further. They identify intelligence as a likely causal phenotype that contributes to income. Finally, as income has a direct effect on the housing budget of an individual, which contributes to the quality of housing and neighbourhood. Which would contribute to a lower score on the Townsend index. Therefore, a moderate to high genetic correlation between income and the Townsend index is expected.

Figures 7.1 to 7.5 show Manhattan plots of the meta-analysis results of the different measures and the meta-analysis of all measures combined. Using the clumping algorithm described above we find 160 approximately independent genome-wide significant lead SNPs for the meta-analysis of all the measures combined, 67 for occupational wages, 48 for household income and 1 for parental income. We find no genome-wide significant SNPs for individual income, which could be attributed to both low sample size and lower heritability.

7.4 Discussion

We meta-analysed GWAS result from over a million observations using four different measures of income (personal income, household income, occupational wages and parental income). We identified 160 independent loci associated with income. Overall, 4.3 to 7.6 percent of the variance of income may be attributed to genetic factors.

Although the genetic correlation between the different measures, and between men and women is high, we do find evidence of genetic heterogeneity both between the different measures of income, and between men and women. Further research has to be done to pinpoint the underlying factors that affect this genetic heterogeneity.

It is important to note, that these results are part of an ongoing research initiative and many follow-up analyses are already planned. First and foremost, a replication study of these findings will be done using data from the Swedish Twin Registry (STR) (Magnusson et al., 2013). In this cohort, data is available on three of the income measures (personal income, household income and occupational wages) for approximately 25,000 individuals (of which 3,500 complete monozygotic twin pairs and 5,500 complete dizygotic twin pairs). This will allow us to replicate our findings using both a population based approach and within families.

Multivariate analyses using MTAG (Turley et al., 2018) and GenomicSEM (Grotzinger et al., 2019) are planned to analyse the full socioeconomic spectrum, where we can utilize GWAS results from related traits such as educational attainment. These multivariate analyses may be used to study unobserved genetic latent factors of the socioeconomic spectrum and boost statistical power for the GWAS results of income as well as all associated traits. The large sample size as well as the boosted power from these multivariate approach might push as closer to create polygenic scores that approach the theoretical upper limit of predictiveness. These polygenic scores will be used for well-powered within-family polygenic prediction in several cohorts.

Finally, these results allow us to comprehensively study relationships between socioeconomic status and health through genetic correlations, phenome-wide association studies and comprehensive bio-annotation. A better understanding of the link between socioeconomic status and health and the channels through which socioeconomic status may influence health is important to the discussion on socioeconomic and health inequality.

This studies adds to the growing availability of publicly available GWAS results for socioeconomic outcomes using increasingly large sample sizes. These GWAS results, made possible due to the rapidly growing availability of genetic data, in combination with advances in statistical methods permit researchers to study the causes socioeconomic inequality and consequences to inequalities in health and well-being in a genetically informed study design. These advances may lead to new insights in various disciplines.

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A7.1 Imputation of occupational wages

A7.1.1 British cohorts

In a recent study Kweon et al. (2020) developed an imputation algorithm to derive expected wages for participants in the UK Biobank using standardized occupation codes (SOC). In their study, they fitted a regression equation (See Equation A7.3) using a sample of 474,367 wage-earning individuals aged 35-64 from the British Labour Force Survey (LFS) to calibrate their model. The LFS is a nationally representative survey that contains detailed information on individual income, occupations and other variables related to income and occupation that can be used to impute income from . Instead of using dummy variables for each SOC they included the mean and median wage for each occupation group, as reported by the British Office of National Statistics and estimated in the Annual Survey of Hours and Earnings.

The accuracy of their model was tested using data from the British Household Panel Survey, where they found that a regression of actual wages on their imputed values yielded an R^2 of approximately 0.50. The regression equation is as follows:

$$\log(Y_i) = \alpha + X_i\beta + Z_i\gamma + interaction_i\delta + \epsilon_i \qquad \text{(A7.3)}$$

where $\log(Y_i)$ are logged hourly wages from employment, X_i is a vector of predictors, which includes dummies for age, sex, year of observation, and 2-digit SOCs. Z_i is a vector that contains log mean and log median hourly wages as well as their interaction term for the 4-digit-level occupation group (by sex) to which individual i belongs. "$interaction_i$" includes interaction terms between sex and the remaining variables in X_i, and the Z_i term.

We use the imputed log hourly wages estimated by Kweon et al. (2020) as a phenotype in the UK Biobank. Furthermore, we apply the same imputation algorithm to a subset of ALSPAC, a British family cohort. While there is a self-reported income measure available for the children in ALSPAC, it is not available for the mothers of ALSPAC. Therefore, we use the imputation algorithm to imputed occupational wages for the subset containing mothers.

A7.1.2 Dutch cohorts

Following the imputation algorithm developed by Kweon et al. (2020) as closely as possible we developed a similar algorithm for cohorts in the Netherlands. Here we use data from the Dutch labour force survey, '*Enquête Beroepsbevolking*' (EBB) (Centraal Bureau voor Statistiek, 2021). The EBB is a national representative survey of the Dutch labour force, conducted by Statistics Netherlands (CBS). We use data a merged dataset containing 479,893 individuals in yearly waves from 2012 to 2017, where we exclude multiple observations per individual by taking the latest observation. The EBB uses standardized occupation codes, BRC, developed by CBS based on the ISCO-08 standard to fit the Dutch labour market (Centraal Bureau voor Statistiek, 2014). As the EBB is the only national representative survey containing standardized occupation codes, we fit the regression model and calculate the mean and median hourly wages per occupation group in the same sample. We standardize hourly wages to the year 2012 using the consumer price index calculated by CBS. We calculate the mean and median wage for each 4 digit occupation code separately for each gender. If there are less than 10 people per occupation code, we calculate the mean and median using a pooled sample of both genders. If there are less than 10 people per occupation code in the pooled sample, we use the 3 digit occupation code instead. If the 3 digit occupation code still does not yield a sufficient sample size, we use the 2 digit occupation code. The model specified in Equation A7.3 is then estimated.

Using this coefficients from this model, we imputed the log hourly wages in two Dutch cohorts: NTR and LifeLines. The accuracy of the model was tested by taking the 2017 EBB subset as a hold-out sample (N = 91,821) and re-estimating the regression model using the 2012 – 2016 subset, excluding those present in both the 2017 and the 2012 – 2016 subset (N = 388,072). Regressing the log hourly wage on the imputed log hourly wage in the 2017 EBB subset yielded an R^2 of 0.47.

A7.1.3 ECGUT

To impute expected wages in the Estonian cohort, ECGUT, we employed a simpler algorithm. Here, we used the mean log wage of each occupation code. The mean log wage was calculated, for men and women separately, using a representative sample of 369,247 individuals aged 25 to 64 from the 2011 labour market census published by Statistics Estonia (Statistics Estonia, 2012). ECGUT uses 3-digit occupation codes based on the ISCO-88 standard and Statistics Estonia uses occupation codes based on the ISCO-08 standard (International Labour Office, 2012). The mean log wages for each ISCO-08 code were matched to the ISCO-88 codes based on the correspondence file published by the International Labour Organisation (ILO). When multiple ISCO-08 corresponded to a single ISCO-88 code, the average was taken.

A7.1.4 HUNT

In the Norwegian cohort HUNT, we used a similar algorithm to that of ECGUT. Here, we use mean wage statistics for men and women in Norway from 2015 to 2019 from registry data, published by the Statistics Norway (Statistics Norway, 2021). While, HUNT uses 3-digit occupation codes based on the ISCO-88 standard, Statistics Norway uses occupation codes based on the ISCO-08. The two are matched together in the same way as was done for ECGUT.

A7.2 Quality Control

We applied a stringent quality-control (QC) protocol to each set of GWAS results of each cohort based on the EasyQC software package (version 9.2) developed by the GIANT consortium (Winkler et al., 2014), as well as additional steps developed by the SSGAC (Karlsson Linnér et al., 2019; Lee et al., 2018; Okbay, et al., 2016). All issues raised during the QC protocol described below were resolved through iterations with cohort analysts, before the meta-analyses.

A7.2.1 Main Reference panel

For the main reference panel we used HRC v.1.1 as the reference panel for quality control of the GWAS summary statistics and to determine the independence of significant SNPs. The quality control of this reference panel has been described in the supplementary materials of Karlsson Linnér et al. (2019).

A7.2.2 Pre-QC inspection

All cohorts were asked to supply their GWAS summary statistics in a pre-specified format, together with a document providing an overview of the descriptive statistics of their sample as pre-specified in the analysis plan[2]. The completeness of this document and the summary statistics, as well as their formatting, was assessed prior to QC.

A7.2.3 EasyQC protocol

The filters applied in the QC protocol are described below in chronological order. While the order of the filters does not affect the set of SNPs in the cleaned summary statistics file, it does affect in which step a given SNP is removed. An overview of the removed SNPs according to the QC steps is given in Table 5.

Step 1: Removal of inadmissible alleles. In the first step we remove all SNPs that have another value than "A", "T", "C" or "G". This step removes all structural variants (e.g. inserts and deletions).

Step 2: Variable Quality. In this step we remove all SNPs with missing values for one of the following columns: SNP identifier, effect allele, other allele, *p*-value, beta coefficient, standard error, effect allele frequency, *N*, imputed or genotyped, and when SNPs were imputed it also removed missing values from the following columns: imputation accuracy, Hardy-Weinberg-Equilibrium *p*-value, call rate. This step also removed non-sensical values: values outside of the interval [0,1] for *p-values*, negative values for the standard error or imputation accuracy, infinite values for the beta coefficient or standard error, and invalid values for the imputed or genotyped column.

Step 3: Removal of the X-chromosome. While cohorts were asked to only supply GWAS summary statistics for the autosomes, some cohorts did provide results for the X-chromosome. These we removed in this step.

[2] The analysis plan can be accessed here: https://osf.io/rg8sh/

Step 4: MAF and MAC filter. In this step SNPs were removed with a minor-allele frequency (MAF) below 0.001 or a minor-allele count (MAC) below 200.

Step 5: Imputation Accuracy. In this step imputed SNPs with a low imputation accuracy were removed. The thresholds for imputation accuracy were dependent on the imputation software that was used. We set the following thresholds: 0.6 for MACH, 0.7 for IMPUTE, 0.8 for PLINK.

Step 6: HWE p-value. In this step we removed directly SNPs that deviated from Hardy-Weinberg Equilibrium according to a direct test *p*-value. We removed SNPs below the *p*-value threshold. The threshold was dependent on cohort sample size: 10^{-3} if $N < 1000$, 10^{-4} if $1000 \leq N < 2000$, 10^{-5} if $2000 \leq N < 10000$. For cohort sample size above 10,000 we did not apply this filter.

Step 7: Duplicate chromosome and base-pair position. In this step we removed SNPs with identical chromosome and base-pair position. This step was applied after harmonizing the chromosome and base-pair positions with the main reference panel.

