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Kweon, Hyeokmoon

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Hyeokmoon Kweon

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BIOLOGICAL PERSPECTIVE OF SOCIOECONOMIC INEQUALITY

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Introduction

Economics, as a discipline that aims to understand human behaviors, has evolved dramatically over the past decades as it embraces other disciplines with different methodological approaches. In particular, the embracement of psychology led to an emergence of behavioral and experimental economics, which has unquestionably become a part of mainstream economics.

One other important aspect in the evolution of modern economics has been its integration of biological perspectives. This was first done by adopting neuroscientific tools and brain imaging data to study economic decision making. It was not a surprise that economists found interest in the brain as biologically the brain is where decisions are made. More recently and similarly, economists have also begun to incorporate molecular genetic data in their research thanks to ever-increasing resources for genetic data. Again, provided that economics is a study of human behaviors, it was far from a surprise that genetic data can be of great use for economic research. It was already shown by decades of twin studies that a substantial portion of variation can be statistically attributed to genetic factors in virtually any human behaviors, including those of particular interest to economists such as risk-taking preference, subjective well-being, personality, and cognition (Polderman et al., 2015). In interdisciplinary collaboration, economists have contributed to understanding genetic mechanisms of such traits in a series of behavioral genetic studies (Okbay et al., 2016; Lee et al., 2018; Karlsson Linnér et al., 2019; Okbay et al., 2022). In recent years, there have been several studies within economics that take direct advantage of molecular genetic data and results from behavioral genetic studies (von Hinke et al., 2016; Barth et al., 2019; Papageorge and Thom, 2020; Karlsson Linnér and Koellinger, 2022).

In a similar vein, this thesis presents interdisciplinary studies that combine economics, neuroscience, and molecular genetics. However, the main goal of this thesis is not about understanding human behaviors themselves; instead, this thesis explores biological correlates of socioeconomic inequality. Biological factors have immense philosophical and ethical importance for socioeconomic inequality. In particular, sources of inequality due to genetic differences, which, for instance, can influence intelligence and personality, can be considered illegitimate and unfair (Roemer, 1998). Such sources of inequality are unfair because individuals do not have controls over what genes to inherit from their parents. Similarly, neural differences can also be unfair sources of inequality as far as the brain development

was shaped by factors over which individuals have no control, including neurobiological consequences of genetic predispositions as well as different rearing environments that affect one's brain development. Hence, biological factors are one of the major elements that constitute inequality of opportunity, a share of inequality that is not due to different levels of effort.

Such unfair portions of inequality are not the notion that only resides in philosophical theories. A large body of empirical evidence has shown that individuals are less tolerant of inequality and in more favor of redistributive policies if they believe that inequality originates mainly from differences in factors beyond one's control rather than from differences in effort and choice (Fong, 2001; Alesina and Giuliano, 2011; Durante et al., 2014; Alesina et al., 2018). Accordingly, the extent to which inequality can be attributed to biological factors has direct policy relevance. It is therefore important to probe biological aspects of socioeconomic inequality to assess the demand for policy interventions which can address unfair portions of inequality. This thesis is a collection of studies that highlight such biological aspects and their relevance for inequality.

Every chapter of this thesis presents results that rely on a genome-wide association study (GWAS) (see Harden and Koellinger (2020) for a detailed introduction). The GWAS scans through the entire genome, examining the association between the outcome and each genetic marker that is additively coded. Here the type of genetic markers used is called single nucleotide polymorphism (SNP), which is the most common type of genetic variation. The GWAS results, a collection of estimated association results of each SNP, can then be used in follow-up analyses in numerous ways. Notably, using only GWAS summary statistics, we can estimate genetic correlations between pairs of traits, even when GWAS results are produced from different samples (Bulik-Sullivan et al., 2015). These pairwise genetic correlations can in turn be used for multivariate approaches which allow researchers to perform a joint analysis of genetically similar traits (Grotzinger et al., 2019; Turley et al., 2018). Most importantly, the GWAS results can be summarized into a single score that additively aggregates individual SNP effects, a so-called polygenic index (PGI). Such a PGI can then be exploited for various purposes: for example, to conduct a polygenic prediction of a trait (Barth et al., 2019), use it as a control variable to account for genetic heterogeneity relevant for a particular trait (DiPrete et al., 2018), and study gene-environment interactions (Barcellos et al., 2018). These tools are actively used throughout this thesis to investigate the genetic factors of socioeconomic outcomes.

The studies presented in this thesis are not the first to link biological factors to inequality. For instance, Barth et al. (2019) showed empirical relationships

between household wealth at retirement and genetic associations of educational attainment, highlighting the role of genetic factors in the intergenerational persistence of wealth. Similarly, Papageorge and Thom (2020) explored the association between labor market outcomes and the polygenic index for educational attainment. Furthermore, the neural correlates of socioeconomic status have also been extensively studied. As reviewed in Noble and Giebler (2020) and Farah (2017), a number of brain features in different modalities at different life stages have now been linked to disparities in socioeconomic outcomes. This thesis adds further layers to this growing body of evidence on the biological aspects of inequality, as outlined below.

Chapter 1 is a direct investigation of the genetic contribution to inequality in education, income, and health. We conducted the first genome-wide association (GWAS) of individual income using data from the UK Biobank (UKB), which allowed us to construct a PGI that summarizes genetic associations of income. By leveraging this PGI along with the natural experiment of random genetic differences between siblings, we show that siblings who "won the genetic lottery", in the sense that they inherited a larger number of genetic variants associated with higher income, are more likely to achieve better outcomes later in their life. These include attaining a higher educational qualification, earning higher income, and having better health status. Hence, genes contribute to differences in lifetime outcomes even among siblings. We also emphasize that these results do not imply biological determinism or irrelevance of policy, by showing that genetic endowments on outcomes partly work via behavioral and environmental channels that can be influenced.

Chapter 2 turns the attention to brain structure. Socioeconomic status (SES) has been shown to correlate with brain structure, while what underlies this relation has not been extensively studied. In this study, we assess genetic and environmental contributions to SES differences in neuroanatomy in an unprecedentedly large sample and detailed anatomical specificity. We first establish robust relations between SES and grey matter volume across a number of brain regions, including both cortical and subcortical regions. By constructing a PGI for SES, we then parse these regional correlates into predominantly genetic factors and those potentially due to the environment. We find that genetic influences are particularly stronger in some areas, such as prefrontal and insular cortices. On the other hand, some areas, cerebellar and lateral temporal regions in particular, show far less genetic influences, suggesting that environmental factors are likely to be more important for SES differences in gray matter volume of these areas. Such a regionally varying

balance of genetic and environmental influences implies a complex interplay of genetic and environmental factors on SES-brain relations.

Chapter 3 extends a part of the work initiated in Chapter 1. This chapter presents results from a large-scale GWAS meta-analysis of income in a sample of approximately 756,000 individuals. We collected GWAS results from 31 cohorts conducted on four income measures: individual, occupational, household, and parental income. We then meta-analyzed these results in a multivariate framework. By comparing our results of the income GWAS with the well-established GWAS results of educational attainment (EA), we show that the genetic associations of EA can be concordant or discordant with respect to income. Here, the concordance implies that the genetic associations of higher EA are well-translated into higher income. However, if discordant, this translation is suppressed. Examining differences between these concordant and discordant genetic associations of EA, we show distinguishable stratified genetic correlations of EA with behavioral and psychiatric traits as well as brain imaging traits. By contrasting the well-powered GWAS of income with the GWAS of EA, our results provide novel insights into the genetic architecture of socioeconomic factors.

Finally, **Chapter 4** describes genetic data collected from 2,598 individuals in the German Socio-Economic Panel (GSOEP) innovation sample. The GSOEP data is one of the most popular panel data sets with a rich set of information on SES, family, personality, preferences, and health, and has been a valuable resource for research. This paper introduces to the research community the genetic data that we collected for the GSOEP's innovation sample. By showing predictiveness of PGIs constructed for body height, body mass index, and EA, we demonstrate potential usefulness of the genetic data of the GSOEP for socioeconomic research.

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Statement of contribution

All the studies presented in this thesis are results of large collaborations with a number of coauthors. For Chapters 1 to 3, I conducted main analyses and made major contributions to the writing and editing. The contribution for Chapter 4 was relatively minor. What follows details individual contributions of each chapter.

Chapter 1. Genetic fortune: winning or losing education, income, and health: Koellinger designed and oversaw the study and led the writing of the manuscript. I was the lead analyst. Koellinger and I made especially major contributions to the writing. Burik constructed polygenic scores and carried out analyses. De Vlaming and DiPrete wrote parts of the methods sections. Karlsson Linnér and Okbay contributed scripts and expertise for genetic analyses. All authors critically reviewed and edited the manuscript. Martschenko brought an adversarial collaborative perspective to this paper.

Chapter 2. Human brain anatomy reflects separable genetic and environmental components of socioeconomic status: Nave, Farah, Koellinger, and I designed the research plan. I carried out the analyses. Nave, Farah, and Koellinger oversaw the study. Farah, Koellinger, and I wrote the paper. Aydogan, Dagher, Bzdok, and Ruff provided helpful advice and feedback on the study design. All authors contributed to and critically reviewed the manuscript.

Chapter 3. Large-scale genome-wide study of income highlights heterogeneous pleiotropy across the genome: This chapter is based on a very large collaborative study involving a number of researchers, including many cohort analysts who conducted GWAS. Burik was the lead analyst for the meta-analysis and responsible for the quality control of individual cohort results. I carried out the main follow-up analyses presented in this chapter, which used the meta-analysis results. Burik and I constructed income measures and conducted several GWAS in some cohorts. Ahlskog conducted the polygenic prediction in the Swedish Twin Registry. Koellinger led and oversaw the study. I wrote the chapter, incorporating texts from Burik, and Koellinger edited the text.

Chapter 4. Genetic data in the German Socio-Economic Panel innovation sample: Koellinger, Hertwig, and Wagner designed and oversaw the study. The genetic data

was collected by Koellinger, Wagner, Zweck, Goebel, and Richter. Okbay and I were responsible for data quality control. Okbay constructed genetic principal components and polygenic indices. Schweinert, Reiber, Richter, Zweck, and I carried out the analyses. Specifically, I contributed to the polygenic prediction analyses and the family-relatedness analysis. Koellinger, Schweinert, Okbay, and I wrote the manuscript. All authors reviewed and edited the manuscript.

Chapter 1

Genetic fortune: winning or losing education, income, and health

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1. Introduction

The origins, extent, and consequences of income inequalities differ across nations, regions, time and social systems (Chetty and Hendren, 2018; Corak, 2013; Kuznets, 1955; Piketty and Saez, 2003; Roine and 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 and 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 and Seshadri, 2018; Jäntti and 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 and La Ferrara, 2005; Almås et al., 2010; Cappelen et al., 2013; Clark and 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 and 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., 2019, 2016; 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 and 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).

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 and 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 and 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, 1979, 1978; 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 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 and Gintis, 2002; Cesarini et al., 2010, 2009; Sacerdote, 2002; Zax and Rees, 2002), most economists

[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).

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 differences in "ability" that may have a genetic component (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 noissier, 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

[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).

[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.

and to obtain more accurate estimates of nongenetic influences (Benjamin et al., 2012; Harden and 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 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.

2. Data

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 and Sirota, 2000). Thus, many research questions that rely on genetic data need to control for unobserved variable bias due to population structure (Price et al., 2006; Young et al., 2019, 2018).

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

[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.

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.

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 (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

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

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 A1** provides a list of these variables and their definitions. In addition, **Tables A2 and A3** show relevant descriptive statistics.

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 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 =1982-84).

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

[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.

[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

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:

$$(1) \quad s_i = \sum_{j=1}^{J} \hat{\beta}_j x_{ij}$$

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., 2019, 2016). 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-being (Sacks et al., 2012; Stevenson and Wolfers, 2013) and health throughout the lifecourse (Adler et al., 1994; Chetty et al., 2016; Wilkinson and 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 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 A7**).[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

[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 and Koellinger, 2020).

[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 and Koellinger, 2020; Okbay et al., 2016).

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 A9**).

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:

$$(2) \quad y_{ij} = \delta s_{ij} + z'_{ij}\theta + \alpha_j + e_{ij}$$

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.

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.

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 $\mathrm{Cov}(u_i^{(1)}, u_i^{(2)}) = 0$. 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 $\mathrm{Cov}(u_i^{(1)}, u_i^{(2)}) = 0$ 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.