Step 8: Alignment to the reference panel. In this step we aligned SNPs to the reference panel. Here SNPs that are not present in the main reference panel are removed. Also SNPs we removed if they had an allele mismatch with the reference panel (e.g. SNPs that have the alleles "A" and "G" while the reference panel as the alleles "A" and "T").

Step 9: Allele frequency outliers. In this step we removed SNPs that had an allele frequency that deviates from the reference panel. Here we used 0.2 in absolute value as a cut-off point.

After applying these steps, the resulting output was inspected to determine if an unusual number of SNPs were removed during one of the steps and when necessary errors were resolved together with the cohort analysts. Table 7.5 gives an overview of the SNPs removed in each step for set of summary statistics from all cohorts.

A7.2.4 Quality control plots

After applying the SNP filters, several diagnostic plots were produced for each cohort to further assess the presence of any issues or errors in the summary statistics. Most of these graphs are standard output from EasyQC and are thoroughly discussed in Winkler et al. (2014). The other plots were developed by the SSGAC (Karlsson Linnér et al., 2019; Lee et al., 2018; Okbay, et al., 2016). and were produced in R.

Allele frequency Plots: Here we plot the reported allele frequency in the summary statistics against the allele frequency in the main reference panel. This plot was produces before Step 9 of the SNP filtering. If the sample closely resembles the main reference panel, then the SNPs should be aligned around the diagonal with a positive slope (bottom left to top right). This plot enables the analyst to detect deviations in ancestry from the main reference panel as well as any errors in the coding of the effect allele or allele frequency (e.g. if the effect allele and other allele are reversed, the SNPs would be plotted across the other diagonal: top left to bottom right). Figure 7.6 shows two examples of these plots. In panel A, the allele frequency plot of the UK Biobank is shown. As this cohort is imputed with both HRC and UK10k reference panels, almost no SNPs fall outside the +-0.2 allele frequency band outside of the diagonal. Panel B shows the same plot a cohort is imputed with the 1000 Genomes Project reference panel. Here we see more SNPs outside of the band around the diagonal, but most still fall within the band, indicating that they belong to the same population. None of these plots showed abnormal results for any of the cohorts.

P-Z plots: This plot shows if the reported *p-value* is consistent with the reported coefficient estimates and their reported standard error. The SNPs are plotted with the reported *p*-value on one axis and the expected *p*-value calculated from the reported coefficient and standard error on the other axis. Figure 7.7 shows this plot for one set of results. As can be seen from this plot, all SNPs fall exactly on the diagonal, as they should when the results are reported correctly. All cohorts showed exactly this result.

Q-Q plots: In the quantile-quantile plot the distribution of the observed *p*-values is plotted against the expected *p*-values under the null hypothesis of no SNPs being associated with the phenotype. This plot allows for visualization of any unaccounted-for stratification in the cohorts, which would deflate the *p*-values. Figure 7.8 shows this plot for a cohort with a large sample size (panel A), a small sample size (panel B) and a small cohort with abnormal results (panel C). In cohorts with a large sample size, one can expect larger deviations from the 45 degree line. Panel B shows results that can be expected for small cohorts, where SNPs should follow the distribution under the null hypothesis, due to a lack of power of analysing results in a single small cohort. Panel C shows an abnormal strong deviation of the null hypothesis in a small cohort, which indicates spurious associations. This particular cohort was dropped from the meta-analysis. All other cohorts showed normal plots in their final set of results.

SE-Expected SE plots: We plot the reported standard error against the expected standard error using the following formula:

$$E(SE) \approx \frac{\hat{\sigma}_y}{\sqrt{(2n_j\ MAF_j\ (1 - MAF_j))}}.$$

Where SE is the standard error, $\hat{\sigma}_y$ the estimated standard error of the phenotype, n_j the sample size for a given SNP and MAF_j the minor allele frequency of a given SNP. This plot allows us to detect issues or errors regarding the reported standard error, allele frequency and sample size. Panel A of figure 7.9 shows this plot one of the cohorts, this plot is exactly as would be expected when the phenotype is standardized. The reported standard error and predicted standard error are very close to each other for all SNPs. The reported standard error is very slightly smaller, which can be attributed to the increased power due to the use of mixed linear models. Panel B shows the same plot for preliminary results from a cohort that had initially misreported the sample size per SNP, this issue was resolved for the final results.

SE Manhattan plot: Finally we plot the standard error ratio (reported standard error divided by the expected standard error) of each SNP in order of their chromosome and base-pair position. This allows for visualization of outliers and groups of outliers in terms of the reported standard errors. Figure 7.10 shows this plot for one cohort. As can be seen from this plot, there were no loci with large outliers. All finalized sets of results showed similar plots.

All plots were inspected for each cohort and all issues were resolved together with the cohort analysts before the meta-analysis. In one case, a cohort was dropped from the meta-analysis.

Finally, as part of our QC protocol we calculate the estimated heritability of the phenotype using LD score regression (Bulik-Sullivan, Loh, et al., 2015) and calculate the genetic correlation with occupational wages in the UK Biobank. As most individual cohorts are small we also estimated the heritability and genetic correlation after meta-analysing the male and female results for each cohort. We meta-analysed these results using METAL (Willer et al., 2010). The results of this meta-analysis were only used for QC purposes, as there may be some family overlap between the male and female results of each cohort, which is addressed in the overall meta-analysis by using MTAG (Turley et al., 2018). Table 7.6 gives an overview the LDSC heritability estimates of the pooled meta-analysis and Table 7.7 gives an overview of the genetic correlation estimates of the pooled meta-analysis, both with additional statistics from LDSC. Any unusual results were discussed with the cohort analyst to solve potential issues.

A7.3 Tables

Table 7.1. Description of participating cohorts

Study short name	Study full name	Sampling	Country	Sample size Personal Income	Household Income	Occupational Wages	Other	Birth Year (Mean / Range)	Fraction Female	Cohort Profile
1958	1958 British Birth Cohort	Birth cohort	United Kingdom	4,748				1958 (1958 - 1958)	0.51	(Power & Elliott, 2006)
AddHealth	The National Longitudinal Study of Adolescent to Adult Health	Population based	United States	4,301				1979 (1974 - 1983)	0.49	(Harris, Halpern, Haberstick, & Smolen, 2013)
ALSPAC - Mothers	Avon Longitudinal Study of Parents and Children	Birth cohort	United Kingdom			7,019		1963 (1947 - 1976)	1.00	(Fraser et al., 2013)
ALSPAC - Children				2,542				1992 (1991 - 1993)	0.65	
CoLaus	Cohorte Lausannoise	Population based	Switzerland		3,717			1953 (1928 - 1970)	0.53	(Firmann et al., 2008)
Croatia - Korcula	Croatia - Korcula	Population based	Croatia		2,537			1956 (1917 - 1994)	0.63	(Rudan, 2009)
EGCUT	Estonian Genome Center, University of Tartu	Population based	Estonia			79,612		1967 (1905 - 2000)	0.66	(Mitt et al., 2017)
ELSA	English Longitudinal Study of Aging	Population based	England	2,745				1947 (1922 - 1970)	0.52	(Oldfield et al., 2020)
FinnTwin	Finish Twin Cohort	Population based	Finland	7,797				1976 (1937 - 1994)	0.53	(Kaprio, 2013)
GFG	Genes for Good	Facebook Users	United States		20,659			1978 (1911 - 2000)	0.72	(Brieger et al., 2019)
GS	Generation Scotland: Scottish Family Health Study	Family based	Scotland		13,367			1957 (1909 - 1980)	0.58	(Smith et al., 2013)
HRS	Health and Retirement Study	Population based	United States	6,812				1943 (1908 - 1979)	0.54	(Sonnega et al., 2014)
HUNT	Nord-Trøndelag Health Study	Population based	Norway			46,342		1954 (1907 - 1989)	0.53	(Krokstad et al., 2013)
iPSYCH	iPSYCH	Case-Control	Denmark				128,724	1955 (1918 - 1987)	0.50	(Pedersen et al., 2018)
KORA - S3	Kooperative Gesundheitsforschung in der Region Augsburg	Population based	Germany		2,715			1948 (1920 - 1970)	0.49	(Wichmann, Gieger, Illig, & Group, 2005)
KORA - S4					3,460			1949 (1925 - 1975)	0.50	
LifeLines - Cyto	The LifeLines Cohort Study	Population based	Netherlands		10,949	6,822		1960 (1921 - 1994)	0.56	(Scholtens et al., 2015)
LifeLines - UGLI					23,514	13,528		1965 (1922 - 1995)	0.57	
MCTFR - Children	Minnesota Center for Twin and Family Research	Family based	United States	2,137				1979 (1972 - 1984)	0.52	(Miller et al., 2012)

MCTFR - Family					4,417		1960 (1926 - 1994)	0.53	
MoBa	Mother and Child Cohort of NIPH	Family based	Norway	20,428			1971 (1940 - 1978)	0.58	(Magnus et al., 2016)
NEO	The Netherlands Epidemiology of Obesity Study	Population based	Netherlands	3,144			1954 (1943 - 1967)	0.49	(de Mutsert et al., 2013)
NTR	Netherlands Twin Registry	Family based	Netherlands			6,778	1960 (1914-1986)	0.35	(Ligthart et al., 2019)
QIMR	Queensland Institute of Medical Research	Family based	Australia	4,167			1957 (1899 - 1975)	0.43	(Heath et al., 2011; Knopik et al., 2004; Medland et al., 2009)
RS I					4,999		1921 (1887 - 1938)	0.57	
RS II	Rotterdam Study	Population based	Netherlands		1,942		1935 (1903 - 1945)	0.53	(Ikram et al., 2017)
RS III					2,739		1950 (1910 - 1960)	0.45	
SHIP	Study of Health in Pomerania	Population based	Germany		3,228		1944 (1918 - 1969)	0.50	(Völzke et al., 2011)
UKB	UK Biobank	Population based	United Kingdom		382,731	282,963	1951 (1934 - 1970)	0.54	(Bycroft et al., 2018; Sudlow et al., 2015)
UKHLS	Understanding Society	Family based	United Kingdom	6,288	8,837		1958 (1912 - 1995)	0.55	(University Of Essex, 2020)
WLS	Wisconsin Longitudinal Study	Family based	United States	7,492	7,602		1939 (1918 - 1964)	0.52	(Herd, Carr, & Roan, 2014)

Note: This table gives an overview of all cohorts and their respective sample sizes.

Table 7.2 Phenotype Description

Study	Phenotype	Registry-based or Self-reported	Single Observation, Average or Panel	Survey Question or Description
1958	Personal	Self-reported	Panel	Total gross pay
AddHealth	Personal	Self-reported	Single Observation	"Now think about your personal earnings. In {2006/2007/2008}, how much income did you receive from personal earnings before taxes—that is, wages or salaries, including tips, bonuses, and overtime pay, and income from self-employment? "
ALSPAC - Mothers	Occupational Wages	Self-reported	Single Observation	Derived variable - Occupational wage from standardized occupation codes
ALSPAC - Children	Personal	Self-reported	Single Observation	What is your total take-home pay each month (after tax and national insurance are removed as appropriate)? If possible, please refer to a recent payslip. If this is not possible, please estimate. If irregular work, please give an average per month.
CoLaus	Household	Self-reported	Single Observation	Quel est le montant total des revenus mensuels bruts de votre foyer? C'est-à-dire la somme des revenus des personnes de votre foyer ou vos propres revenus si vous vivez seul(e), quelle qu'en soit l'origine.
Croatia - Korcula	Household	Self-reported	Single Observation	Monthy Household Income using 6 categories
EGCUT	Occupational Wages	Self-reported	Single Observation	Derived variable - What is your current occupation?
ELSA	Personal	Self-reported	Panel	Derived variable - Individual earnings after tax and other deductions
FinnTwin	Personal	Self-reported	Single Observation	How much is Your monthly income, pretax?
GFG	Household	Self-reported	Single Observation	What is your best estimate of the current total yearly income of all individuals living in your household (for example, family members) with whom you share finances? Please include all sources of income, before taxes, in U.S. Dollars.
GS	Household	Self-reported	Single Observation	Average total income before tax of your entire household? 1 - <10,000,2 - 10,000-30,000,3 - 30,000-50,000,4 - 50,000-70,000,5 - 70,000+,6 - prefer not-answer
HRS	Personal	Self-reported	Panel	Derived variable - Individual earnings, the sum of wage/salary income, bonuses/overtime pay/commissions/tips, 2nd job or military reserve earnings, professional practice or trade income.
HUNT	Occupational Wages	Self-reported	Single Observation	Derived occupational wage from occupation codes
iPSYCH	Parental Proxy	Registry-based	Average	Average income of their mothers or fathers between age 30 and 55
KORA - S3	Household	Self-reported	Single Observation	What is the monthly household income, i.e. the net income, that all of you have available after taxes and social contributions?
KORA - S4	Household	Self-reported	Single Observation	What is the total monthly net income of your household, i.e. the income of all household members after taxes and social contributions? Please indicate the corresponding number from the list.
LifeLines - Cyto	Household	Self-reported	Single Observation	Hoeveel bedraagt het netto inkomen per maand. Dus wat contant en/of op uw bank/giro ontvangt. LET OP: als u het huishouden met iemand deelt, dan ook de inkomsten van uw partner(s) meetellen.
	Occupational Wages	Self-reported	Single Observation	What is your current or last occupation? (recoded into isco, recoded into income)
LifeLines - UGLI	Household	Self-reported	Single Observation	Hoeveel bedraagt het netto inkomen per maand. Dus wat contant en/of op uw bank/giro ontvangt. LET OP: als u het huishouden met iemand deelt, dan ook de inkomsten van uw partner(s) meetellen.

	Occupational Wages	Self-reported	Single Observation	What is your current or last occupation? (recoded into isco, recoded into income)
MCTFR - Children	Personal	Self-reported	Single Observation	"What is your annual income from salary before taxes?"
MCTFR - Family	Household	Self-reported	Single Observation	"What is the total gross income from all sources (before taxes but after business expenses) for your household."
MoBa	Personal	Self-reported	Single Observation	What was your gross income (before tax) last year? (using categories)
NEO	Personal	Self-reported	Single Observation	What is your net monthly income? (that is the amount paid into your account each month by your employer or benefits agency)
NTR	Occupational Wages	Self-reported	Single Observation	Derived income - Income derived from ISCO codes based on job description
QIMR	Personal	Self-reported	Single Observation	(1) [older studies] "Thinking of the income you make from all sources -- salary, investments, pensions, and other sources - approximately how much did you earn before tax (gross) during the last financial year ?" [in 8 bins from 0 to AU$50000; the midrange income for the bin was used in analysis, or the low end of the bin if the highest bin]; or (2) [newer studies] "What is your current combined household gross income, that is before tax. Just give me the letter." followed by list of list of 12 bins from 0 to AU$150000;
RS	Household	Self-reported	Single Observation	"Could you indicate on this map what income represents the current total monthly income of your household?" and "How many people, including you, have to live from this income?"
SHIP	Household	Self-reported	Single Observation	Wie hoch ist etwa das monatliche Haushaltseinkommen, das heißt das Nettoeinkommen, das Ihnen allen zusammen nach Abzug der Steuern und Sozialabgaben zur Verfügung steht? Es würde uns helfen, wenn Sie die Einkommensgruppe nennen könnten, zu der Ihr Haushalt gehört.
UKB	Household	Self-reported	Single Observation	What is the average total income before tax received by your HOUSEHOLD?
	Occupational Wages	Self-reported	Single Observation	Derived variable - Occupational wage from standardized occupation codes
	Regional Income	Self-reported	Single Observation	Derived from home location: Local average weekly household income in 2011, estiamted at Middle Layer Super Output Area
UKHLS	Personal	Self-reported	Panel	Derived variable - monthly gross labour income
	Household	Self-reported	Panel	Derived variable - gross household income, the month before interview
WLS	Personal	Self-reported	Single Observation	Base hourly wage rate at current/last job.
	Household	Self-reported	Single Observation	Total income for respondent's entire household in the last 12 months

Note: This table gives an overview of the phenotypes for each cohort

Table 7.3 Genotyping and Imputation

Study	Platform	SNP level exclusions			Subject level exclusions			Imputation software and reference sample			
		MAF	Call Rate	HWE *P*-value	Call rate	Income exclusions	Other exclusions	Software	Sample	Version	EUR / ALL
1958	illumina_1.2m, affymetrix_v6, infinium_humanhap_550k_v1.1, infinium_humanhap_550k_v3	0.001	0.95	1E-04	0.9		1) Ancestry Outliers 2) Sex mismatch 3) Duplicates	Minimac4	HRC	1.1	ALL
AddHealth	Illumina Human Omni1-Quad BeadChip, Illumina Human Omni-2.5 Quad BeadChip	0.001	0.95	1E-04	0.95		1) Ancestry outliers 2) Sex mismatch 3) Autosomal Hetero-/Homozygosity Outliers 4) Duplicates	Minimac	1000 Genomes Phase	3	EUR
ALSPAC - Mothers	Illumina human660W quad	0.01	0.95	5E-07	0.95		1) Close relatives 2) Ancestry outliers 3) Sex mismatch 4) Autosomal Hetero-/Homozygosity Outliers	IMPUTE2	1000 Genomes Phase 1	3	ALL
ALSPAC - Children	Illumina HumanHap550 quad	0.01	0.95	5E-07	0.95		1) Close relatives 2) Ancestry outliers 3) Sex mismatch 4) Autosomal Hetero-/Homozygosity Outliers	IMPUTE2	1000 Genomes Phase 1	3	ALL
CoLaus	Affymetrix 500K	0.01	0.9	1E-07	0.9		1) Close relatives 2) Ancestry outliers	MiniMac3	1000 Genomes Phase 3	5	ALL
Croatia - Korcula	Illumina Human370CNV-Quad	0.01	0.98	1E-06	0.97		1) Sex mismatch 2) Autosomal Hetero-/Homozygosity Outliers	PBWT - Sanger imputation server	HRC	1.1	EUR
EGCUT	GSA MD-24v3-0	0.01	0.95	1E10-5	0.95		1) Close relatives 2) Ancestry outliers 3) Sex mismatch 4) Autosomal Hetero-/Homozygosity Outliers	BEAGLE	HRC and Estonia specific reference sample	1.1 / Mitt et al, EJHG 2017	EUR
ELSA	HumanOmni2.5 BeadChips (HumanOmni2.5-4v1, HumanOmni2.5-8v1.3)	0.01	0.95	1E10-4	0.99		1) Ancestry Outliers 2) Sex mismatch 3) Duplicates 4) Autosomal Hetero-/Homozygosity Outliers	IMPUTE2	1000 Genomes Phase 1	3	ALL

FinnTwin	Illumina Human610-Quad v1.0 B, Human670-QuadCustom v1.0 A, Illumina HumanCoreExome- (12 v1.0 A, 12 v1.1 A, 24 v1.0 A, 24 v1.1 A, 24 v1.2 A), Affymetrix FinnGen Axiom array	0.01	0.95 (batch 2) 0.975 (batch 1 and 3)	1E-06	0.98 (batch 1), 0.95 (batch 2 and 3)	1) Ancestry Outliers 2) Sex mismatch 3) Duplicates 4) Autosomal Hetero-/Homozygosity Outliers	MiniMac3	HRC	1.1	EUR
GFG	Illumina Infinium CoreExome-24 v.1.0 and v.1.1	0.00005	0.95	8E-08	0.99	1) Sex mismatch 2) Duplicates	MiniMac4 - Michigan Imputation Server	1000 Genomes Phase 3	5	ALL
GS	Illumina HumanOmniExpressExome-8 v1.0 and v1.2	0.01	0.98	1E-06	0.98		IMPUTE2	HRC	1.1	EUR
HRS	HumanOmni2.5 BeadChips (HumanOmni2.5-4v1, HumanOmni2.5-8v1)	0.01	0.98	1E-04	0.98	1) Ancestry Outliers 2) Sex mismatch 3) Duplicates	IMPUTE2	1000 Genomes Phase 1	3	ALL
HUNT	Illumina HumanCoreExome	0	0.99	1E-04	0.99	1) Ancestry Outliers 2) Gonosomal constellations other than XX and XY 3) Sex mismatch 4) Duplicates 5) Mendelian Errors 6) Autosomal Hetero-/Homozygosity Outliers	Minimac3	HRC and HUNT WGS	1.1	EUR
iPSYCH	Illumina PsychChip	0.001	0.9	1E-06	0.99	1) Close relatives 2) Ancestry outliers 3) Sex mismatch 4) Duplicates 5) Autosomal Hetero-/Homozygosity Outliers	IMPUTE2	1000 Genomes Phase 3	5	ALL
KORA - S3	Illumina Omni	0.01	0.98	5E-06	0.97	1) Ancestry Outliers 2) Sex mismatch 3) Duplicates 4) Autosomal Hetero-/Homozygosity Outliers	IMPUTE2	1000 Genomes Phase 3	5	EUR
KORA - S4	Affymetrix Axiom	0.02	0.98	5E-10	0.97	1) Ancestry Outliers 2) Sex mismatch 3) Duplicates 4) Autosomal Hetero-/Homozygosity Outliers	IMPUTE2	1000 Genomes Phase 3	5	EUR