Table 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**
Dependent variable				
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
(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 external causes	-0.035***	-0.030	-0.015**	-0.002
(N = 17,692 | 35,132)	(0.008)	(0.018)	(0.004)	(0.011)

Table 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**
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.

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., 2017a; Wilkinson and Marmot, 2003). Natural experiments show that higher education has a positive causal effect on health (Grossman, 2006, 2000). 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 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 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 and La Ferrara, 2005; Almås et al., 2010; Cappelen et al., 2013; Gromet et al., 2015).

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.

Table 2. 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.

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 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

[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.

[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.

Table 3. 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
(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 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.

adjusted for multiple hypothesis testing using Holm's method (Holm, 1979) in each set of analyses.[16]

Figure A1 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 2** and **3**. The OLS estimates reported in the first column of **Table 2** and **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 A2**). 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-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

[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%.

(Bulik-Sullivan et al., 2015; Harden and 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 A2**). 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 **Tables 2** and **3**.

We repeated these analyses with a PGI for income that was not augmented by using MTAG (**Table A13**) 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 A13**), 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).

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 I.A, 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 favorable 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:

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

(4) $m_{ij} = \alpha^m{}_j + \gamma s_{ij} + z'_{ij}\theta^m + e^m{}_{ij}$

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

(5) $\delta = \tilde{\delta}_1 + \gamma \cdot \tilde{\delta}_2$

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 (3) and (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 signaling 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.

Table 4. Decomposition of the genetic lottery effects in the UK Biobank siblings

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

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.

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,

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

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 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 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 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 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.

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

[19] See footnote 5.

partially rooted in genetic factors (Griliches, 1977; 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 (Heckman et al., 2006). The 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:

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

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

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

$$(9) \quad s_{y,i}{}^{(1)} = \delta_1{}^{u} s_{y,i}{}^{(2)} + \delta_2{}^{u} edu_i + z'_i \theta^u + u_i{}^{u}$$

where GIV-C and GIV-U are described by equations (6) and (7) as well as (8) and (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 estimate.

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 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; 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%).

Table 1. 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
R^2	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
R^2	0.105	0.108	0.111	0.114	0.106	0.109	0.111	0.114								
Obs.	8310	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Table 1. 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 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
R^2	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.

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 A10**, 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.

8. 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 and 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., 2017b; Wilkinson and 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 and 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 behavior, 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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Chapter 2

Human brain anatomy reflects separable genetic and environmental components of socioeconomic status

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1. Introduction

Socioeconomic status (SES), typically measured by income, education, occupation, and neighborhood quality, is a powerful predictor of important life outcomes including physical and mental health, academic achievement, and cognitive abilities (Adler and Stewart, 2010; Chetty et al., 2016; Ridley et al., 2020; Sacks et al., 2012; Stringhini et al., 2017). The brain plays a central role in these relations, most obviously in mental health and intellectual capabilities, but also in physical health through neuroendocrine and inflammatory pathways (McEwen and Gianaros, 2010; Muscatell, 2018). Thus, neuroscience provides a window on the biosocial pathways linking SES and human health and capabilities.

Neuroscience research on SES has revealed a generally positive relation with overall brain volume, as well as with regional cortical and subcortical volumes and cortical surface areas (Farah, 2017; Merz et al., 2019; Noble and Giebler, 2020). We note variability across studies in the regions most associated with SES, which may be due in part to the relatively small samples studied, to differences in the ways SES has been measured and analyzed (e.g., choices of covariates) (Button et al., 2013; Noble and Giebler, 2020), and to different environments with different levels of assistance to individuals of low SES (Walhovd et al., 2021; Weissman et al., 2021). One of the goals of the present study is to establish the relation of SES to regional grey matter volumes (GMV), in the largest sample so far examined for voxel-level data, using a comprehensive measure of SES and controls for a number of potential confounds, based on a well-powered, pre-registered analysis plan.

The second goal of the study is to differentiate genetic from environmental causes of the SES-GMV relation. The role of genes and environment in various outcomes associated with SES has been debated for decades and has provoked controversy in part because of perceived implications for policy (Herrnstein and Murray, 1994).

Here, we pursue these two goals using data from the UK Biobank (UKB), a large-scale prospective epidemiological study of individuals aged 40–69 years at recruitment (Bycroft et al., 2018; Miller et al., 2016). We conducted voxel-based morphometry (VBM) analysis to investigate GMV associations with SES, which was measured by a rich set of SES indicators. To probe the genetic basis of the SES-GMV relation, we constructed a polygenic index of SES from multiple genome-wide association study (GWAS) results (effective N = 849,744), which included a large-scale meta-analysis of educational attainment (Lee et al., 2018). We then examined to which extent the estimated SES-GMV associations can be attributed to the shared common genetic architectures of SES.

2. Results

After selecting participants who had undergone both MRI and genotyping, and had complete SES information related to occupation, income, education, and neighborhood quality, we excluded participants with clinical diagnoses related to brain pathology, morbid obesity, heavy alcohol drinking, or low data quality. The resulting sample was 23,931 individuals, with a mean age of 62, 57% of whom were female. This sample size provides 90% statistical power to detect effects as small as $R^2 > 0.17\%$ at the 5% significance level (corrected for multiple testing by permutation testing; uncorrected $p < 2.19\times10^{-6}$; see Section 4.3). T1 images were preprocessed with the Computational Anatomy Toolbox (CAT) 12, and anatomical regions were labeled according to the Neuromorphometrics atlas.

SES was represented in the analyses to follow by two summary measures, derived from available SES variables using a generalized version of principal component (PC) analysis (**Figs. 1 and S2**). This approach better accommodates measurement error and allows us to appreciate the multidimensional nature of SES with just two components. $PC1_{SES}$ mainly captures the positive correlations between the different SES measures and is most strongly influenced by occupations, occupational wages, and education. $PC2_{SES}$ primarily reflects occupations and neighborhood qualities that are not strongly linked with educational attainment or income, e.g., individuals who live in relatively poor neighborhoods despite having high educational attainment. As shown later, $PC2_{SES}$ contributes to capturing non-genetic variation in SES.

2.1. Socioeconomic status and grey matter volume

We first examined the relation between total intracranial volume (TIV) and SES by regressing TIV on $PC1_{SES}$ and $PC2_{SES}$, controlling for sex, age, genetic population structure, and a number of image-related technical covariates (see Section 4.2). $PC1_{SES}$ is positively associated with TIV (standardized $\beta = 0.10$; $p = 1.1\times10^{-87}$; 95% CI [0.09, 0.11]), while for $PC2_{SES}$ the relation is statistically indistinguishable from zero (standardized $\beta = 0.01$; $p = 0.14$; 95% CI [-0.00, 0.02]). The two PCs together explain 1.6% of the variance of interest in TIV beyond the covariates (partial R^2)—slightly higher than TIV's relation to educational attainment (1.4%), and lower than its relation to fluid intelligence (2.6%) (Nave et al., 2019).

Next, we conducted VBM analysis to test the association of these two PCs with regional GMV across the brain, using the same set of covariates. Higher SES is associated with larger GMV across the brain (**Fig. 2A**). 89.5% of the voxels have a statistically significant association with SES at a familywise error rate of 5%, all of

which are positive. For statistically significant voxels, the average partial R^2 is 0.4% and the highest is 1.2%, with the strongest associations in the left ventral striatum and the right frontal pole. Thus, the positive relation between total brain volume and SES arises from many relatively small sources of structural variation that are widespread across the brain.

Accordingly, when TIV is controlled for, just 8.5% of the voxels have a statistically significant association with SES and the average effect size in partial R^2 is reduced by over half to 0.17% for the statistically significant voxels (see Section 4.3.1). As shown in **Fig. 2B**, the strongest positive associations between SES and relative GMV fall in the prefrontal, insular, frontal opercular, lateral parietal, and lateral temporal regions, as well as in subcortical areas including the cerebellum, striatum, and thalamus. While SES-GMV associations are mainly driven by $PC1_{SES}$, $PC2_{SES}$ contribute relatively more in lateral temporal, cerebellar, and ventromedial prefrontal regions than in other regions (**Figs. 2B and S4A**).

The regions implicated in these analyses include many reported in previous studies of SES and brain structure. While the cerebellum has not often been linked to SES, this may reflect its omission from many morphometric studies (but see Cavanagh et al. (2013), for a study of SES and cerebellar volume specifically, with positive findings). Conversely, hippocampus volume is often noted to correlate with SES. Although this was also found in the present study, it was not among the strongest relations.

We also explored the influence of individual aspects of SES, such as education and income, by conducting a cluster-based analysis (**Figs. S8 and S9**) as well as VBM on each measure separately (**Figs. S5 and S11**). The overall pattern of results is similar, with years of schooling being most strongly associated.

SES-health relations are often stronger at lower levels of SES, where more extreme deprivation may impose unique effects on health (Adler and Ostrove, 1999; Schnittker, 2004) and this pattern is also seen in SES effects on the cortex in children (Noble et al., 2015). Stronger SES-GMV associations were found here in the lower SES participants of our sample as well (**Fig. S6**) (Rose and Pevalin, 2003). Regionally, this is particularly apparent in the striatum (low SES, N = 15,611, max partial R^2 = 0.65%, TIV adjusted; high SES, N = 8,320, max partial R^2 = 0.17%, TIV adjusted).

An alternative measure of the strength of the SES-GMV relation is the ability of aggregate GMV measures to predict SES. Indeed, the small effect sizes for individual voxels do not imply that the association between SES and overall GMV structure is also small. To show this, we constructed brainwide GMV scores to predict $PC1_{SES}$ and $PC2_{SES}$ via a stacked block ridge regression (Mbatchou et al., 2021) with 5-fold cross-validation. These scores predict ΔR^2 = 4.9% (95% CI [4.4, 5.4]) of

out-of-sample variation in $PC1_{SES}$ and ΔR^2 = 0.5% (95% CI [0.3, 0.7]) in $PC2_{SES}$ (see Section 4.3.2 for details).

2.2. Genetic and environmental components of SES-GMV relation

The second question to be addressed is the contribution of genetic and environmental influence to the SES-GMV relations reported here. We approached this by first estimating the SNP-based heritability of SES and brain measures as well as the pairwise genetic correlations among them, which indicated that the genetic architectures of SES and brain structure are partly overlapping (see Section 4.6.1). We then constructed a polygenic index for SES (PGI_{SES}) using the results of the genome-wide association study (GWAS). In view of the sensitivity of GWAS results to differences in ancestry, we derived the index from UKB participants of European ancestry only, excluding the scanned participants and other participants genetically related to them. The genetic data consisted of relatively common genetic variants (single-nucleotide polymorphisms or SNPs) with minor allele frequency ≥1%, which were related to educational attainment, occupational wages, household income, local average income, and neighborhood quality, combined using Genomic SEM (Grotzinger et al., 2019; Lee et al., 2018) (effective N = 849,744). PGI_{SES} is strongly associated with $PC1_{SES}$ (ΔR^2 = 7.1%, $p < 10^{-300}$) and weakly with $PC2_{SES}$ (ΔR^2 = 0.02%, p = 0.03) (see Section 4.2.4 for details). PGI_{SES} could then be used with images from participants of European ancestry (N = 20,799) to help discriminate genetic from environmental causes of GMV differences.

PGI_{SES} was then used to predict TIV (ΔR^2 = 0.8%, $p = 7.4\times10^{-64}$) and GMV across the entire brain via VBM. The latter analysis revealed positive associations in widely distributed voxels (**Fig. 3A row b.**), with the most pronounced associations in the anterior insula, frontal operculum, prefrontal, anterior cingulate, and striatum. There is substantial overlap between the neuroanatomical correlates of SES and PGI_{SES}. Controlling for TIV, approximately 41% of the GMV voxels associated with SES are also associated with PGI_{SES}. This overlap is especially apparent in the insular and prefrontal cortices, with roughly 96% and 64% of the voxels associated with PC_{SES} also associated with PGI_{SES}, respectively.

We then examined to which extent the shared common genetic architectures of SES and GMV account for the observed phenotypic associations by comparing TIV-adjusted regression results of GMV on SES with and without controlling for PGI_{SES}. For 13% of the voxels significantly associated with SES before PGI_{SES} is controlled for, there is a statistically significant change in at least one of the coefficients for $PC1_{SES}$ and $PC2_{SES}$ after accounting for PGI_{SES}. Controlling for PGI_{SES}

reduces the SES-GMV associations across the entire brain, with the greatest reduction in the anterior insula, frontal operculum, ventrolateral prefrontal cortex, and ventral striatum of both hemispheres, consistent with VBM of PGI_{SES} mentioned earlier (**Fig. 3B**). When we correct for measurement error in PGI_{SES} using genetic instrumental variable regression (DiPrete et al., 2018), we estimate that PGI_{SES} accounts for more than half of the SES-GMV associations for many of these regions. On average, 38% of the SES-GMV associations (*min* = 3%, *max* = 87%) can be statistically attributed to PGI_{SES} (see Section 4.3.3 for details).