LifeLines - Cyto	HumanCytoSNP-12 BeadChip	0.01	0.95	1E-04	0.8		1) Ancestry Outliers 2) Sex mismatch 3) Duplicates 4) Autosomal Hetero-/Homozygosity Outliers	MiniMac	GoNL and 1000 Genomes Phase 1	3 (1000 Genomes)	EUR
LifeLines - UGLI	Illumina global screening array (GSA) Beadchip-24 v1.0	0	0.99	1E-06	0.8		1) Ancestry Outliers 2) Sex mismatch 3) Duplicates 4) Autosomal Hetero-/Homozygosity Outliers	PBWT - Sanger imputation server	HRC	1.1	EUR
MCTFR	Illumina Human660W-Quad array	0.01	0.99	1E-07			1) Ancestry Outliers	MiniMac	1000 Genomes Phase 3	5	EUR
MoBa	Illumina HumanCoreExome-12 v1.1 and HumanCoreExome-24 v.1.0	0.01	0.98	1E-06	0.98		1) Ancestry Outliers 2) Sex mismatch 3) Pedigree mismatch 4) Duplicates 5) Autosomal Hetero-/Homozygosity Outliers	PBWT - Sanger imputation server	HRC	1.1	ALL
NEO	Illumina HumanCoreExome-24v1	0	0.98	1E-06	0.98		1) Close Relatives 2) Ancestry Outliers 3) Sex mismatch 4) Duplicates 5) Autosomal Hetero-/Homozygosity Outliers	IMPUTE2	1000 Genomes Phase 1	3	ALL
NTR	Illumina 370K, 660K, Omni 1M, Perlegen-Affymetrix 5.0, 6.0 907K	1E-06	0.95	1E-06	0.9	Phenotypic Outiers	1) Ancestry Outliers 2) Genotype mismatches between batches and zygosity 3) Sex mismatch 4) Duplicates 5) Autosomal Hetero-/Homozygosity Outliers	Minimac3	1000 Genomes Phase 3	5	ALL
QIMR	Illumina 317, 370, 610, 660K, Core+Exome, PsychArray, Omni2.5, OmniExpress	0.01	0.95	1E-06	0.97		1) Ancestry Outliers 2) Sex mismatch 3) Pedigree mismatch 4) Mendelian Errors	Minimac3 - Michigan Imputation Server	HRC	1.1	ALL
RS	Illumina 550 (+duo), 610-Quad	0.01	0.9	1E-06	0.975		1) Close Relatives 2) Ancestry Outliers 3) Sex mismatch 4) Duplicates	MaCH	HRC	1.1	EUR

SHIP	Affymetrix SNP 6.0	0	0.95	1E-04	0.92		1) Sex mismatch 2) Duplicates 3) Autosomal Hetero-/Homozygosity Outliers	Minimac3 - Michigan Imputation Server	HRC	1.1	ALL
STR											
UKB	Various versions of Affymetrix UK Biobank Axiom array	0.01	0.9	1E-12	Flagged with heterozygosity outliers		1) Sex mismatch 2) Autosomal Hetero-/Homozygosity Outliers	IMPUTE4	HRC and UK10K	1.1 (HRC)	ALL
UKHLS	Illumina CoreExome v1.0	0	0.98	1E-04	0.98	Self-reported income ≤ 0	1) Close Relatives 2) Ancestry Outliers 3) Genotype mismatch 4) Sex mismatch 5) Pedigree mismatch 6) Duplicates 7) Autosomal Hetero-/Homozygosity Outliers	IMPUTE2	1000 Genomes Phase 1 and UK10K	3	ALL
WLS	Illumina OmniExpress	0.0001	0.9	1E-04	0.98	Self-reported income ≤ 0	1) Ancestry Outliers 2) Sex mismatch 3) Duplicates	IMPUTE2	1000 Genomes Phase 1	3	ALL

Note: This table gives an overview of genotyping platforms, cohort level exclusion criteria and imputation panel used.

Table 7.4 Association Analyses

Cohort	Software	Variables omitted	Additional controls	Familial adjustment
1958	GCTA-fastGWA v1.93.2b			Linear Mixed Model
AddHealth	GCTA-fastGWA v1.93.2b			Linear Mixed Model
ALSPAC	SNPTEST v2.5.4			None
CoLaus	GCTA 1.92.1		Dummy variable for retirement benefits	None
Croatia - Korcula	RegScan v0.2			GenABEL
EGCUT	SAIGE 0.29.4.2			Linear Mixed Model
ELSA	GCTA v1.91.7			Linear Mixed Model
FinnTwin	RVTESTS v2.0.9			Linear Mixed Model
GFG	BOLT-LMM		Dummy variables for unemployment, materinity, stay at home parents, disabled and retired, and number of adults in the household	Linear Mixed Model
GS	BOLT-LMM v2.3.2			Linear Mixed Model
HRS	GCTA v1.91.7			Linear Mixed Model
HUNT	BOLT-LMM v2.3.4		Dummy variables for genotyping batches	Linear Mixed Model
iPSYCH	BOLT-LMM v2.3.2		Dummy variables for disease status and survey wave, number of adults in the household (household income only)	Linear Mixed Model
KORA	SNPTEST v2.5.4			None
LifeLines	BOLT-LMM v2.3.4			Linear Mixed Model
MCTFR	GCTA v1.92.2			Linear Mixed Model
MoBa	BOLT-LMM v2.3.4		Dummy variables for genotyping batches	Linear Mixed Model
NEO	SNPTEST v2.5.4			None
NTR	Saige v0.38		Dummy variables for genotyping platforms	Linear Mixed Model
QIMR	BOLT-LMM v2.3.2	Birth year variables	Dummy variables for year of measurement and genotyping platforms	Linear Mixed Model
RS	RVTESTS			None
SHIP	EPACTS 3.2.6		Number of adults in the household	None
UKB	BOLT-LMM v2.3.4		Dummy variables for assessment center (all) and Employment status (only for household income and regional income	Linear Mixed Model
UKHLS	SNPTEST v2.5.2			None
WLS	GCTA-fastGWA v1.93.2b		Dummy variable for sibling respondents	Linear Mixed Model

Note: This table gives an overview of the analyses run in each cohort

Table 7.5 SNP filtering

Cohort	Phenotype	Gender	Variants in cohort summary before EasyQC steps	Step 1: Inadmissible alleles	SNPs in cohort summary statistic before QC	Step 2: Variable quality	Step 3: Drop X Chromosome	Step 4: *MAF or MAC*	Step 5: Imputation quality	Step 6: HWE *P*value	Step 7: Duplicated *Chr Pos ID*	Step 8a: SNP not in reference file	Step 8b: Allele mismatch	Step 9: AF outlier	SNPs remaining after QC	λ_{GC}
1958	Personal	female	10416124	0	10416124	0	0	5178615	0	77	484	18094	0	0	5218370	1.001
		male	10416083	0	10416083	0	0	5207851	1	42	472	18019	0	0	5189226	1.001
		female	8186285	0	8186285	0	0	4088453	4014	9	922	10812	0	2	4081151	1.002
AddHealth	Personal	male	8186385	0	8186385	0	0	4042925	4015	49	1000	10863	0	0	4126533	1.003
ALSPAC - Mothers	Occupational	female	27375080	1306612	26068468	9555456	0	8807059	393920	8	25	562101	61	1795	6748018	1.027
ALSPAC - Children	Personal	female	27375080	1306612	26068468	12920399	0	7668049	149776	30	14	446744	23	1763	4881656	1.004
		male	27375080	1306612	26068468	14200769	0	7495647	101088	234	6	367662	17	1733	3901306	1.005
CoLaus	Household	female	46126171	2953963	43172208	27199373	0	10496974	593778	298	0	442833	63	2801	4436088	0.991
		male	46126171	2953963	43172208	27527420	0	10462512	543111	280	0	425152	60	2790	4210883	1.054
Croatia - Korcula	Household	female	12279963	0	12279963	7454	0	7129583	42120	16	0	16241	0	144	5084405	0.989
		male	11887575	0	11887575	5905	0	7678281	28261	321	0	13465	0	254	4161088	0.987
EGCUT	Occupational	female	26056411	1909335	24147076	3490	0	12857013	42887	0	3507	856857	2458	2155	10375202	1.059
		male	26032907	1907473	24125434	3448	0	14273482	20430	0	3198	599061	962	2154	9219501	1.002
ELSA	Personal	female	7938151	0	7938151	3	0	2737154	0	3544	4542	564053	182	6409	4617729	0.996
		male	7938151	0	7938151	0	0	2846994	0	3480	4349	553346	177	6370	4519093	1.019
FinnTwin	Personal	female	39127678	0	39127678	1894227	0	30692939	20526	1158	3417	21941	0	447	6489615	1.015
		male	39127678	0	39127678	1953484	0	30812517	19314	711	3174	21619	0	376	6313318	1.016
GFG	Household	female	23272178	1978465	21293713	5581688	0	8042511	996807	0	8174	592281	169	3605	6060317	1.047
		male	23103551	1966398	21137153	7833940	0	6295183	772959	3	7223	563429	142	3607	5653454	1.000
GS	Household	female	12378367	0	12378367	0	0	5406833	55404	0	3013	22594	0	28	6887483	1.000
		male	12378367	0	12378367	0	0	4896335	70395	0	3607	23433	0	36	7380955	1.047
HRS	Personal	female	8591082	352	8590730	167485	0	2898084	0	305844	0	425719	80	1454	4792064	1.005
		male	8591082	352	8590730	245541	0	3015791	0	299385	0	412493	67	1439	4616014	0.996
HUNT	Occupational	female	24390720	736232	23654488	827685	0	12824699	108974	0	7557	635839	327	552	9241311	1.097
		male	24390720	736232	23654488	1067988	0	12859922	99932	0	7131	616695	272	525	8994906	1.047