The remaining associations between GMV and SES could be either due to environmental influences on both or due to rare SNPs, structural variants (e.g. inversions, deletions), or interactions among genes (i.e. epistasis) that PGI_{SES} does not fully account for. Forty-three percent of the voxels significantly associated with SES fall into this category, remaining associated with SES after controlling for PGI_{SES} (**Fig. 3A row c.**). The SES-GMV association is least attenuated by genetic controls in the cerebellum and lateral temporal, lateral parietal, posterior cingulate and primary motor regions, as well as some areas of the dorsolateral and ventromedial prefrontal cortex (vmPFC) and the thalamus. Controlling for PGI_{SES} accounts for less than 30% of the SES-GMV association in many of these regions. These results suggest that the aforementioned regions may be particularly susceptible to the influence of the socioeconomic environment. This is consistent with the relatively stronger association of $PC2_{SES}$ to GMV in many of these areas, as $PC2_{SES}$ was found to be barely heritable (see Section 4.6.7). In sum, a substantial portion of the SES-GMV relation is attributable to known genetics, and that portion varies according to region of the brain. The remaining portion of this relation is also substantial, and likely includes the effects of the environment.

Next, we sought to extend our evidence concerning environmental influences through the study of a specific environmental factor. Numerous environmental exposures are associated with SES and are plausible causal contributors to the SES-GMV relation found here. These include prenatal and childhood factors with lifelong effects, as well as adulthood exposures such as chronic life stress, nutritional status, physical exercise, environmental toxins, smoking and other substance use. Experimental research with animals and human research with longitudinal, quasi-experimental or experimental studies show that these are all capable of impacting the brain. On the basis of recent research with the same sample relating mid-life obesity to cognitive and brain aging (Morys et al., 2021), we chose to extend our analyses by including body mass index (BMI) as marker for a set of behavioral factors that could mediate the SES-GMV relation, including nutrition, physical activity, and obesity, which can impact the brain

through their downstream effects on blood pressure, blood lipids, glucose metabolism and inflammation. In addition to the logical point that *PGI*$_{SES}$ controls would account for genetic influences of BMI on the SES-GMV relation, there is also experimental evidence of SES affecting BMI through the environment: increasing SES causes BMI to decrease (Ludwig et al., 2011).

BMI accounts for an average of 44% of the SES-GMV associations that remain after controlling for *PGI*$_{SES}$ (**Figs. 3C and 4**). This result is not due to neurological disease associated with BMI, such as stroke or neurodegenerative disease, because neurological disease was an exclusionary criterion for our sample. The effect is particularly large in the thalamus and the cerebellum as well as the lateral temporal region and some areas of the vmPFC. Furthermore, for the 91% of the voxels with significant SES-GMV association in the European ancestry sample, at least 50% of the estimated SES-GMV association can be statistically attributed to *PGI*$_{SES}$ and BMI combined, with 67% on average.

We then explored the possible functional implications of the volumetric differences observed here by relating them spatially to the results of meta-analyzed fMRI studies, based on NeuroQuery and 492 cognitive concepts from the Cognitive atlas knowledge base (**Figs. 5 and S15**) (Dockès et al., 2020; Poldrack et al., 2011). The neuroanatomical correlates of SES are most strongly expressed in language, perceptual cognitive functions, self-monitoring, and communication with statistical significance at the false discovery rate of 5%. These functional associations of SES appear to be driven by genetic influences (*PGI*$_{SES}$), while *PGI*$_{SES}$ also distinctly reflects functions related to decision-making (risk and uncertainty), altruism, and empathy as well as broader categories of concepts as shown. The regions presumed to be more environmentally susceptible (**Fig. 5C**) tend to relate more to functions pertaining to executive control and learning and memory, none of which, however, were statistically significant at the false discovery rate of 5%.

3. Discussion

In sum, our results show that socioeconomic status is linked with brain anatomy through a regionally varying balance of genetic and environmental influences. The functions of the implicated brain regions span many cognitive and affective capacities. A measurement-error corrected polygenic index enabled us to separate regions whose correlations with SES can be partly attributed to common genetic variants, at least in individuals of European ancestry, from other regions more susceptible to environmental and behavioral exposures that correlate with SES, notably BMI. Our results suggest that brain health is more susceptible to SES-related

environmental stressors in specific regions, including reduced grey matter volume in the cerebellum among individuals with low SES.

Our study is not the first to introduce the genetic aspect in neuroscience of SES (Judd et al., 2020; Mitchell et al., 2020; Raffington et al., 2019). Notably, global and regional measures of cortical regions have been found to have association with a polygenic index for educational attainment (Judd et al., 2020; Mitchell et al., 2020). Total surface area has also been shown to correlate independently with both parental education and a polygenic index for educational attainment (Judd et al., 2020). To our knowledge, our study is the first to show varying degrees of the genetic contribution to the relationship between SES and brainwide regional measures, including subcortical regions. Specifically, we identified many regions that remained associated with SES even after adjusting for genetic controls (PGI_{SES}).

In an age of growing inequality and socioeconomic disparities in health, achievement and wellbeing, understanding the neural embedding of SES has social as well as scientific relevance. Poverty and social deprivation are associated with widespread regional reductions of grey matter volume, which the present results confirm with unprecedented certainty and anatomical specificity. A novel implication of our findings is that this association can be explained in part, but only in part, by genetic predisposition to different degrees across the brain. It has been argued that genetically caused disadvantages cannot, at present, be ameliorated by policies that improve the social and economic environment (Murray, 2020). However, this reasoning is invalid for at least two reasons. First, even entirely genetic conditions can be treated with environmental interventions, for example phenylketonuria (Paul, 2015). Second, genetic contributions to complex behavioral outcomes such as SES are likely to work via environmental channels that can be influenced (Harden and Koellinger, 2020; Jencks, 1980). In particular, the variance captured by PGI_{SES} is expected to contain indirect genetic effects such as genetic nurture (Kong et al., 2018) that work via different family environments, including family-specific differences in child-rearing and neighborhood quality. An extensive note in Section 4.5 concerns the interpretation and limitations of our results.

For policy purposes, genetic influences should not be taken as a sign of intractability (Goldberger, 1979; Jencks, 1980). Rather, our findings imply that biological and social factors both contribute to neural disparities and that policy interventions may influence and interact with biological factors. While it would be premature to base specific policies on our results, future research in this direction could provide insights that can be translated into targeted interventions (see Farah (2018) for in-depth discussion). For example, further insights into whether cognitive

stimulation during early life or anti-poverty policies (Farah et al., 2021; Noble et al., 2021; Weissman et al., 2021) reduce neural disparities would be valuable.

4. Supplementary methods and materials

4.1. Sample description

We used publicly available data from the UKB, which recruited ≈500,000 participants from the general population of the UK (Littlejohns et al., 2020; Miller et al., 2016). Study participants were 40-69 years old at recruitment between 2006-2010. Our study sample originates from 40,681 individuals whose structural T1 MRI images were available in January 2020 (data field 20252). To derive voxel-level grey matter volumes, we processed T1 images from 38,545 genotyped individuals with the Computational Anatomy Toolbox (CAT) 12 for SPM (see Section 4.2.1 for details). We then applied several filters to ensure data quality and avoid spurious findings. We excluded:

- 24 individuals with mismatch between genetic (data field 22001) and self reported sex (data field 31)
- 1,818 individuals with clinical diagnoses related to brain pathology (including dementia, Alzheimer's, Parkinson's, and chronic degenerative neurological diseases, Guillan-Barré syndrome, multiple sclerosis, other demyelinating diseases, stroke or ischaemic stroke, brain cancer, brain haemorrhage, brain or intracranial abscess, cerebral aneurysm, cerebral palsy, encephalitis, epilepsy, head injury, infections of the nervous system, meningeal cancer, meningioma, meningitis, ALS, neurological injury or trauma, spina bifida, subdural haematoma, subarachnoid haemorrhage, or transient ischaemic attack; see the pre-registered plan for ICD10 codes - https://osf.io/kg29c)
- 2,705 individuals who were morbidly obese (BMI > 35)
- 2,427 individuals who were current heavy drinkers, where heavy drinking is defined as consuming more than 24 drinks per week for males and more than 18 drinks per week for females (Aydogan et al., 2019; Daviet et al., 2022), which is defined as the sum of data fields 1568,1578,1588,1598, and 1608.
- 11 individuals with the image-quality rating (computed by CAT12) lower than "C"
- 230 individuals with a sample homogeneity measure (mean voxel correlation) lower than the 1% quantile (0.805 based on all 38,545 individuals). To compute the homogeneity measure, we first estimated a

correlation matrix with elements being correlation estimates between individuals computed from voxel-level GMV. The mean voxel correlation corresponds to column-wise (or equivalently row-wise) averages of this matrix

After applying these exclusion criteria, 31,330 individuals remained in our sample. 7,215 individuals were further excluded due to missing data for the variables listed in Section 4.2. In order to rule out that our results are influenced by shared family environments among related individuals, we also removed close relatives by randomly dropping one from each pair of siblings or parent-offsprings. Our final sample for the main analysis included N = 23,931 individuals. In analyses that employed genetic data, we included N = 20,799 individuals of European ancestry from this sample.

4.2. Measures

4.2.1. Imaging-derived phenotypes (IDPs)

We extracted GMV on the voxel level from T1-weighted structural brain MRI images provided in NIFTI format (data field 20252). The UKB scanned the participants with a Siemens Skyra 3T scanner using a standard 32-channel head coil (Siemens Healthcare, Erlangen, Germany) in three assessment centers (Cheadle, Newcastle, and Reading). The scanning and processing protocols are detailed in the UKB's brain imaging documentation (https://biobank.ctsu.ox.ac.uk/crystal/crystal/docs/brain_mri.pdf) as well as in publications (Alfaro-Almagro et al., 2018; Miller et al., 2016).

We first pre-processed the T1 images with the Computational Anatomy Toolbox (CAT) 12 for SPM (www.fil.ion.ucl.ac.uk/spm/software/spm12/). The images were corrected for bias-field inhomogeneities, tissue-segmented, spatially normalized to the MNI space with 1.5mm resolution by linear and non-linear transformations, and were modulated to ensure that the total amount of signal in the original image was preserved during spatial normalization. 8-mm Full-Width-at-Half-Maximum Gaussian kernel was then used to spatially smooth the pre-processed images. More details can be found in our pre-registered analysis plan (https://osf.io/kg29c/) as well as in the recent publications of BIG BEAR consortium (Aydogan et al., 2019; Daviet et al., 2022).

Following the standard VBM procedures (see e.g. SPM/CAT12 http://www.neuro.uni-jena.de/cat12/CAT12-Manual.pdf), we decided to exclude all voxels from the VBM analyses that did not contain any or sufficient grey matter. To

determine this, we first computed the average of all GMV images and then thresholded the average brain image at 250 GMV intensity units. The resulting binarized image was then applied as a pre-mask to all individual images. After applying a gray matter mask derived from the data and dropping the voxels unlikely to contain any gray matter (Aydogan et al., 2019), GMV estimates from 504,426 voxels were used in the analysis.

4.2.2. SES measures

The UKB offers a rich set of SES indicators, including education, income, occupation, and neighborhood quality. In order to make full and efficient use of the data, we took a data-driven approach to measure SES by extracting principal components (PC) that capture overall SES from all SES measures available in the UKB. Our approach can be summarized as follows: We (1) collected every available source of information relevant to SES in the UKB; (2) combined measures or derived new variables when possible or appropriate; (3) extracted PCs that represent a sparse, but accurate overall measure of SES; (4) and jointly tested for neuroanatomical association of these PCs based on an *F*-test.

There are several important reasons that motivated us to use this approach. First, it allowed us to take into full account the multidimensional nature of SES. While each SES dimension tends to share the same direction of correlation, there often are cases that do not agree with such correlation in reality: for instance, a plumber may have less education than a university lecturer, but may earn higher income. Furthermore, the quality of a neighborhood in which an individual lives is an important dimension of SES, but it may be imperfectly correlated with education and income. Such complex aspects of SES cannot be represented by a single SES measure such as education or income alone.

Second, our data-driven approach is useful for efficiently testing for the association between SES and neuroanatomy by summarizing the available measures and thereby decreasing the multiple testing burden and increasing the statistical power of our analyses.

Third, this approach also makes it possible to use the detailed occupation data of the UKB to a fuller extent. Because it is difficult to handle many occupational categories in a single analysis, studies often use an aggregated summary of occupation by classifying occupations into a small number of predefined categories. One example is using the UK's National Statistics Socio-economic Classification, which reduces the occupation data to 3 or 8 classes. Such a predefined classification can discard potentially useful information and may not truly represent different

levels of SES. A data-driven approach can efficiently reduce wide categorical data of occupation into lower continuous dimensions, while minimizing information loss.

Fourth, our approach addresses important limitations of educational attainment measures in the study sample. In the UKB, qualifications are reported in only six non-hierarchical categories, some of which cover a wide range of educational levels. Furthermore, participants were allowed to indicate multiple categories without a specific instruction, which led to a large degree of variation in responses. For this reason, we chose not to use years of schooling as often done (Lee et al., 2018), but instead determined the highest qualification for each participant in a data-driven way and used it as a categorical variable.

4.2.2.1. Available measures of SES in the UK Biobank

We collected and constructed an extensive set of SES measures as described below. We derived some of the variables by relying on external data sources or aggregating several measures. The participants visited the assessment center up to four times and brain images were taken during the third or fourth visit (the fourth visit was for repeated imaging of a subset of participants). While the data used here was primarily collected during the brain imaging visit at the assessment centers, we used the latest available information if a measure was missing from this visit.

- Occupation (81 categories) - fields 132, 20024, 22617
  - Job codes for the latest job held before the age of 65, coded in 3-digit UK standard occupational classification (SOC) 2000.
- Log occupational wages (continuous) - fields 132, 20024, 22617
  - Sex-specific average occupational wage matched to 4-digit SOC codes. The wage data are obtained from the UK's Office for National Statistics, averaged over 2002-2010.
- Household income (5 categories) - field 738
  - Average total household income before tax.
- Housing type (6 categories) - field 680
  - e.g., own outright, own with mortgage, rent
- Log local average household income (continuous) - fields 20074, 20075
  - Derived by matching home locations to Middle-layer Super Output Areas. The income data are obtained from the UK's Office for National Statistics (England and Wales only)
- Neighborhood SES score (continuous) - fields 26411, 26412, 26414

  - Weighted average of three composite deprivation indices for income, employment, and education, constructed at the level of Lower-layer Super Output Areas (England only). The weights were derived by using the inverse of the correlation matrix. This method takes a weighted average of multiple outcomes such that outcomes highly correlated with each other are assigned less weight, while outcomes receive more weight if they are less correlated and therefore represent new information. See (Anderson, 2008) for details.
- Highest qualification (7 categories) - field 6138
  - See the following description.

** Highest qualification*

This subsection describes how we derived the highest qualification. During the assessment, participants were asked to choose qualifications that they have from the below options:

1 College or University degree
2 A levels/AS levels or equivalent
3 O levels/GCSEs or equivalent
4 CSEs or equivalent
5 NVQ or HND or HNC or equivalent
6 Other professional qualifications eg: nursing, teaching
7 None of the above

Because participants were able to choose multiple qualifications and also because the vocational category (NVQ or HND or HNC or equivalent) covers an extensive range of educational levels, it was not straightforward to determine the highest qualification for qualifications below college degree. Preferably, a better qualification should correspond to a better SES. We therefore used the following procedure to determine the rank of each qualification.

We first created a new categorical qualification variable that treats each combination of multiple choices as a unique response. Using the method described below, we extracted the first PC from this variable along with the rest of SES variables listed above. The average of the first PC was then computed for each qualification from a group of people who reported having that qualification. Note that these groups are not mutually exclusive as the individuals can belong to multiple groups. We then determined the SES-rank of qualifications based on these average PC scores. This approach yielded the following ranking:

1 College or University degree
2 A levels/AS levels or equivalent

6 Other professional qualifications eg: nursing, teaching
3 O levels/GCSEs or equivalent
5 NVQ or HND or HNC or equivalent
4 CSEs or equivalent
7 None of the above

The highest qualification was chosen for each individual according to this rank, which was then included as a categorical variable in the principal component analysis described below.

4.2.2.2. Data reduction by principal component analysis

We reduced the dimensions of the data by extracting PCs, which represent overall SES implied by the available indicators. Standard principal component analysis (PCA) is only suitable for non-categorical data. Thus, to account for the fact that we have both non-categorical and categorical SES indicators, we employed a method that is often called factorial analysis of mixed data, which is essentially a generalization of PCA that can handle such mixed data (M. O. Hill and A. J. E. Smith, 1976; Pagès, 2014). This method combines ordinary PCA for non-categorical data with multiple correspondence analysis for categorical data and is implemented in the R package PCAmix (Chavent et al., 2017). Our purpose here was not a factor extraction that finds all relevant factors as typically done, but to exploit only the most meaningful variation in the UKB's SES data to facilitate efficient discovery of neuroanatomical correlates of SES. For this purpose, it was optimal to use the minimal number of PCs that could sufficiently capture the multidimensional nature of SES. Given this objective, we used the first two PCs ($PC1_{SES}$ and $PC2_{SES}$) as aggregate indicators of SES because these PCs were sufficient to explain the overall SES.

Figs. 1B and S2 clearly demonstrate that the first two PCs are both necessary and sufficient to reasonably differentiate major SES groups. The later PCs no longer appear to contribute to distinguishing different SES levels. $PC1_{SES}$ mainly distinguishes high and low SES groups and appears to reflect the positive correlation among different SES measures. $PC1_{SES}$ mostly loads individual differences in occupation, educational attainment, and income (Fig. 1A). On the other hand, $PC2_{SES}$ contributes more to explaining the residual variation in the lower SES groups and illustrates more subtle aspects of SES. $PC2_{SES}$ primarily reflects occupation and neighborhood qualities that are not strongly linked with educational attainment or income (Figs. 1A and S2 and Table S2).

Furthermore, the PCA results reveal the complex nature of SES within lower SES groups. Fig. 1B shows that the lower SES a group represents, the more positively correlated the two components are. While the highest SES group even has a lower mean value of $PC2_{SES}$ compared to that of the lower SES groups, relatively better-off individuals within the lower SES groups tend to have higher levels of both $PC1_{SES}$ and $PC2_{SES}$. These observations imply that the dimensions of SES are more complex in the lower SES groups. Overall, these results demonstrate the multidimensional nature of SES, which cannot be sufficiently described by a single SES measure.

Fig S3 plots the eigenvalues of the extracted PCs. $PC1_{SES}$ represents a dominantly large part of the variation from our SES measures (eigenvalue=2.77). The eigenvalues decrease substantially from $PC2_{SES}$, which nonetheless explains an important amount of variation (eigenvalue=1.44). While the eigenvalues of the third and fourth PCs are not very different from that of $PC2_{SES}$, these PCs do not appear to explain the meaningful variation in SES as shown earlier.

Prior to the analyses, we standardized $PC1_{SES}$ and $PC2_{SES}$ so that they have zero mean and unit variance.

4.2.3. Control variables

We used the following variables as baseline control variables.

- Age at brain scan (linear, squared, and cubed terms) - field 21003
- Sex - field 31
- Age (linear, squared, and cubed terms) × Sex
- Total intracranial volume - estimated from CAT12
- Site of acquisition (Cheadle, Reading, or Newcastle) - field 54
- A natural cubic spline function of acquisition date (number of days when the acquisition happened since the acquisitions started) with 3 degrees of freedom - field 53
- Time of test (in seconds) - field 21862
- Interaction terms of acquisition site with all of the above
- The first 40 PCs of the genetic data - field 22009
- Genotyping array (UK BiLEVE or UK Biobank Axiom array) - field 22000

The acquisition date and time were included as control variables based on a recent paper (Alfaro-Almagro et al., 2020), indicating that these variables account for subtle differences in the UKB's assessment protocols over time. For instance, Fig S1 demonstrates that there is a subtle temporal pattern over time since the UKB

started collecting MRI images. We used a natural cubic spline function in order to capture highly non-linear patterns flexibly (the analysis plan specified 5 degrees of freedom for this, but we used 3 degrees of freedom due to rank deficiency). The first 40 genetic PCs were also used to control for the genetic population structure and the genotyping array to control for potential confounds in the genetic PCs due to different arrays used. The genetic PCs were derived internally by the UKB from unrelated individuals of mixed ancestries.

It is important to note that psychological characteristics that are correlated with SES, such as cognitive ability and mental health status, were not covaried. Our reasoning was that correcting for these traits would result in findings less typical of higher and lower SES. By analogy, consider covariates appropriate for assessing sex differences in the brain. Sports participation is more common in men than women throughout the lifespan, for reasons of biology and culture, and would also be expected to impact brain structure though cardiovascular and other mechanisms. However, one might wonder how and whether correcting for sports participation distorts our understanding of sex differences. Our primary interest is presumably not in comparing men who play less sport than typical for their sex to women who play more, but rather men and women behaving according to their motivations and abilities. Returning to SES and associated psychological traits, here we have opted to focus on brain structure in higher and lower SES, rather than on particularly smart and well-adjusted low-SES individuals and particularly less smart and well-adjusted high-SES individuals.

4.2.4. Genome-wide association studies and construction of the polygenic index for SES

As a measure of genetic variation associated with SES, we used a polygenic index (PGI) that additively summarizes the effects of more than 1 million genetic markers. The genetic markers used here are single nucleotide polymorphisms (SNP), which are the most common form of genetic variation. A PGI s_i of individual i is a weighted sum of SNPs:

$$s_i = \sum_{j=1}^{M} \hat{\beta}_j x_{ij}$$

where x_{ij} represents the genotype of individual i for SNP j coded as the count of the reference allele. We estimated the weights $\hat{\beta}_j$ from genome-wide association studies (GWAS), which conduct univariate regressions of an outcome on each SNP across the genome. The resulting estimates were then adjusted for the correlation between the SNPs to obtain the weights $\hat{\beta}_j$.

We constructed a PGI for SES (PGI_{SES}) by combining multiple GWAS results of SES indicators, which included educational attainment, occupational wages, household income, local average income, and neighborhood score (see further details below). We conducted GWAS on each of these measures with the UKB participants of European ancestry, excluding those in the analysis sample of this study as well as their close relatives (up to the third degree of relatedness, which corresponds to everyone in the relatedness table reported by the UKB (minimum kinship coefficient = 0.04). We ran each GWAS with a linear mixed model, estimated by BOLT-LMM (Loh et al., 2015b).

Educational attainment (years of schooling) was coded in the same way as the recent large-scale GWAS (Lee et al., 2018). *Household income* was coded as the natural log of the midpoint income of each income bracket (for the lowest and highest brackets, which are open-ended, 3/4 times the upper bound and 4/3 times the lower bound were used as the midpoint, respectively). The remaining indicators were the same as described in Section 4.2.2. Except for educational attainment, GWAS was run on male and female samples separately and the male and female results of each measure were meta-analyzed by the meta-analysis version of MTAG (Turley et al., 2018) to account for possible sex heterogeneity in socio-economic outcomes. Here MTAG was used especially because it is robust to the relatedness between the samples. MTAG can be viewed as a generalization of the conventional inverse-variance-weighted meta-analysis. The sample sizes for each measure varied from 250,865 to 401,026 participants. For educational attainment, the GWAS result was meta-analyzed with the existing GWAS meta-analysis result of educational attainment (Lee et al., 2018), which excludes the UKB. More details of these GWAS are summarized in Table S4.

Finally, we combined these GWAS results to represent general SES by the common-factor GWAS function of Genomic SEM (Grotzinger et al., 2019). The effective sample size of this common-factor SES GWAS amounts to 849,744 (Mallard et al., 2019). We then constructed the PGI for SES for those of European ancestry in the analysis sample (N = 20,799). To adjust for the correlation between the SNPs, we used a Bayesian approach called LDpred (Privé et al., 2020; Vilhjálmsson et al., 2015) with a reference panel from the Haplotype Reference Consortium (version 1.1) (McCarthy et al., 2016). The SNPs included in the PGI_{SES} were limited to the autosomal bi-allelic SNPs established by the International HapMap 3 Consortium (International HapMap 3 Consortium et al., 2010), which are known to work well for phenotype predictions (Lee et al., 2018; Okbay et al., 2016). The SNPs were also filtered to ensure minor allele frequency > 0.01, the imputation score (INFO) > 0.7,

and the missing rate < 0.05. As a result, 1,020,632 SNPs were used for PGI_{SES}. The PGI_{SES} was standardized to have zero mean and unit variance.