iPSYCH	Parental Proxy	female	6874560	0	6874560	320	0	0	185984	0	0	541778	97	2200	6144181	1.047
		male	6874560	0	6874560	320	0	0	185984	0	0	541778	97	2202	6144179	1.097
KORA - S3	Household	female	19529344	1691975	17837369	11152	0	12440562	92431	9	4628	554249	106	4358	4725252	0.997
		male	19747966	1701792	18046174	12538	0	12575508	94282	5	4761	560046	106	4361	4789812	1.002
KORA - S4	Household	female	21136235	1768030	19368205	19275	0	13514618	195217	11	5334	579671	112	4820	5043819	1.011
		male	21213858	1770381	19443477	19149	0	13560487	196425	17	5408	581978	113	4799	5069699	1.000
LifeLines - Cyto	Household	female	45837198	1969771	43867427	15470807	0	20742155	179880	10	10536	575819	216	8299	6869172	1.000
		male	45837198	1969771	43867427	16371761	0	20259384	151772	10	9976	550802	170	8290	6505289	1.047
LifeLines - Cyto	Occupational	female	45837198	1969771	43867427	17024376	0	19920075	134310	10	9623	531538	137	8334	6229404	1.000
		male	45837198	1969771	43867427	18093699	0	19319113	110134	10	9018	501424	109	8323	5816581	1.000
LifeLines - UGLI	Household	female	39595748	0	39595748	11034355	0	20361152	90730	21	85236	1583	0	1345	8004177	1.047
		male	40297838	0	40297838	12495263	0	19934708	102773	75	163176	2439	0	1343	7571419	1.000
LifeLines - UGLI	Occupational	female	39595748	0	39595748	13522409	0	18674499	65109	316	76623	1417	0	1331	7238577	1.000
		male	40297838	0	40297838	15359686	0	17929765	79192	344	143372	2306	0	1321	6757545	1.000
MCTFR - Children	Personal	female	16163077	0	16163077	0	0	11684203	15799	385	866	17953	0	19	4442992	1.019
		male	15707463	0	15707463	0	0	11354474	14829	383	776	17560	0	16	4318655	1.046
MCTFR - Family	Household	female	20005293	0	20005293	0	0	14373347	23005	135	1867	20551	0	21	5584507	1.048
		male	19549783	0	19549783	0	0	14084332	21452	134	1673	20242	0	14	5420270	1.039
MoBa	Personal	female	39131578	0	39131578	10687718	0	20469440	48953	0	4865	24129	0	31	7891585	1.047
		male	39131578	0	39131578	12197702	0	19413069	38434	19883	4234	23355	0	25	7430649	1.000
NEO	Personal	female	29736423	1378071	28358352	15450836	0	7763627	411077	0	0	324625	57	963	4407167	1.011
		male	29736423	1378071	28358352	15338899	0	7786367	422815	0	0	329468	60	961	4479782	1.012
NTR	Occupational	female	31485106	2541975	28943131	50	1283974	20350825	714123	0	7460	589193	131	3844	5986080	0.995
		male	27565102	2325045	25240057	1914	1174838	17697732	497563	0	5863	540561	113	3824	5311791	1.006
QIMRB	Personal	female	39117105	4436735	34680370	16693228	0	12782800	70828	0	1156	19070	0	7	5112127	1.012
		male	39117105	4436735	34680370	15346902	0	13701037	84636	0	1523	19953	0	8	5524790	0.996
RS I	Household	female	7746023	0	7746023	1	0	1796561	58938	7	2105	20797	0	0	5865514	1.044
		male	7746630	0	7746630	3	0	2213536	51726	9	1638	20118	0	0	5457967	1.043
RS II	Household	female	7746467	0	7746467	5	0	3380201	36645	35	748	17299	0	0	4310790	1.055
		male	7737562	0	7737562	4	0	3607310	33919	333	627	16534	0	0	4078212	1.047

RS III	Household	female	7746535	0	7746535	5	0	2742355	41415	53	1119	19037	0	0	4941436	1.034
		male	7748321	0	7748321	5	0	3096952	37258	42	890	18177	0	0	4594111	1.021
SHIP	Household	female	39127678	0	39127678	22330316	0	11692277	44649	0	1276	13722	0	603	5043564	1.013
		male	39127678	0	39127678	22312093	0	11712729	44679	0	1274	13721	0	601	5041312	1.007
UKB	Household	female	18391744	1764390	16627354	729160	0	2810952	683982	0	10334	1572285	1614	308	10808402	1.147
		male	18392183	1764416	16627767	729160	0	2815983	683394	0	10326	1571623	1608	307	10805057	1.147
UKB	Occupational	female	18391410	1764386	16627024	729159	0	2811585	683167	0	10334	1571363	1607	310	10809183	1.147
		male	18391316	1764376	16626940	729160	0	2817453	682360	0	10330	1570630	1609	309	10804776	1.147
UKB	Regional	female	18392637	1764426	16628211	729160	0	2810293	683283	0	10347	1571474	1613	312	10811400	1.200
		male	18392004	1764403	16627601	729159	0	2817416	682200	0	10339	1570372	1603	313	10805877	1.147
UKHLS	Household	female	24727462	1938967	22788495	3464376	0	12564855	219143	0	8	510141	96	1571	6028303	1.017
		male	24727458	1938967	22788491	4263405	0	12133710	184146	0	8	492561	90	1567	5713002	0.999
UKHLS	Personal	female	24727454	1938967	22788487	4693995	0	11885188	168763	0	7	483221	87	1558	5555667	1.014
		male	24727454	1938967	22788487	5305272	0	11543235	149351	0	7	468439	79	1559	5320544	1.003
WLS	Household	female	13965879	1187461	12778418	0	0	6743084	0	133	6300	473609	164	2336	5546500	0.994
		male	13544776	1156654	12388122	0	0	6441917	0	132	6117	467317	163	2341	5464026	0.993
WLS	Personal	female	13725404	1169865	12555539	0	0	6564513	0	132	6222	470409	163	2338	5505548	0.996
		male	13669800	1165930	12503870	0	0	6552112	0	132	6116	467748	163	2340	5469151	0.985

Note: This table gives an overview of the QC filtering and the number of SNPs removed in each step

Table 7.6 Estimated heritability from LDSC

Cohort	Phenotype	h^2	S.E.	*Z*-score	*P*-value	λ_{gc}	mean χ^2	LDSC intercept	LDSC intercept S.E.	Ratio	Ratio S.E	N
1958	Personal	0.134	0.100	1.34	1.8E-01	1.008	1.012	0.998	0.007	NA*	NA*	4,748
AddHealth	Personal	0.086	0.120	0.72	4.7E-01	1.026	1.015	1.007	0.008	0.472	0.549	4,301
ALSPAC - Mothers	Occupational	0.089	0.069	1.30	1.9E-01	1.029	1.031	1.019	0.007	0.589	0.231	7,019
ALSPAC - Children	Personal	0.054	0.198	0.28	7.8E-01	1.005	1.005	1.002	0.009	0.339	1.845	2,542
CoLaus	Household	0.032	0.212	0.15	8.8E-01	1.035	1.033	1.031	0.009	0.941	0.283	2,716
Croatia - Korcula	Household	-0.029	0.202	-0.14	8.9E-01	1.008	1.007	1.008	0.009	1.237	1.322	2,716
EGCUT	Occupational	0.038	0.008	4.83	1.3E-06	1.108	1.114	1.054	0.007	0.469	0.064	79,694
ELSA	Personal	0.128	0.162	0.79	4.3E-01	1.005	1.001	0.993	0.008	NA*	NA*	2,745
FinnTwin	Personal	-0.236	0.055	-4.27	2.0E-05	1.011	1.004	1.041	0.008	11.109	2.029	7,797
GFG	Household	0.081	0.029	2.85	4.4E-03	1.047	1.052	1.018	0.008	0.344	0.157	20,659
GS	Household	0.030	0.037	0.80	4.2E-01	1.077	1.072	1.064	0.006	0.891	0.090	13,367
HRS	Personal	0.098	0.067	1.47	1.4E-01	1.011	1.006	0.993	0.007	NA*	NA*	6,812
HUNT	Occupational	0.063	0.014	4.56	5.1E-06	1.156	1.157	1.098	0.008	0.627	0.049	46,342
iPSYCH	Parental	0.046	0.006	8.00	1.2E-15	1.102	1.108	1.000	0.008	0.003	0.074	105,667**
KORA - S3	Household	-0.252	0.154	-1.64	1.0E-01	0.990	0.992	1.007	0.006	NA*	NA*	3,460
KORA - S4	Household	-0.083	0.127	-0.65	5.1E-01	1.002	1.002	1.008	0.007	4.409	3.890	2,715
LifeLines - Cyto	Household	0.087	0.043	2.05	4.1E-02	1.038	1.038	1.019	0.007	0.501	0.177	10,949
LifeLines - Cyto	Occupational	0.088	0.068	1.28	2.0E-01	1.041	1.038	1.026	0.008	0.689	0.200	6,822
LifeLines - UGLI	Household	0.042	0.019	2.18	2.9E-02	1.062	1.059	1.040	0.007	0.681	0.116	23,514
LifeLines - UGLI	Occupational	0.042	0.036	1.19	2.3E-01	1.044	1.045	1.034	0.007	0.756	0.154	13,528
MCTFR - Children	Personal	0.235	0.242	0.97	3.3E-01	1.047	1.041	1.031	0.008	0.740	0.201	2,137
MCTFR - Family	Household	0.169	0.122	1.39	1.6E-01	1.146	1.149	1.134	0.008	0.898	0.053	4,417
MoBa	Personal	0.065	0.022	2.96	3.0E-03	1.029	1.027	1.002	0.007	0.053	0.243	20,428
NEO	Personal	0.174	0.182	0.96	3.4E-01	1.008	1.012	0.999	0.010	NA*	NA*	3,144
NTR	Occupational	-0.022	0.075	-0.30	7.7E-01	1.026	1.030	1.033	0.008	1.105	0.258	6,778
QIMRB	Personal	0.170	0.114	1.49	1.4E-01	1.020	1.024	1.009	0.007	0.373	0.305	4,167
RS I	Household	0.125	0.090	1.39	1.6E-01	1.041	1.039	1.026	0.007	0.669	0.177	4,999
RS II	Household	0.356	0.279	1.27	2.0E-01	1.065	1.060	1.045	0.009	0.755	0.154	1,942
RS III	Household	0.291	0.193	1.51	1.3E-01	1.038	1.042	1.025	0.008	0.598	0.196	2,739
SHIP	Household	0.035	0.141	0.25	8.0E-01	1.011	1.012	1.009	0.007	0.794	0.631	3,228
UKB	Household	0.066	0.003	20.59	3.1E-94	1.449	1.555	1.045	0.011	0.081	0.020	382,731
UKB	Occupational	0.094	0.004	22.29	5E-110	1.453	1.581	1.035	0.011	0.060	0.018	282,963
UKB	Regional	0.056	0.003	19.45	3.0E-84	1.540	1.624	1.161	0.011	0.259	0.017	401,856
UKHLS	Household	0.090	0.054	1.67	9.5E-02	1.017	1.024	1.008	0.008	0.325	0.318	8,837
UKHLS	Personal	0.116	0.072	1.62	1.1E-01	1.011	1.012	0.997	0.007	NA*	NA*	6,288

WLS	Household	0.043	0.061	0.70	4.8E-01	1.008	0.994	0.987	0.007	NA*	NA*	7,602
WLS	Personal	0.011	0.057	0.19	8.5E-01	0.993	0.994	0.993	0.007	NA*	NA*	7,493

Note: This table gives an overview of LDSC heritability estimates for each cohort

*LDSC does not calculate the ratio when the mean χ^2 or LDSC intercept is below 1

**Maximum of equivalent N

Table 7.7 Estimated genetic correlation with UKB Occupational Wages

Cohort	Phenotype	Gen Cov	S.E.	*Z*-score	*P*-value	r_G	S.E.	*Z*-score	*P*-value	N
1958	Individual	0.1033	0.0153	6.75	1.5E-11	0.97	0.48	2.03	4.2E-02	4,748
AddHealth	Individual	*Could not be estimated**				*Could not be estimated**				4,301
ALSPAC - Mothers	Occupational	0.123	0.013	9.63	0.0E+00	1.05	0.40	2.67	7.7E-03	7,019
ALSPAC - Children	Individual	*Could not be estimated**				*Could not be estimated**				2,542
CoLaus	Household	*Could not be estimated**				*Could not be estimated**				2,716
Croatia - Korcula	Household	0.033	0.018	1.82	6.8E-02	*Could not be estimated**				2,716
EGCUT	Occupational	0.069	0.004	16.14	1.3E-58	1.12	0.10	11.63	2.8E-31	79,694
ELSA	Individual	0.025	0.020	1.23	2.2E-01	0.18	0.17	1.07	2.9E-01	2,745
FinnTwin	Individual	0.030	0.010	3.00	2.7E-03	*Could not be estimated**				7,797
GFG	Household	0.069	0.007	9.45	3.3E-21	0.78	0.13	6.11	9.9E-10	20,659
GS	Household	0.071	0.009	8.16	3.3E-16	1.12	0.48	2.36	1.8E-02	13,367
HRS	Individual	0.070	0.012	5.81	6.3E-09	0.67	0.22	2.98	2.8E-03	6,812
HUNT	Occupational	0.062	0.005	11.83	2.8E-32	0.82	0.10	8.34	7.5E-17	46,342
iPSYCH	Parental	0.057	0.004	14.30	2.2E-46	0.87	0.05	16.83	1.6E-63	105,667**
KORA - S3	Household	0.041	0.017	2.42	1.6E-02	*Could not be estimated**				3,460
KORA - S4	Household	-0.019	0.017	-1.10	2.7E-01	*Could not be estimated**				2,715
LifeLines - Cyto	Household	0.060	0.009	6.74	1.6E-11	0.69	0.21	3.27	1.1E-03	10,949
LifeLines - Cyto	Occupational	0.076	0.012	6.34	2.3E-10	1.05	0.73	1.43	1.5E-01	6,822
LifeLines - UGLI	Household	0.051	0.006	8.43	3.6E-17	0.89	0.24	3.68	2.3E-04	23,514
LifeLines - UGLI	Occupational	0.064	0.008	7.86	3.7E-15	0.91	0.34	2.67	7.6E-03	13,528
MCTFR - Children	Individual	0.052	0.021	2.47	1.3E-02	0.36	0.26	1.37	1.7E-01	2,137
MCTFR - Family	Household	0.073	0.014	5.13	3.0E-07	0.60	0.26	2.34	1.9E-02	4,417
MoBa	Household	0.056	0.007	8.37	5.6E-17	0.80	0.18	4.44	9.0E-06	20,428
NEO	Individual	0.087	0.018	4.87	1.1E-06	0.68	0.41	1.68	9.3E-02	3,144
NTR	Occupational	0.063	0.012	5.07	3.9E-07	*Could not be estimated**				6,778
QIMRB	Individual	0.061	0.014	4.30	1.7E-05	0.49	0.20	2.44	1.5E-02	4,167
RS I	Household	0.037	0.012	3.07	2.2E-03	0.35	0.18	1.92	5.5E-02	4,999
RS II	Household	0.021	0.023	0.92	3.6E-01	0.12	0.14	0.85	3.9E-01	1,942
RS III	Household	0.090	0.020	4.61	4.1E-06	0.49	0.17	2.85	4.4E-03	2,739
SHIP	Household	*Could not be estimated**				*Could not be estimated**				3,228
UKB	Household	0.071	0.003	22.09	4E-108	0.90	0.01	66.93	0.0E+00	382,731
UKB	Occupational	*Target phenotype*				*Target phenotype*				282,963
UKB	Regional	0.060	0.003	21.54	7E-103	0.83	0.02	40.87	0.0E+00	401,856
UKHLS	Household	0.086	0.011	7.93	2.3E-15	0.93	0.28	3.36	7.8E-04	8,837
UKHLS	Individual	*Could not be estimated**				*Could not be estimated**				6,288
WLS	Household	*Could not be estimated**				*Could not be estimated**				7,602
WLS	Individual	-0.004	0.011	-0.33	7.4E-01	*Could not be estimated**				7,493

Note: This table gives an overview of LDSC correlation estimates for each cohort with occupational wages in the UK Biobank

* LDSC can fail to deliver estimates when heritability is low and/or the number of observations is low, which is the case for most individual cohorts

**Maximum of equivalent N

Table 7.8 LDSC Heritability

(A)

Phenotype	h^2_{pooled}	S.E.	*Z*-score	*P*-value	N pooled*	*P*-value ($h^2_{\text{men}} = h^2_{\text{women}}$)
Personal Income	0.043	0.0076	5.62	1.9E-08	72,175.1	6.0E-12
Household Income	0.059	0.0028	20.96	0.0E+00	474,266.3	0.0E+00
Occupational Wages	0.076	0.0031	24.55	0.0E+00	421,053.6	0.0E+00
Parental Income	0.046	0.0058	8.00	1.3E-15	105,667.0	0.0E+00

(B)

Phenotype	h^2_{men}	S.E.	*Z*-score	*P*-value	N men
Personal Income	0.054	0.016	3.39	7.0E-04	33,833
Household Income	0.066	0.004	17.42	0.0E+00	229,061
Occupational Wages	0.069	0.004	16.38	0.0E+00	193,466
Parental Income	0.048	0.010	4.71	2.4E-06	63,886

(C)

	h^2_{women}	S.E.	*Z*-score	*P*-value	N women
Personal Income	0.034	0.012	2.76	5.8E-03	38,781
Household Income	0.056	0.003	16.38	0.0E+00	267,347
Occupational Wages	0.089	0.004	20.63	0.0E+00	249,598
Parental Income	0.052	0.011	4.54	5.8E-06	64,838

Note: This table reports the estimated heritability for each income measure. Panel A shows pooled results, while panels B and C show the results for men and women respectively

*Maximum of equivalent N

Table 7.9 Estimated genetic correlation between men and women

Phenotype	r_G	S.E.	*Z*-score	*P*-value (r_G = 0)	*P*-value (r_G = 1)	N men	N women
Personal Income	1.05	0.32	3.34	8.0E-04	1.0E+00	33,833	38,781
Household Income	0.94	0.028	33.02	4.5E-239	1.4E-02	229,061	267,347
Occupational Wages	0.91	0.027	33.83	8.2E-251	7.8E-04	193,466	249,598
Parental Income	0.78	0.111	7.07	1.6E-12	2.5E-02	63,886	64,838

Note: This table reports the genetic correlation between men and women for each of the cohorts

Table 7.10 Estimated genetic correlation main phenotypes with related phenotypes

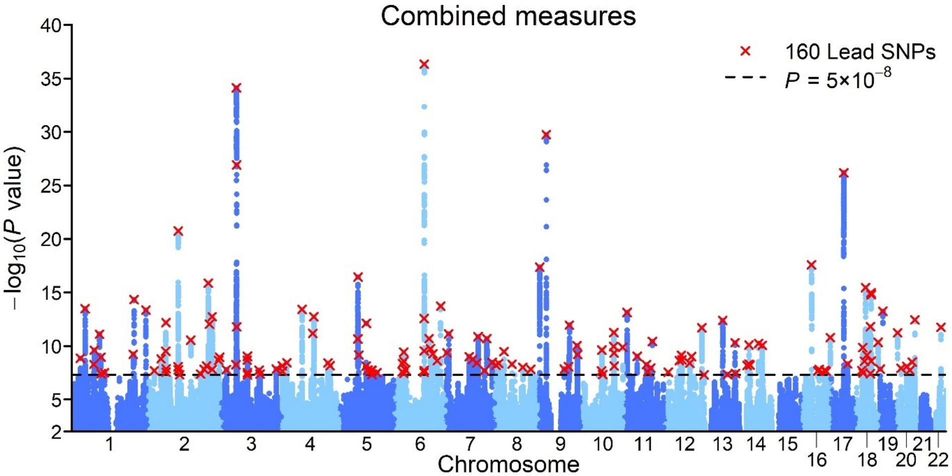
Phenotype 1	Phenotype 2	r_G	S.E.	*Z*-score	*P*-value (r_G = 0)	*P*-value (r_G = 1)	N1*	N2*
Educational Attainment	Personal Income	0.78	0.061	12.69	0.0E+00	1.2E-04	766,345	72,175
Educational Attainment	Household Income	0.79	0.013	60.29	0.0E+00	0.0E+00	766,345	474,266
Educational Attainment	Occupational Wages	0.93	0.010	92.97	0.0E+00	1.0E-12	766,345	421,054
Educational Attainment	Parental Income	0.90	0.011	84.04	0.0E+00	0.0E+00	766,345	105,667
Educational Attainment	Combined Measures	0.90	0.008	111.96	0.0E+00	0.0E+00	766,345	887,680
Cognitive Performance	Personal Income	0.41	0.055	7.51	5.9E-14	0.0E+00	257,828	72,175
Cognitive Performance	Household Income	0.59	0.018	33.08	0.0E+00	0.0E+00	257,828	474,266
Cognitive Performance	Occupational Wages	0.67	0.015	46.17	0.0E+00	0.0E+00	257,828	421,054
Cognitive Performance	Parental Income	0.52	0.044	11.95	0.0E+00	0.0E+00	257,828	105,667
Cognitive Performance	Combined Measures	0.64	0.017	37.80	0.0E+00	0.0E+00	257,828	887,680
Townsend Index	Personal Income	-0.45	0.086	-5.26	1.5E-07	0.0E+00	423,218	72,175
Townsend Index	Household Income	-0.61	0.024	-25.43	0.0E+00	0.0E+00	423,218	474,266
Townsend Index	Occupational Wages	-0.47	0.028	-16.54	0.0E+00	0.0E+00	423,218	421,054
Townsend Index	Parental Income	-0.77	0.093	-8.32	0.0E+00	0.0E+00	423,218	105,667
Townsend Index	Combined Measures	-0.55	0.031	-17.99	0.0E+00	0.0E+00	423,218	887,680
Combined Measures	Personal Income	0.93	0.078	11.83	0.0E+00	1.7E-01	887,680	72,175
Combined Measures	Household Income	0.98	0.007	147.73	0.0E+00	7.6E-05	887,680	474,266
Combined Measures	Occupational Wages	0.96	0.005	194.98	0.0E+00	0.0E+00	887,680	421,054
Combined Measures	Parental Income	0.94	0.043	22.05	0.0E+00	7.8E-02	887,680	105,667
Personal Income	Household Income	0.87	0.086	10.15	0.0E+00	6.4E-02	72,175	474,266
Personal Income	Occupational Wages	0.81	0.075	10.74	0.0E+00	5.0E-03	72,175	421,054
Personal Income	Parental Income	1.11	0.15	7.22	5.2E-13	2.4E-01	72,175	105,667
Household Income	Occupational Wages	0.89	0.013	68.78	0.0E+00	0.0E+00	474,266	421,054
Household Income	Parental Income	0.91	0.058	15.83	0.0E+00	7.0E-02	474,266	105,667
Occupational Wages	Parental Income	0.86	0.049	17.56	0.0E+00	1.5E-03	421,054	105,667

Note: This table shows the results of LDSC genetic correlation estimates between income measures and with related phenotypes. Educational attainment results are obtained from the publicly available results of Lee et al. (2018). Cognitive performance results were obtained by running a GWAS in the UK Biobank using data fields 20016 and 20191 and meta-analyzing the results. Townsend Index results were obtained by running a GWAS in the UK Biobank using data field 189.