PGI_{SES} predicts about ΔR^2=7.1% of the variation of $PC1_{SES}$ out-of-sample among individuals of European ancestries, above and beyond the control variables (age, age^2, age^3, sex, interactions between sex and the age terms, genotyping array, and the first 40 genetic PCs). On the contrary, PGI_{SES} barely predicts $PC2_{SES}$, explaining ΔR^2=0.02% of its variation.

4.3. Statistical analyses

4.3.1. Voxel-based Morphometry (VBM) analysis

4.3.1.1. Baseline analysis

Our baseline analysis estimated the associations between voxel-level GMV and the two SES PCs. For each voxel j, we estimated the following regression model via ordinary least square (OLS):

$$(1) \quad GMV_i{}^j = \beta_1{}^j PC1_{SES,i} + \beta_2{}^j PC2_{SES,i} + Z_i{}^T \gamma^j + \varepsilon_i{}^j$$

where the GMV of voxel j is regressed on the two SES PCs. The vector Z_i include the control variables listed in Section 4.2.3. $\varepsilon_i{}^j$ is the error term. The GMV and the SES PCs were standardized to have zero mean and unit variance. An F-test was used for each voxel to test whether there is significant association between voxel j's GMV and the SES PCs jointly with the the null hypothesis $\beta_1{}^j = \beta_2{}^j = 0$. We measured the association size by the variance of interest in GMV explained by the SES PCs beyond the covariates of no interest, *i.e.*, partial $R^2 := (R^2_{PC+Z} - R^2_Z) / (1 - R^2_Z)$. R^2_{PC+Z} is the R^2 from the unrestricted model, which includes the two SES PCs and the covariates of no interest, and R^2_Z is the R^2 from the restricted model, which only includes the covariates of no interest. We also quantified the relative contribution of $PC1_{SES}$ in the overall association size by $(R^2_{PC1+Z} - R^2_Z) / (R^2_{PC+Z} - R^2_Z)$. We used permutation testing to correct for multiple hypothesis testing across voxels (see Section 4.3.1.3 for details).

After the estimation, we anatomically labeled the voxels using the Neuromorphometrics atlas provided in CAT12 (http://Neuromorphometrics.com). For a summary purpose, we also generated cluster-based estimates. Each cluster consists of at least 200 neighboring voxels within the lobe (limbic, cerebellum, insular, frontal, parietal, occipital, temporal) which are significant at the familywise error rate of 5% in the baseline model. We then repeated the same analysis with mean GMV of these clusters.

4.3.1.2. Controlling for total intracranial volume (TIV)

Analyses that aim to identify associations between localized GMV and outcomes typically control for TIV, since volumetric brian measures scale with the head size. However, controlling for TIV as a linear covariate has important statistical implications for identifying localized GMV patterns linked to SES, because TIV is positively correlated with both SES and regional GMV. In Fig. 2B, GMV of some voxels appear to have negative association with SES when the TIV is included as a control variable in the model. On the contrary, Fig. 2A shows that almost all the voxel-level GMV are positively associated with SES when TIV is not controlled for. This result indicates that the absolute GMV-SES association is unlikely to be negative in any brain region.

To formally illustrate this point, consider a VBM model for SES with only the TIV as a covariate without loss of generality:

$$(2) \quad GMV_i = \beta_{\sim TIV} SES_i + \gamma TIV_i + \varepsilon_i$$

where GMV_i is the GMV of some voxel and $\beta_{\sim TIV}$ denotes the association between the voxel's GMV and SES while TIV is accounted for. Each variable is standardized to have zero mean and unit variance without loss of generality. γ corresponds to the association between the GMV and the TIV, conditional on SES. The linear dependence between the TIV and SES can be described as: $E[TIV_i|SES_i] = \lambda SES_i$. If we denote β as the coefficient of SES from the regression of the GMV on SES without the TIV as a covariate, $\beta_{\sim TIV}$ can be written as:

$$(3) \quad \beta_{\sim TIV} = \beta - \lambda\gamma$$

Therefore, if both λ and γ are positive and large, $\beta_{\sim TIV}$ can be negative even when β is positive. Our data suggests that this is indeed the case: With the baseline model, we estimated $\widehat{\lambda} = 0.10$ for $PC1_{SES}$ and $\widehat{\lambda} = 0.01$ for $PC2_{SES}$. $\hat{\gamma}$ was on average 0.46 with the minimum=0.11 (right exterior cerebellum) and the maximum=0.72 (left gyrus rectus). Since estimates of β are positive for the vast majority of the voxels, one cannot conclude that the absolute GMV-SES association is truly negative even when estimates of $\beta_{\sim TIV}$ are negative. Instead, such negative estimates are evidence that $\lambda\gamma$ is large relative to β and that the GMV-SES association is essentially very small or non-existent for these regions. Note that here we did not interact TIV with the site of acquisition for simplicity when obtaining these estimates. There was not much difference in TIV due to images taken in different acquisition sites.

Therefore, caution is warranted when interpreting the results when TIV was adjusted for as a covariate. For this reason, we reported the VBM results both with

or without TIV included as a covariate. Furthermore, given the above, our results suggest that SES is associated with greater gray matter across almost all brain regions investigated, despite small exceptions with negative estimates after adjusting for the TIV. Note that TIV was always included as a control variable unless otherwise stated.

4.3.1.3. Multiple testing correction

To correct for multiple testing across voxels, we used permutation testing to determine a *p*-value threshold that controls the familywise error (FWE) rate of 5% (Nichols and Hayasaka, 2003). Following a comprehensive simulation study that examined several permutation approaches for the brain-imaging (Winkler et al., 2014), we applied the method developed by Freedman and Lane (1983) to construct an empirical distribution of test statistics (Freedman and Lane, 1983). Consider an $N \times M$ matrix Y where column j is a length-N vector of voxel j's GMV with M the number of the voxels. Each column was first residualized of the covariates of no interest (Z_i). Matrix Y was then permuted row-wise so that the correlation structure among the voxels was preserved. We then regressed each of the permuted GMV on the non-permuted, original regressors and recorded the maximum *F*-statistic. We repeated this process 5,000 times to form a distribution of the maximum *F*-statistics. We used the *p*-value computed from the 95th percentile of this distribution (F = 13.04) as the *p*-value threshold for 5% FWE-corrected significance level, which corresponds to $p = 2.193 \times 10^{-6}$ (uncorrected).

While in principle the permutation testing has to be performed for each different analysis, the resulting *p*-value thresholds differed only marginally and the threshold for the baseline model was the most conservative. Therefore, we used the 2.193×10^{-6} threshold for every voxel-based analysis.

4.3.1.4. Stratified analysis of high and low SES groups

To investigate potential heterogeneity across different SES groups, we conducted the same VBM analysis separately on high and low SES groups. High and low SES groups were defined by National Statistics Socio-economic Classification of the UK (Rose and Pevalin, 2003): high SES group holds a managerial, administrative, or professional occupation and low SES group holds intermediate, routine, or manual occupation (N_{high} = 15,611, N_{low} = 8,320).

4.3.1.5. VBM of Individual SES measures

To gain additional insight into the neuroanatomical correlates of SES, we conducted additional VBM analyses on each of the five individual numerical SES measures used to construct the SES PGI, described in Section 4.2.4. Note that the main purpose of these analyses was not to discover novel neuroanatomical correlates from each SES measure, but rather to compare neuroanatomical correlates across these measures.

4.3.2. Estimating the overall association between SES and GMV structure

Our VBM results demonstrate that the association between SES and an individual GMV IDP is small and does not exceed partial R^2 of 1% with TIV adjusted for. One might then ask how large the brainwide association between SES and the gray matter structure is if we can aggregate individual SES-GMV association estimates from individual voxels. Estimating the overall association is not an easy task because of the high dimension of the voxel-level GMV data and the strong spatial correlation among the voxels. We addressed these challenges by constructing a brainwide GMV score for SES with a machine learning technique. We used a stacked block ridge regression approach inspired by a recent whole-genome regression method (Mbatchou et al., 2021). This approach allows us to tackle the high dimension issue by stacked regressions and the spatial correlation by the use of ridge regressions without excessive computational burden. Ridge regressions also ensure that we only capture linear relationships between SES and the GMV structure.

We constructed a brainwide GMV score for each SES PC in two steps:

(1) Voxels were first partitioned into blocks of 10,000 adjacent voxels. For each block, we ran a ridge regression of each SES PC on its 10,000 voxel-level GMVs with arbitrarily-chosen varying shrinkage parameters: {100, 100^2, 100^3}. We then computed predictions for each SES PC for each value of the shrinkage parameters, resulting in 3 predictors for each SES PC from each block. This resulted in 153 predictors from 51 blocks partitioned from 504,426 voxels.

(2) After collecting the predictors from all the blocks, a ridge regression was run on them together again. The prediction from this regression was used as a brainwide GMV score.

Both steps were implemented in 5-fold nested cross-validation: In the outer loop, the sample was split into 20% test set and 80% training set, the latter of which was again split into 20% validation set and 80% training set in the inner loop. In the inner

loop, cross-validation was used to tune the shrinkage parameter for the step-2 ridge regression. The outer loop was used to train the final model and obtain predictions for the test set given the obtained value of the shrinkage parameter from the inner loop. We ensured that no information from the test set was used in the model training.

To measure the overall association between each SES PC and the GMV structure, we used a change in R^2 after including the corresponding brianwide GMV score to the regression. The covariates used were age, age^2, age^3, sex, interactions between sex and the age terms, TIV, genotyping array, and the top 40 genetic principal components. We computed confidence intervals with 1,000 bootstrapped samples.

Of note, we do not claim here that this approach is the best way of constructing a brainwide score or estimating the brainwide association. The primary goal of this analysis is to demonstrate that SES is associated with GMV structure to a substantial degree.

4.3.3. Incorporating genetics

4.3.3.1. VBM with PGI

Using PGI_{SES}, we conducted the following additional VBM analyses: (1) VBM of SES PCs only with individuals of European Ancestry (2) VBM of PGI_{SES} (3) VBM of the SES PCs controlling for PGI_{SES}. These VBMs were carried out in the same way as the baseline analysis detailed in Section 4.3.1. We then examined which GMV voxels are significantly associated with the SES PCs and/or the PGI and examined changes in SES-GMV associations before and after the PGI was controlled for. Note that we measured partial R^2 of the PCs for VBM of the SES PCs controlling for PGI_{SES} as $(R^2_{PC+PGI+Z} - R^2_{PGI+Z}) \,/\, (1 - R^2_Z)$ to be able to compare it with partial R^2 from VBM of SES PCs. In addition to probing the difference in statistical significance after the PGI was controlled for, we directly tested whether controlling for the PGI significantly altered the SES-GMV association.

4.3.3.2. Testing differences in SES-GMV associations with and without PGI as a control variable

We used a Wald test to examine whether there was a significant difference in the SES-GMV association before and after the PGI_{SES} was controlled for. More specifically, consider a model where PGI_{SES} is added to the model (1) and also set up an auxiliary regression of the PGI on the SES PCs and the covariates for each voxel:

(4) $GMV_i{}^j = \tilde{\beta}_1{}^j PC1_{SES,i} + \tilde{\beta}_2{}^j PC2_{SES,i} + \theta^j PGI_i + Z_i{}^T \tilde{\gamma}^j + \tilde{\varepsilon}_i{}^j$

(5) $PGI_i = \delta_1 PC1_{SES,i} + \delta_2 PC2_{SES,i} + Z_i{}^T \psi + u_i$

Using vector notations: $\beta^j = [\beta_1{}^j \ \beta_2{}^j]^T$, $\tilde{\beta}^j = [\tilde{\beta}_1{}^j \ \tilde{\beta}_2{}^j]^T$, $\delta = [\delta_1 \ \delta_2]^T$, which are all length-2 vectors, it can be shown:

(6) $\beta^j - \tilde{\beta}^j = \theta^j \cdot \delta = \Delta^j$

Therefore, the vector Δ^j represents the difference in the SES-GMV association for voxel *j* due to controlling for *PGI*SES. Δ^j can be estimated as the product of estimates of $\hat{\theta}^j$ and $\hat{\delta}$ from the model (4) and (5), respectively. A Wald test was then used to test the null $\Delta^j = 0$ with the test statistic: $\hat{\Delta}^{j^T} \widehat{Var}(\hat{\Delta}^j)^{-1} \hat{\Delta}^j \sim \chi^2{}_2$, where $\widehat{Var}(\hat{\Delta}^j)$ was approximated by the delta method: $\widehat{Var}(\hat{\Delta}^j) \approx \widehat{Var}(\hat{\theta}^j)\hat{\delta}^T\hat{\delta} + \hat{\theta}^{j^2}\widehat{Var}(\hat{\delta})$. Note that this analysis is statistically equivalent to a mediation analysis with *PGI*SES being a mediator (MacKinnon et al., 2000). We conducted this test only for the voxels whose GMV was significantly associated with the PCs. Then, the multiple testing was corrected for using Bonferroni correction (the corrected 5% threshold = 1.46×10^{-6} with 34,188 tests).