*MTAG equivalent N for internally run GWAS.

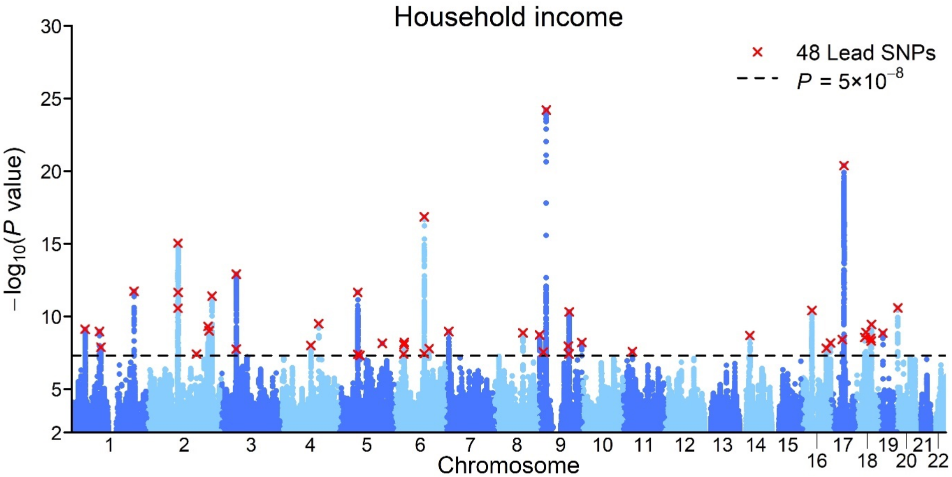
A7.4 Figures

Figure 7.1 Manhattan plot combined measures



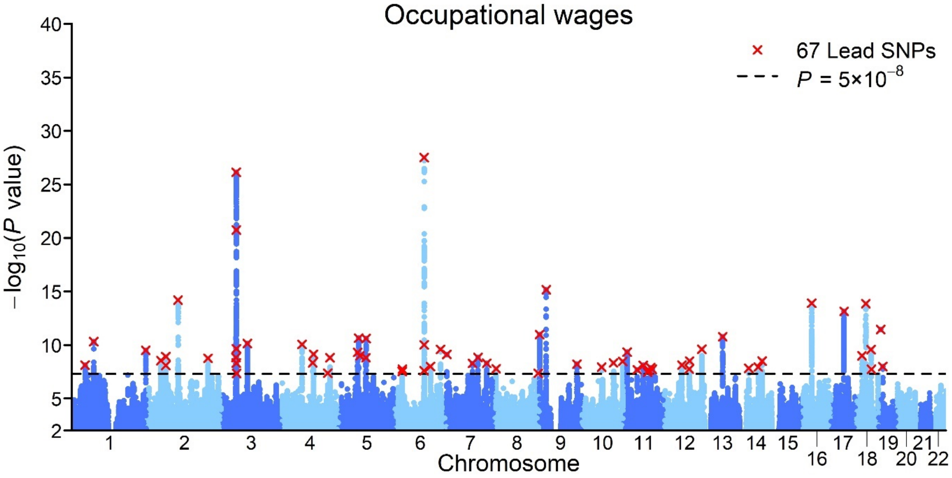
Note: This figure shows a Manhattan plot for the meta-analysis combining all income measures. The log p-value is reported on the y-axis and the chromosome and base pair on the x-axis. The lead SNPs are calculated using a clumping algorithm described in the methods section.

Figure 7.2 Manhattan plot household income



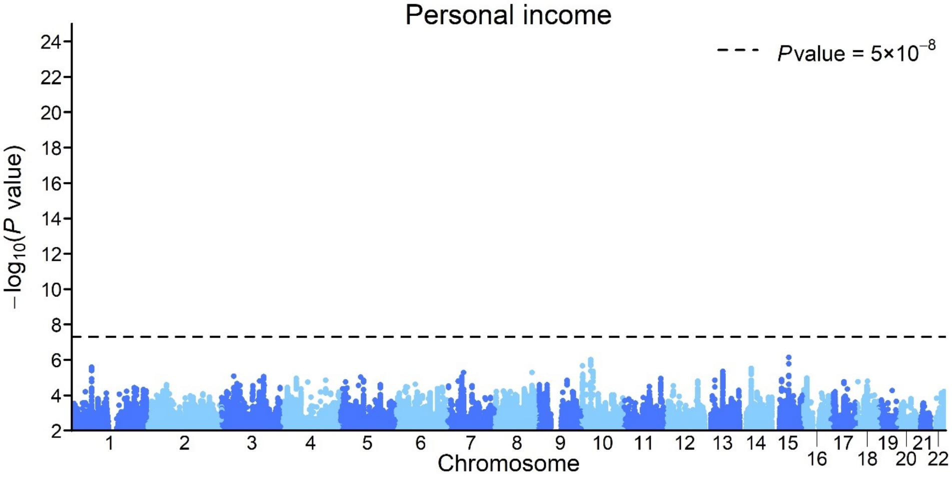
Note: This figure shows a Manhattan plot for household income. The log p-value is reported on the y-axis and the chromosome and base pair on the x-axis. The lead SNPs are calculated using a clumping algorithm described in the methods section.

Figure 7.3 Manhattan plot occupational wages



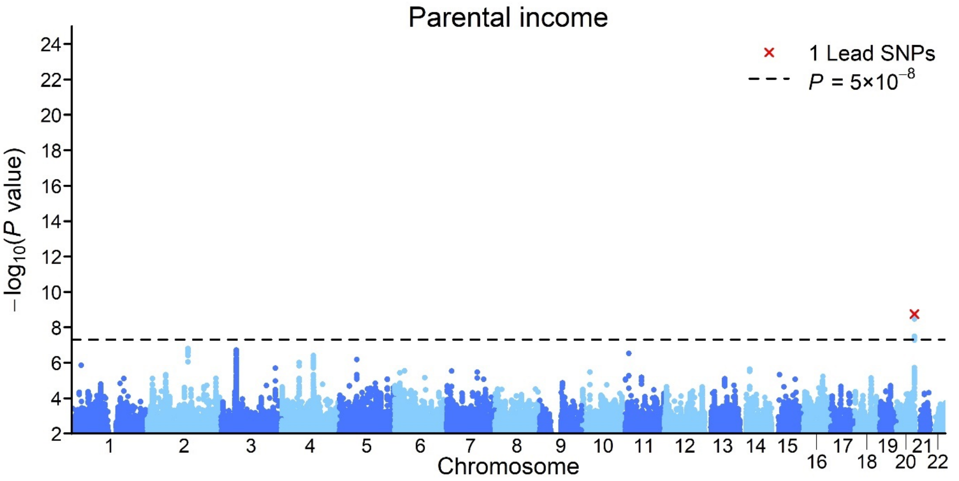
Note: This figure shows a Manhattan plot for occupational wages. The log p-value is reported on the y-axis and the chromosome and base pair on the x-axis. The lead SNPs are calculated using a clumping algorithm described in the methods section.

Figure 7.4 Manhattan plot personal income



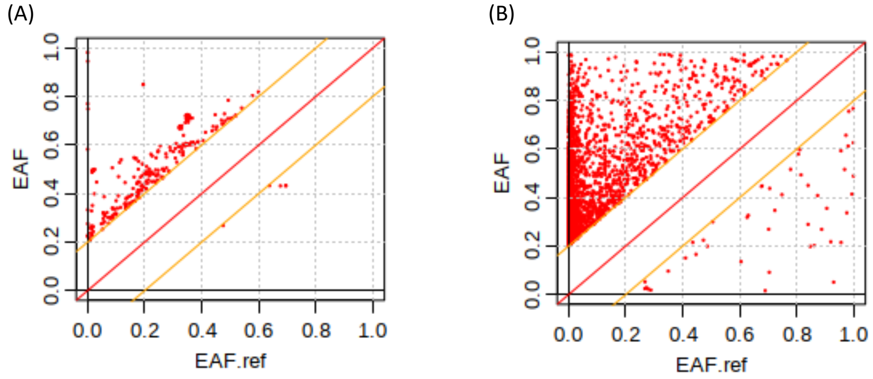
Note: This figure shows a Manhattan plot for personal income. The log p-value is reported on the y-axis and the chromosome and base pair on the x-axis. The lead SNPs are calculated using a clumping algorithm described in the methods section.

Figure 7.5 Manhattan plot parental income



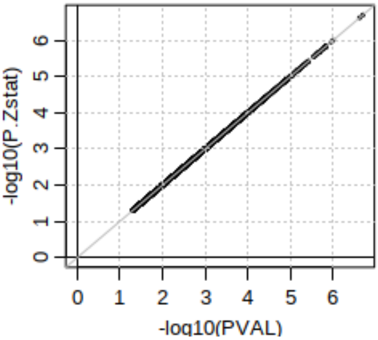
Note: This figure shows a Manhattan plot for parental income. The log p-value is reported on the y-axis and the chromosome and base pair on the x-axis. The lead SNPs are calculated using a clumping algorithm described in the methods section.

Figure 7.6 Allele frequency plots



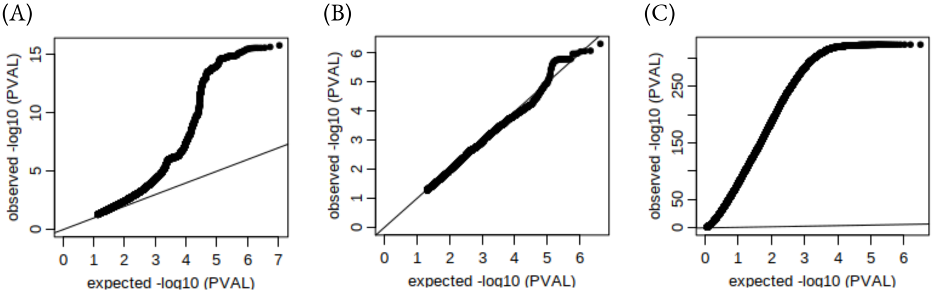
Note: This figure shows two allele frequency plots, where the allele frequency of the cohort (y-axis) is plotted against the allele frequency in the reference sample (x-axis). In panel A, the allele frequency plot of the UK Biobank is shown. As this cohort is imputed with both HRC and UK10k reference panels, almost no SNPs fall outside the +-0.2 allele frequency band outside of the diagonal. Panel B shows the same plot a cohort is imputed with the 1000 Genomes Project reference panel. Here we see more SNPs outside of the band around the diagonal, but most still fall within the band, indicating that they belong to the same population. For computational reasons the center band has not been plotted.

Figure 7.7 P-Z plot



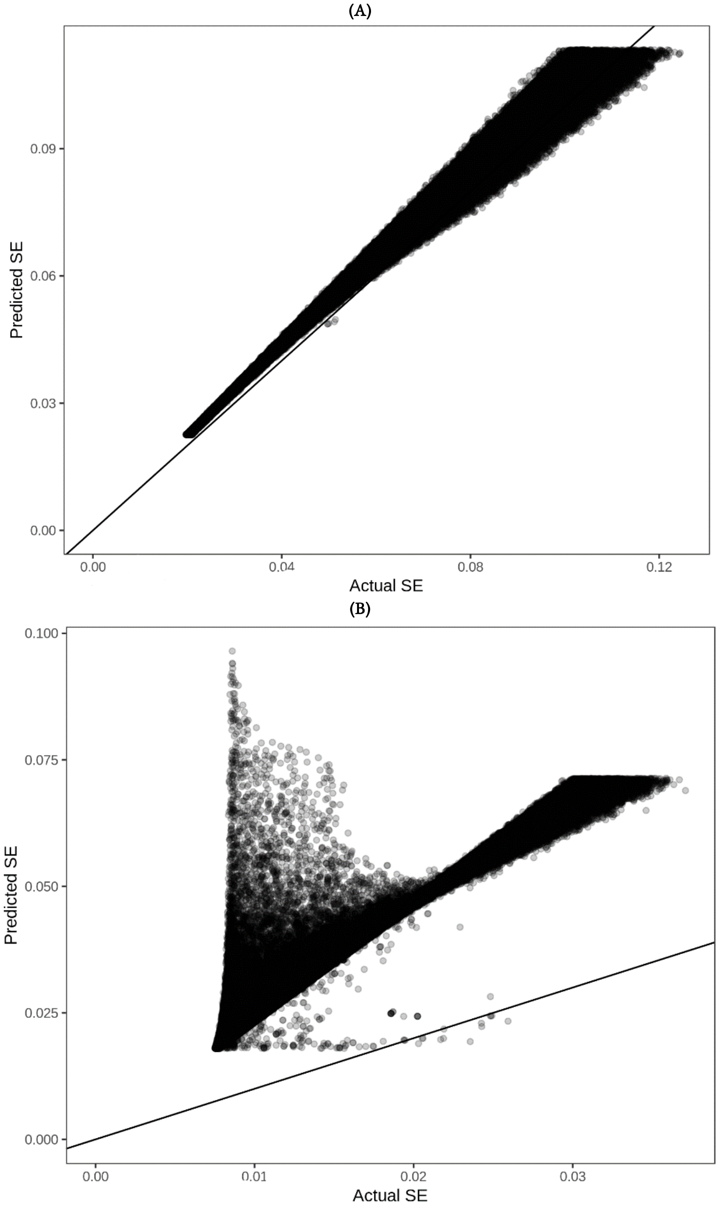
Note: This figure shows an example of P-Z plot, where the p-value calculated from the z-statistic (y-axis) is plotted against the reported p-value (x-axis).

Figure 7.8 Three QQ plots



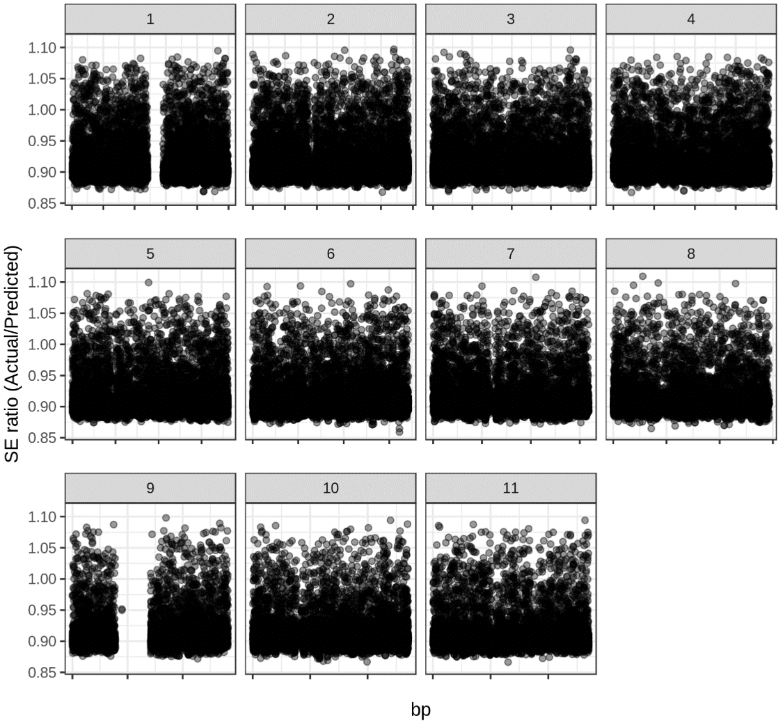
Note: This figure shows three examples of QQ plots, where the distribution of the observed p-values (y-axis) is plotted against the expected p-value under the null-distribution (x-axis). Panel (A) shows the results for a large cohort. Panel (B) shows the results for a small cohort. Panel (C) shows the results for a small cohort with abnormal results. The results in panel (C) are a clear sign of spurious associations.

Figure 7.9 SE-N plots



Note: This figure shows two examples of SE-N plots with the predicted standard error from the minor allele frequency and reported sample size on the y-axis and the reported standard error on the x-axis. Panel (A) shows results as one would expect, where the reported standard error is close to the predicted standard error. Panel (B) shows an example of a cohort where the reported sample size was misreported.

Figure 7.10 SE Manhattan plot



Note: This figure shows an example of a standard error Manhattan plot, where the standard error ratio (reported standard error divided by the predicted standard error) is plotted on the y-axis, against the base pair position on each chromosome on the x-axis for each chromosome. This figure shows an example for the first 11 chromosomes.

Acknowledgements

"True education is a kind of never-ending story — a matter of continual beginnings, of habitual fresh starts, of persistent newness."

J.R.R. Tolkien

Six and a half years ago my supervisor, Philipp, gave a presentation at Tinbergen Institute on the research he did in the field of social science genetics. There was a promise of big data, interesting statistics, and a new and quickly developing field. I was immediately excited about the opportunity to learn new things outside of all the economics and econometrics I had been studying for some time. While I wasn't quite sure whether I wanted to pursue a PhD, I decided to send him a message about writing my MPhil thesis in his field. Slowly but surely, the ball started rolling and my journey as an academic began.

I am writing this a month after starting a new job as a data science consultant, six months after handing in my manuscript for review and five years after I started as a PhD candidate at the Vrije Universiteit. Now, I'm reflecting and looking back on those years, and I am thankful for all the people who've helped me get to where I am. It has been a journey with highs and lows. I had the opportunity to travel to many conferences in Europe and the United States, learn so much, and meet so many new people. I even ended up getting a $\hat{\beta}$ tattoo from a classmate during a course in Santa Barbara. Thank you for all the fun! Sadly, it has also been a journey with moments of getting stuck at dead-ends in research, deadlines and stress. I'm also thankful for all the people who've helped me move passed those.

Now, I would like to thank several people in particular: First, my supervisors, thank you very much, I have learned a lot from you. Philipp, thank you for your guidance, feedback and support, the Christmas parties (including all the cocktails), and giving me the freedom to work from the other side of the globe. Aysu, thank you for your advice and teaching me so much and of course, thank you for all the drinks at conferences. Ronald, thank you for all your help and feedback. From the time you helped me recover my work after I deleted everything in my project folder by accidently adding a space in "`rm * .log`" to writing efficient python code for our simulations. I learned a great deal from working together.

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My dearest friends and colleagues at the SSGAC and everyone I've met at conferences, workshops and courses, you've made me feel right at home in this small field of social science genetics.

I want to thank all my family and friends for all their love and support. My paranymphs, Bas and Mick, I thank you for all your support and much needed distraction during my PhD with dinners, drinks, parties and festivals. Taking a tram with Bas to Pakistan and ending up in Thailand. Being festival buddies with Mick and becoming colleagues. Thanks buddies. Evert, from nerdy kids in primary school to nerdy data scientists as adults. From living together as flatmates to visiting each other while we live in different countries. It's always a blast, and we always have fun. Thank you for everything. Eline, we've been through so much together and I am so grateful we always had each other. You have always been incredibly kind to everyone around you which is something I greatly admire. I'm thankful we're siblings and close friends. Mayra, we've been together for over a decade now and you supported me in so many ways that I could never thank you enough. I love all the adventures we've been on together. It has been amazing so far and I can't wait to get married soon and keep on adventuring.

Love,

Casper Burik

Amsterdam, October 2021

The Tinbergen Institute is the Institute for Economic Research, which was founded in 1987 by the Faculties of Economics and Econometrics of the Erasmus University Rotterdam, University of Amsterdam and VU University Amsterdam. The Institute is named after the late Professor Jan Tinbergen, Dutch Nobel Prize laureate in economics in 1969. The Tinbergen Institute is located in Amsterdam and Rotterdam. The following books recently appeared in the Tinbergen Institute Research Series:

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This dissertation develops statistical methods in genetics and with their application answers both old and new questions related to genetics, income and inequality. Chapter 2 develops a new method to support identification of causal effects in nonexperimental data. Additionally, a new method for estimating heritability using two polygenic indices (PGI) from independent genome-wide association studies (GWAS) is developed. In Chapter 3 this new heritability method is explored further and compared to the established and widely used method, genome-based restricted maximum likelihood (GREML). Chapter 4 aims to remove several barriers for researchers wanting to use PGI in their study. In this chapter a broad array of PGI are constructed, covering a wide range of phenotypes for a number of datasets used by social scientists. Furthermore, in this chapter a theoretical framework is introduced for interpreting associations with PGI. In Chapter 5, the first large scale GWAS on personal income is conducted, using data from the UK Biobank. It is shown that a higher PGI is linked to higher education and better health. Chapter 6 builds upon the results of the previous chapter and further investigates the genetic and environmental factors underlying socioeconomic and health inequality. A lower bound is estimated for the relevance of genetic factors and early-childhood environment for differences in education, income and body mass index. Chapter 7 presents the first results of an ongoing research project where the first large-scale GWAS meta-analysis on personal income is performed. The meta-analysis has a total sample size of 1,161,574 observations from approximately 756,000 individuals.

Casper Burik holds a BSc in Economics and Business from the University of Amsterdam, a BSc in Econometrics and Operations Research from the University of Amsterdam, and an MPhil in Econometrics from Tinbergen Institute. His research has been published in leading peer-reviewed journals such as Nature Communications, Nature Human Behaviour, Molecular Psychiatry and Proceedings of the National Academy of Sciences of the United States of America.