4.3.3.3. Measuring differences in SES-GMV associations with and without PGI as a control variable

To represent the relative size of Δ^j in relation to partial R^2, we used the relative change in the net variation explained by the SES PCs after adding *PGI*SES to the model with the covariates of no interest: $[(R^2_{PC+Z} - R^2_Z) - (R^2_{PC+PGI+Z} - R^2_{PGI+Z})] \ / \ (R^2_{PC+Z} - R^2_Z)$. This measure is bounded between 0 and 1 as long as the sign of the coefficients for *PC1*SES and *PC2*SES do not change after controlling for *PGI*SES. This expression can be interpreted as the percent change in the SES-GMV associations due to controlling for *PGI*SES and essentially the part of the SES-GMV association that can be attributed to *PGI*SES. Note that, because *PC2*SES is barely predicted by *PGI*SES and even barely heritable (Table S5), the percent change in SES-GMV association after controlling for *PGI*SES is essentially due to the change in *PC1*SES-GMV association. We can therefore rewrite the earlier expression as:

(7) $$\begin{aligned}&[(R^2_{PC+Z} - R^2_Z) - (R^2_{PC+PGI+Z} - R^2_{PGI+Z})] \ / \ (R^2_{PC+Z} - R^2_Z)\\ &\approx [(R^2_{\boldsymbol{PC1}+Z} - R^2_Z) - (R^2_{PC1+PGI+Z} - R^2_{PGI+Z})] \ / \ (R^2_{PC+Z} - R^2_Z)\\ &= \Delta_{PC1} \ / \ (R^2_{PC+Z} - R^2_Z)\\ &= [\Delta_{PC1} \ / \ (R^2_{PC1+Z} - R^2_Z)] \times [(R^2_{PC1+Z} - R^2_Z) \ / \ (R^2_{PC+Z} - R^2_Z)]\end{aligned}$$

where $\Delta_{PC1} = (R^2_{\boldsymbol{PC1}+Z} - R^2_Z) - (R^2_{PC1+PGI+Z} - R^2_{PGI+Z})$, the change in the net variance explained by *PC1*SES after controlling for *PGI*SES. Hence, the percent change in SES-GMV association is roughly the product of the percent change in *PC1*SES-GMV association ($\Delta_{PC1} / (R^2_{PC1+Z} - R^2_Z)$) and the relative contribution of *PC1*SES in the overall SES-GMV association ($(R^2_{PC1+Z} - R^2_Z) / (R^2_{PC+Z} - R^2_Z)$). A larger share of SES-GMV association can be attributed to *PGI*SES if genetic factors linked to SES play a bigger role for *PC1*SES-GMV association and/or if *PC2*SES contributes relatively less to the overall SES-GMV association.

4.3.3.4. Measurement error correction for PGI

*PGI*SES is a noisy proxy of true linear effects of common genetic variants that are linked to SES because GWAS estimates of individual SNP effects are obtained from finite sample sizes. The difference between the true PGI and the available PGI can be viewed as the classic measurement error, which leads to an attenuation bias in the coefficient estimate for the *PGI*SES. Nonetheless, it is still possible to account for the linear effects of common genetic variants that the true *PGI*SES would capture under reasonable assumptions. We addressed this attenuation bias by using genetic instrumental variable (GIV) regression (DiPrete et al., 2018). The essential idea is that the true *PGI*SES can be recovered from a noisy *PGI*SES(1) by using another *PGI*SES(2) as an instrumental variable that was derived from a different GWAS sample. The crucial assumption here is that the noise in *PGI*SES(1) and *PGI*SES(2) is uncorrelated to each other. GIV regression can address the measurement error in *PGI*SES to the extent that this assumption holds.

To obtain *PGI*SES(1) and *PGI*SES(2), we randomly split the UKB GWAS sample into two subsamples (*N*=105,517~170,945) such that each subsample has the same male-female ratio and no individuals in one subsample are related to anyone in the other subsample with more than the third degree of relatedness. With each subsample, GWAS was run for the five numerical SES measures and the results were combined with Genomic SEM as described in Section 4.2.4. Then, *PGI*SES(1) and *PGI*SES(2) were constructed from one of the two independent GWAS subsample results in the main imaging sample.

Using *PGI*SES(1) and *PGI*SES(2), we fitted the model (4) by the GIV estimation, which is two-stage least squares (TSLS).

$$(8) \quad GMV_i{}^j = \tilde{\beta}_1{}^j PC1_{SES,i} + \tilde{\beta}_2{}^j PC2_{SES,i} + \theta^j PGI_i{}^{(1)} + Z_i{}^T \tilde{\gamma}^j + \tilde{\varepsilon}_i{}^j$$

where $PGI_i{}^{(1)}$ is the PGI estimated from the first subsample. The first-stage equation can be written as:

$$(9) \quad PGI_i^{(1)} = \alpha_1 PGI_i^{(2)} + \alpha_2 PC1_{SES,i} + \alpha_3 PC2_{SES,i} + Z_i^T \eta + e_i$$

where the PGI estimated from the second subsample, $PGI_i^{(2)}$, is used as an instrument for $PGI_i^{(1)}$. We obtained the TSLS estimates by fitting the following equation:

$$(10) \quad GMV_i^j = \tilde{\beta}_1^j PC1_{SES,i} + \tilde{\beta}_2^j PC2_{SES,i} + \theta^j \hat{PGI}_i^{(1)} + Z_i^T \tilde{\gamma}^j + \tilde{\varepsilon}_i^{*j}$$

where $\hat{PGI}_i^{(1)}$ is the fitted value from the equation (8). The statistical inference was then conducted but in the standard TSLS framework to test the association between the GMV and SES for each voxel conditional on PGI_{SES} (Wooldridge, 2002).
We computed Partial R^2's based on adding or excluding $\hat{PGI}_i^{(1)}$ in model (10) instead of the unadjusted PGI. Similarly, we measured the difference in SES-GMV association after controlling for the PGI by GIV as $[(R^2_{PC+Z} - R^2_Z) - (R^2_{PC+\hat{PGI}^{(1)}+Z} - R^2_{\hat{PGI}^{(1)}+Z})] \ / \ (R^2_{PC+Z} - R^2_Z)$

4.4. Functional annotations

We connected our anatomical findings to known functional localizations by leveraging Cognitive Atlas and the extrapolatable meta-analysis tool NeuroQuery (Dockès et al., 2020; Poldrack et al., 2011). We first took the 518 cognitive concepts from Cognitive Atlas which were categorized into 10 functional categories (taken from https://www.cognitiveatlas.org/concepts/categories/all on 2 July 2021). Then, for each concept, we generated a meta-analyzed Z-score brain map using NeuroQuery. This toolbox allows users to generate a predictive MRI-derived spatial distribution for any term, based on very large-scale meta-analyses containing mostly functional MRI studies. We excluded 12 concepts containing a term for which NeuroQuery failed to generate a brain map as well as 14 concepts where none of the voxels had a non-zero Z score. As a result, 492 concepts remained.

For each concept-associated brain-map, we calculated the difference in mean χ^2 between voxels statistically significant nominally at 1% level and the rest of voxels in the VBM results. We then computed a pseudo *T* score for the difference in mean χ^2. These steps were implemented by regressing χ^2 scores on the binary indicator for a voxel having *p*-value < 0.01. A similar approach has previously been used (Alexander-Bloch et al., 2018)

We then obtained its *p*-value from 10,000 spatial permutations of the *F* statistics map from the VBM. We used a generative model approach developed by Burt et al. (2020) for permutation, which allowed us to permute the volumetric brain map with subcortical regions while preserving spatial autocorrelation. For model parameters, we set *ns* = 1,500, *knn* = 800, *pv* = 25, resampling = *True*, which yielded a

reasonable fit. We used these permutation-based *p*-values as a summary measure to evaluate the strength of signal for a given functional concept in relation to SES. We defined statistical significance corrected for multiple testing at the false discovery rate of 5% as we aimed to identify functions with stronger evidence compared to the rest. The full results are reported in Table S17.

4.5. Interpretation

4.5.1. Brain, SES, and genetics

To aid interpretation of the association between SES and brain anatomy observed in late adulthood, Fig. S19 describes a simple model that illustrates how adulthood brain anatomy can be linked to SES, family environments, and genetics. The model is depicted in a directed acyclic graph (DAG), a popular graphical framework for identifying confounding variables (Greenland et al., 1999; Shrier and Platt, 2008; Tennant et al., 2020). The model does not attempt to include all possibly relevant factors and mediating pathways. Rather, its purpose is to identify what effects are potentially captured in the estimated GMV-SES association in relation to genetics and family environments.

It is important to note that each arrow in the DAG represents a unidirectional causal relationship between two variables (nodes). For instance, the arrow from "*SES adult*" to "*Brain adult*" only indicates the environmental effect of adult SES on the adult brain. A path is a set of one or more arrows that connects multiple nodes. A path can be either open or closed. An open path channels statistical associations, which can be closed by conditioning on a variable in the middle. A path can be closed due to a collider, which is a variable that receives two arrows. Conditioning on a collider opens up a closed path, which induces a collider bias.

Though fairly simple, the model is capable of describing key relevant pathways. First, child brain development is determined by genetics and family environments ("*Own genes → Brain child*" and "*Family environment → Brain child*"). Second, SES in adulthood is a function of genetics, family environments, and child brain development ("*Own genes → SES adult*", "*Family environment → SES adult*", and *"Brain child → SES adult*"). Third, the transition to the (late) adulthood brain is partly influenced by adult SES ("*Brain child → SES adult → Brain adult*" and *"Brain child → Brain adult*"). Therefore, the model describes the roles of both genetics and family environments in causing differences in SES and the brain. Furthermore, the feedback between SES and the brain is illustrated by the path: "*Brain child → SES adult → Brain adult*". One could extend the model by distinguishing late and early adulthood phases and including another feedback effect. Such an extension,

however, will not provide additional key insights as long as socioeconomic mobility is limited during adulthood.

Another important feature is that the model recognizes so-called genetic nurture effects (Kong et al., 2018). Childhood family environments shaped by the parents are known to be associated with the genes of the parents (*"Parental genes → family environment"*), which are passed on to their child (*"Parental genes → Own genes")*. These links induce statistical associations between own genetics and family environments (*"Own genes ← Parental Genes → family environment"*). This fact statistically blurs the common dichotomy between genetics and family environments.

In this study, we regressed voxel-level GMV on an adult SES measure with a goal to estimate the SES-GMV association. If our aim were to estimate the causal effect of adult SES environments on the GMV structure (*i.e.*, *"SES adult → Brain adult"*), a resulting regression estimate will clearly be biased due to the open confounding paths, which transmit statistical associations. Therefore, the estimated SES-GMV associations in this study are expected to encompass the direct environmental effect of adult SES on adult brain and all the effects due to the open paths, which can be summarized as follows:

1) Environmental effects of adult SES on adult brain: *SES adult → Brain adult*
2) Brain causing SES: *SES adult ← Brain child → Brain adult*
3) Genetic effects: *SES adult ← Own genes → Brain child → Brain adult*
4) Family environment effects: *SES adult ← Family environment → Brain child → Brain adult*
5) Genetic nurture effects on brain*: SES adult ← Own genes ← Parental genes → Family environment → Brain child → Brain adult*
6) Genetic nurture effects on SES: *SES adult ← Family environment ← Parental genes → Own genes → Brain child → Brain adult*

Notably, the DAG in Fig. S19 demonstrates that one needs to account for either childhood brain measures (*i.e.*, lifetime longitudinal data) or measures of both family environments and genetics in order to identify the causal effect of the adult SES on the brain (*"SES adult → Brain adult")*, assuming the absence of no other unobserved confounders.

4.5.2. Interpretation of the polygenic index for SES

While statistical analysis using PGI_{SES} is straightforward, careful interpretations are required. Most importantly, the remaining associations between the GMV and SES

after conditioning on *PGI$_{SES}$* cannot entirely be interpreted as environmental effects of SES on the brain anatomy because *PGI$_{SES}$* only captures noisy estimates of the effects of measured common genetic variants. It does not include the potential effects of structural or rare genetic variants that are not (or only partly) captured by the observed common genetic variants. Nonetheless, the GMV-SES association that is robust to controlling for *PGI$_{SES}$* can point to regions of the brain that are more likely to be affected by environmental factors linked with SES.

To interpret the results, we first need to probe what effects are likely to be summarized in *PGI$_{SES}$*. On the basis of the DAG presented in Fig. S19, the GWAS of SES will capture the direct genetic effects on SES ("*Own genes → Brain child → SES adult"* and "*Own genes → SES adult"*) as well as the effects due to confounders, namely genetic nurture effects ("*Own genes ← Parental genes → Family environment → SES adult"* and *"Own genes ← Parental genes → Family environment→ Brain child → SES adult"*). All of these effects will therefore be incorporated in *PGI$_{SES}$*. Furthermore, it is important to note that the paths via the adult brain will not be captured in *PGI$_{SES}$* due to the adult brain being a collider: "*Own genes → Brain child → Brain adult ← SES adult".*

These observations lead to the following interpretations for the SES-GMV association estimates conditional on *PGI$_{SES}$*. First and most importantly, *PGI$_{SES}$* is expected to capture a part of the SES-GMV association due to different family environments and parental SES. A PGI captures the association between a phenotype and genetic variants, rather than causal effects of genetic variants. For this reason, *PGI$_{SES}$* will contain genetic nurture effects as described above. Studies have shown that such genetic nurture effects tend to be larger for socio-economic phenotypes (Kong et al., 2018; Selzam et al., 2019). Therefore, *PGI$_{SES}$* is likely to overstate the genetic effects associated with SES.

Second, what we effectively control for by controlling for *PGI$_{SES}$* is the shared genetic architecture between SES and developmental neuroanatomy that is captured by the measured genetic variants and their estimated linear associations with SES. Hence, controlling for *PGI$_{SES}$* is not necessarily equivalent to controlling for the entire common genetic variants behind the GMV-SES association. More specifically, in light of the DAG, *PGI$_{SES}$* will account for the following genetic effects on SES: "*Own genes → SES adult"* and *"Own genes → Brain child → SES adult"*, the latter of which works via the child brain. On the other hand, *PGI$_{SES}$* will not account for the genetic effects on the adult brain that do not work through adult SES: "*Own genes → Brain child → Brain adult*". In fact, in order to account for the underlying genetic effects in the SES-GMV association, it would be required to construct a *PGI* for a brain IDP conditional on adult SES. However, it is currently difficult to

construct such a *PGI* with sufficient predictive power due to a limited sample size available for conducting a required GWAS. Moreover, such a *PGI* will need to be constructed for each IDP representing a sufficiently narrow region.

Despite these challenges for interpretation, PGI_{SES} is still useful for identifying brain regions likely to be more susceptible to the influence of socio-economic environments than that of genetic factors. If the estimated SES-GMV association is relatively less attenuated after controlling for PGI_{SES}, the observed SES-GMV association is likely to be a result of environmental effects of SES rather than genetic factors. One reason is because PGI_{SES} tends to overestimate the effects of common genetic variants on SES. Also, at least for healthy individuals, it is highly unlikely that the SES-GMV association is dominantly driven by rare or structural genetic variants with only negligible contribution from common genetic variants associated with SES.

4.6. Supplementary analyses

4.6.1. Heritability and genetic correlation

We estimated SNP-based heritability of SES, TIV, and the brainwide GMV scores as well as their pairwise genetic correlation, using genomic-relatedness-based restricted maximum likelihood (GREML) estimation (Lee et al., 2012; Yang et al., 2010). The method estimates the genetic contribution to the phenotypic variance based on a linear mixed model, where the genetic effects are modeled as random. Its extension to a bivariate model estimates genetic correlation between two phenotypes.

We randomly dropped one of a pair of individuals with estimated relatedness greater than 0.05, which resulted in N = 20,447 (Evans et al., 2018). We used a slightly pruned set of the SNPs used to construct PGI_{SES} with the following pruning parameters: window size = 1,000 variant counts, step size = 5, r^2 = 0.95. As a result, 452,190 SNPs were included. As covariates, we included age, age^2, age^3, sex, interaction terms between the sex and age terms, genotyping array indicator, and top 40 genetic PCs. The estimation was implemented in BOLT-REML (Loh et al., 2015a).

The results are reported in Table S5. TIV and the GMV score for $PC1_{SES}$ were both partly heritable (h^2 = 0.41, SE = 0.02; and h^2 = 0.28, SE = 0.02, respectively). $PC1_{SES}$ was moderately heritable (h^2 = 0.16, SE = 0.02) and positively genetically correlated with TIV (r_g = 0.37, SE = 0.06). Furthermore, $PC1_{SES}$ had a moderate genetic correlation with the values of the brainwide GMV score that we constructed for $PC1_{SES}$ (r_g = 0.57, SE = 0.06). Similar estimates for $PC2_{SES}$ and GMV score for $PC2_{SES}$

were either smaller or had much larger standard errors (h^2 = 0.05, *SE* = 0.02 for $PC2_{SES}$; h^2 = 0.14, *SE* = 0.02 for GMV score; r_g = 0.18, *SE* = 0.10 with TIV; r_g = 0.34, *SE* = 0.18 with the GMV score). Overall, these results demonstrate that the genetic architectures of SES and brain structure are partly overlapping.

4.6.2. Testing differences in residual SES-GMV associations due to BMI

As presented in Figs. 3C and 3D, the remaining SES-GMV associations after controlling for PGI_{SES} can be substantially attributed to individual differences in BMI. Here we formally tested whether this is the case statistically. In other words, we tested whether there is a statistically significant change in at least one of the coefficients for $PC1_{SES}$ and $PC2_{SES}$ after accounting for BMI in addition to PGI_{SES}. The testing procedure was analogous to the one conducted for PGI_{SES}, which is described in Section 4.3.3.2, except that GIV regression was used to estimate each model. As it was done for PGI_{SES}, we conducted this test only for the voxels that had significant association with the PCs and then the multiple testing was corrected for using Bonferroni correction. As a result, we found that 84.4% of 34,188 voxels tested had a significant change in at least one of the coefficients for $PC1_{SES}$ and $PC2_{SES}$ after controlling for BMI in addition to PGI_{SES}. This result confirms that BMI can indeed statistically account for the remaining SES-GMV associations after adjusting for PGI_{SES}.

Note that, to measure the contribution of BMI in explaining the remaining SES-GMV associations after controlling for PGI_{SES}, we again used the relative change in the net variation explained by the SES PCs. Hence, following the same logic, we computed the contribution of BMI as:

$$\left[\left(R^2_{PC+P\hat{G}I^{(1)}+Z} - R^2_{P\hat{G}I^{(1)}+Z}\right) - \left(R^2_{PC+P\hat{G}I^{(1)}+BMI+Z} - R^2_{P\hat{G}I^{(1)}+BMI+Z}\right)\right] / \left(R^2_{PC+P\hat{G}I^{(1)}+Z} - R^2_{P\hat{G}I^{(1)}+Z}\right)$$

4.6.3. Heterogeneity

Sex and age are two important factors for both SES and neuroanatomy. Therefore, we tested whether the SES-GMV associations are heterogeneous with respect to *i)* different sex (sex interaction) and *ii)* different ages (age interaction). We examined each aspect of heterogeneity separately by using the voxel clusters and including the interaction terms with $PC1_{SES}$ and $PC2_{SES}$. The interaction terms were then tested jointly with *F*-tests.

The results are reported in Table S23-24. The SES-GMV associations were generally larger for men, with the largest difference found in the biggest cluster from the prefrontal cortex. One exception was found in a small cluster in the

cerebellum, where the SES-GMV association was larger for women. However, none of the regions would survive the brainwide multiple testing correction. The SES-GMV associations also tended to increase with age, while the age interaction estimates were not large enough to be statistically significant even at the uncorrected 5% level, except for one cluster from the anterior insular and the frontal operculum. These null results for age interaction may be due to the survival effect because the majority of the participants were older than 60.

4.6.4. Controlling for alcohol consumption

Our baseline analyses implicitly adjusted for heavy drinking by excluding heavy drinking individuals. A recent study has shown that even moderate alcohol consumption is associated with reduction in GMV even when educational attainment is adjusted for (Daviet et al., 2022). Since alcohol drinking behavior is known to be related to SES, it may be hypothesized that the alcohol consumption is a factor that constitutes the observed SES-GMV associations. However, because individuals with high SES tend to consume a greater amount of alcohol (Collins, 2016), controlling for the alcohol consumption is expected to only increase estimates for the SES-GMV associations.

Our data confirms that this is indeed the case. In a cluster-based analysis, we controlled for the alcohol consumption (the number of drinks per week) with linear and square terms. The results show that the SES-GMV associations measured in partial R^2 increased by up to 31%, but only marginally in general (Table S25). Therefore, our positive estimates for the SES-GMV associations cannot be directly attributed to the alcohol consumption. Rather, when not adjusted for, the alcohol intake is a factor that reduces the GMV difference between high and low SES individuals.

4.6.5. Controlling for cognitive ability and mental health

As with alcohol consumption, there may be several other pathways that may underlie the SES-GMV associations, notably cognitive ability and mental health. Since cognitive ability is positively associated with both SES and GMV, controlling for a cognitive ability measure is expected to decrease the magnitude of a SES-GMV association estimate. Similarly, since mental health status is likely to be negatively associated with both SES and GMV, controlling for a mental health proxy is also expected to decrease the magnitude of a SES-GMV association estimate. Such reduction in the estimate due to controlling for cognitive ability or mental health

can be interpreted as the part of SES-GMV association that can be *statistically* attributed to cognitive ability or mental health.

Using GMV clusters with a fluid intelligence score (field 20016) and self-reported mental health proxies (field 2050, 2060, 2070, 2080, 2090, 2100), we examined how much of observed SES-GMV association can be statistically attributed to cognitive ability or mental health. The testing procedure was equivalent to the analysis described in Section 4.3.3.2. While this procedure for the fluid intelligence score was straightforward by replacing PGI_{SES} with the fluid intelligence score, some modification was required for mental health.

Since we have multiple proxies of mental health, an auxiliary regression, which corresponds to model (5), was needed for each of six mental health proxies. Accordingly, let each of the parameters δ_1, δ_2, and θ^j now represent a length-6 column vector. The difference in the coefficients for $PC1_{SES}$ and $PC2_{SES}$ can be expressed as: $\beta^j - \tilde{\beta}^j = [\theta^{jT}\delta_1 \;\; \theta^{jT}\delta_2]^T = \Delta^j$, which analogously represents the difference in the SES-GMV association for cluster j due to controlling for the mental health proxies. A Wald test was again used to test the null $\Delta^j = 0$ with the test statistic: $\hat{\Delta}^{j^T}\widehat{Var}\,(\hat{\Delta}^j)^{-1}\hat{\Delta}^j \sim {\chi^2}_2$, where $\widehat{Var}\,(\hat{\Delta}^j)$ was approximated by the delta method: $\widehat{Var}\,(\hat{\Delta}^j) \approx [\hat{\delta}_1 \;\; \hat{\delta}_2]^T\widehat{Var}\,(\hat{\theta}^j)[\hat{\delta}_1 \;\; \hat{\delta}_2] + [\hat{\theta}^j \;\; \hat{\theta}^j]^T\widehat{Var}\,(\hat{\delta})[\hat{\theta}^j \;\; \hat{\theta}^j]$. $\widehat{Var}\,(\hat{\delta})$ is the covariance matrix for a vector stacking $\hat{\delta}_1$ and $\hat{\delta}_2$. To fully estimate the off-diagonal elements of $\widehat{Var}\,(\hat{\delta})$, we employed a seemingly unrelated regression framework to estimate the auxiliary regression equations.

The results indeed suggest that both cognitive ability and mental health are possible downstream consequences that constitute the relationship between SES and the brain (Fig. S16). Except for a few clusters, controlling for cognitive ability and mental health led to statistically significant differences in the SES-GMV association. While Fluid intelligence accounted for about a half of the overall SES-GMV association for some clusters, mental health accounted for much less on average with 25.2% at the maximum.

To conclude, we emphasize that the purpose of these control analyses was *not* to show that factors such as cognitive ability and mental health are *confounders* to SES-GMV *association*. Our aim was to robustly identify the associations between the brain structure and SES, not the causal effect of SES on the brain structure or vice versa. Since our target was an associational quantity, our approach does not necessarily require isolating potential mediators or potential downstream consequences. Instead, our main analyses only controlled for the upstreatm sources of variation in SES and the brain structure, which included differences due to sex, age, and genetic population structure. Factors such as cognitive ability and mental

health are co-variations of key interest, which could constitute the link between SES and the brain rather than confound it (see Section 4.2.3). Controlling for cognitive abilities and mental health could lead to understating the magnitude of the relationship between SES and the brain as well as the relevant role of genetics. Therefore, we did not control for such factors in our main analysis.

4.6.6. Heterogeneity between genetic ancestry groups

In the first set of our analyses, where we aimed to identify robust SES-GMV associations, we included samples with multiple genetic ancestry groups. Therefore, it may be of interest to explore heterogeneity between genetic ancestry groups. Because the majority of the UKB sample is those of European ancestry, we conducted a stratified analysis on samples of European (EUR) ancestry and Non-European (Non-EUR) ancestry, by using GMV clusters. The results suggest some degree of heterogeneity between EUR and non-EUR samples (Fig. S17). However, the estimates for the non-EUR sample were often too noisy to be informative. Although the results do not find statistically significant differences in the results for the European and non-European ancestry groups, we believe that some degree of heterogeneity between the two samples could exist due to the fact that the non-European sample is from social and ethical minority groups in the UK, which implies that the two samples represent different underlying population samples.

As an additional robustness check, we also conducted a meta-analysis of the EUR and non-EUR specific results. We meta-analyzed the stratified analysis results with inverse-variance weights. Fig. S18 shows that the meta-analyzed results are essentially identical to the original results from the pooled analysis. These results also match statistical expectations. By the law of total covariance, it can be analytically shown that the OLS estimator with the pooled sample produces a weighted average of the estimates from each stratified group as well as the estimate reflecting the between-group differences. Because the between-ancestry difference in SES and the brain phenotype can be accounted for by the genetic PCs, our results already represented a weighted average of the European and the Non-European ancestry subsamples as shown in Fig. S17. The weights from this pooled analysis are almost identical to the inverse-variance weights used in the meta-analysis because the OLS estimator also exploits inverse-variance weights to minimize the variance. As a result, the meta-analysis produced barely different results.

4.6.7. The second principal component of SES

We pre-registered to use the two PCs because the first two PCs are both necessary and sufficient to explain the overall SES variation in the UKB sample as demonstrated in Figs. 1B and S2. Whenever possible, we refrained from reporting results for each PC because our statistical quantity of main interest, as pre-registered, is the joint association of the two PCs with brain structure phenotypes. For this reason, we measured SES-GMV association with partial R^2 throughout the paper. While it was not our intention to examine each PC separately, we briefly reported results for each PC as by-products for some analyses.

As shown in Figs. 2 and S4A, $PC2_{SES}$ turned out to have much weaker associations with the brain than does $PC1_{SES}$. Nonetheless, we deemed $PC2_{SES}$ to be relevant *ex-post* for two reasons: First, it gave us more power to identify brain regions significantly associated with SES. Second, $PC2_{SES}$ contributed to capturing non-genetic variation in SES.

Despite its weaker associations with GMV, $PC2_{SES}$ still captures the difference in GMV above and beyond what $PC1_{SES}$ does, which is also statistically detectable for some voxels. As a result, examining the joint association of the two PCs allowed us to find 11% more voxels significantly associated with SES compared to when only $PC1_{SES}$ was used.

More importantly, $PC2_{SES}$ turned out to be barely heritable as reported in Section 4.6.1. If we excluded $PC2_{SES}$ in the analysis, we would have only kept the part of SES-GMV association that is more heritable; consequently, we would have overstated the role of genetics than what the data actually suggests. The regions that have relatively larger association with $PC2_{SES}$, such as lateral temporal and cerebellar regions, tend to overlap with the regions that we found to be susceptible to the influence of the socioeconomic environment. Therefore, $PC2_{SES}$ played a crucial role in differentiating genetic and environmental influences to the SES-GMV relation.

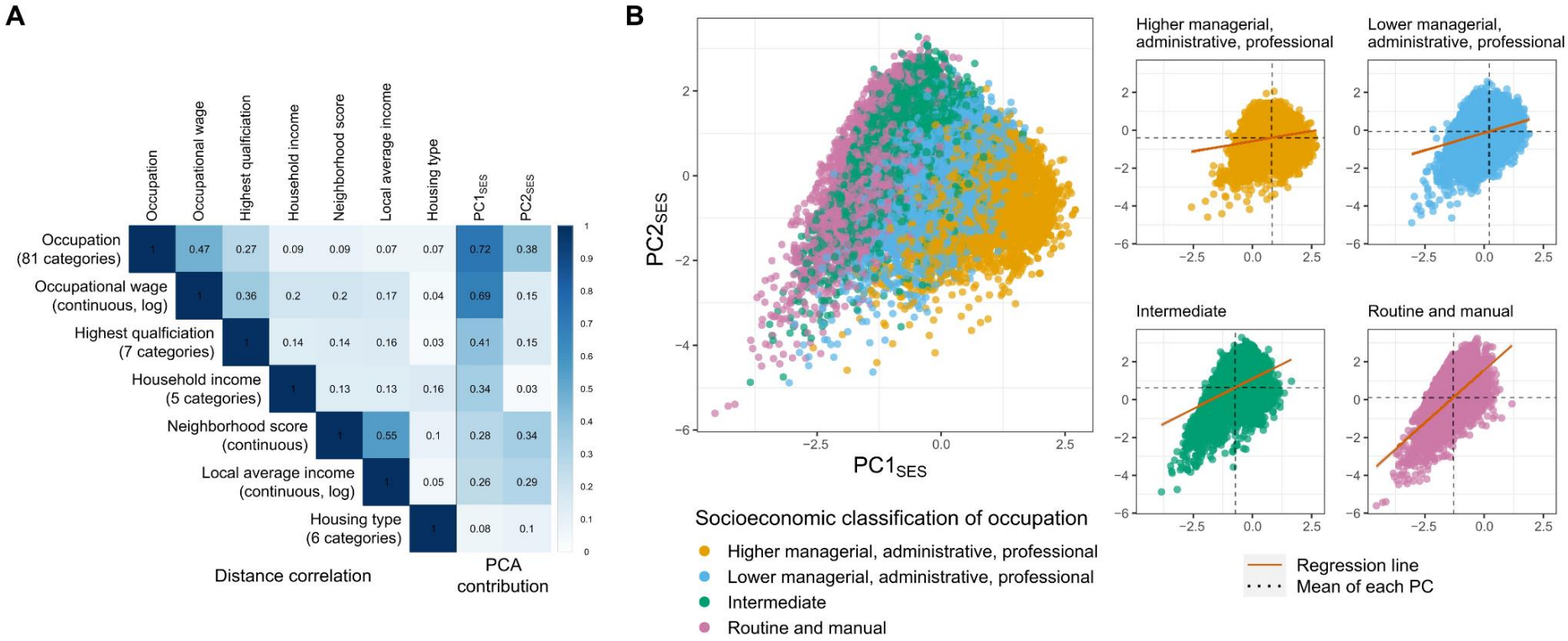

Fig. 1. Measures of SES and PCA

A. On the left, a distance correlation matrix is plotted for seven indices of socioeconomic status (SES). On the right, the squared loadings for each principal component are indicated.

B. Scatter plots of the first principal component ($PC1_{SES}$) against the second component ($PC2_{SES}$). The points in different colors represent four SES groups defined by National Statistics Socio-economic Classification, which are approximately clustered by the two PCs. On the right, the same scatter plots are presented for each SES group. The mean values of each PC are indicated for each group. The regression lines are plotted to describe that SES is more complex for the lower SES groups.

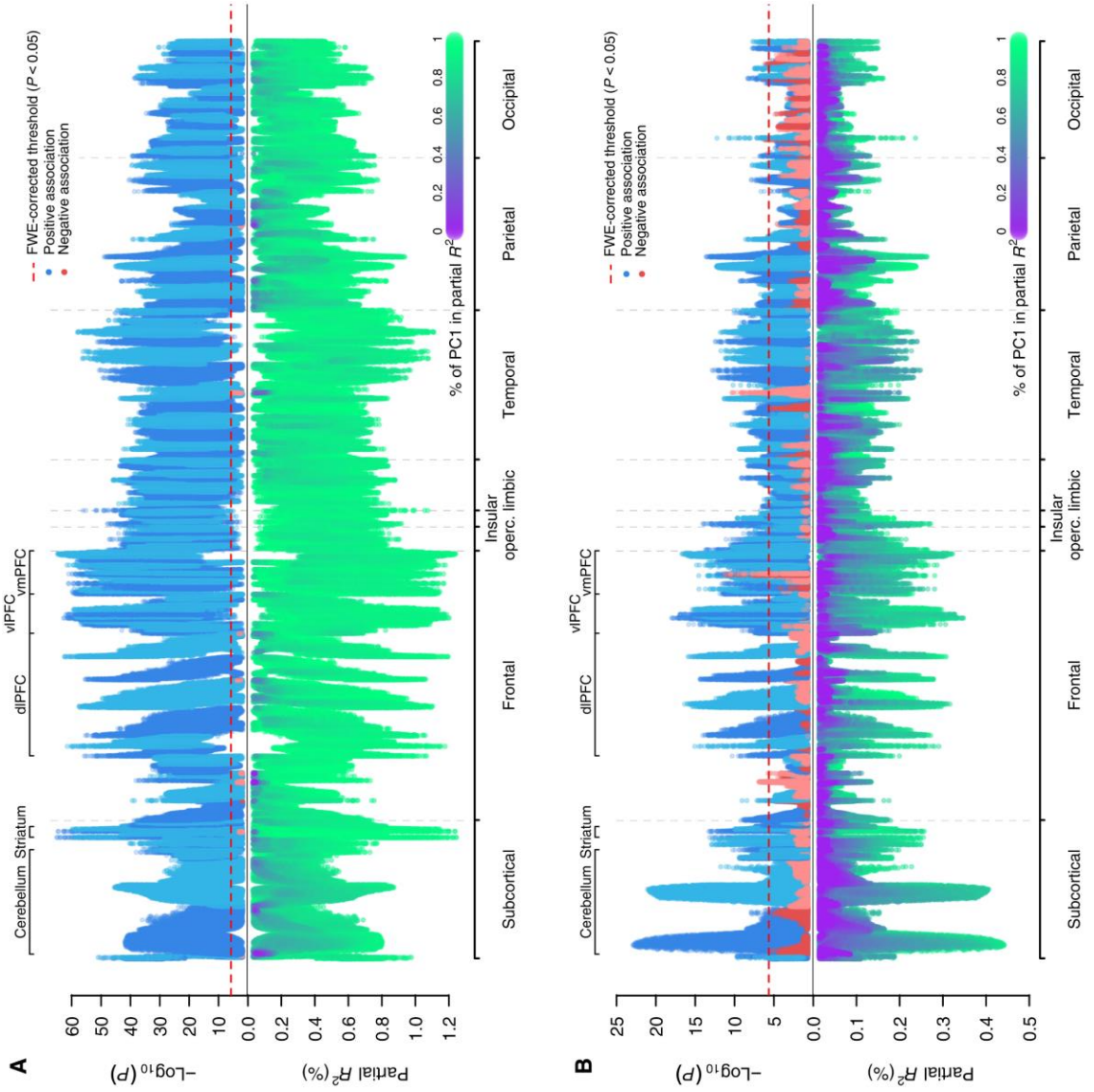

Fig. 2. Manhattan plots: VBM of GMV and SES.
A. Univariate VBM results on the two PCs for SES. These regressions did not control for TIV. *p*-values on log_{10} scale (upper) and partial R^2 (lower) are plotted for each voxel. The sign of the association is that of the first PC. The voxels were anatomically labeled according to the Neuromorphometrics atlas and grouped by the labeled regions. Within each region, the voxels were ordered by their distance to the medoid of their region.
B. Univariate VBM results with TIV controlled for.

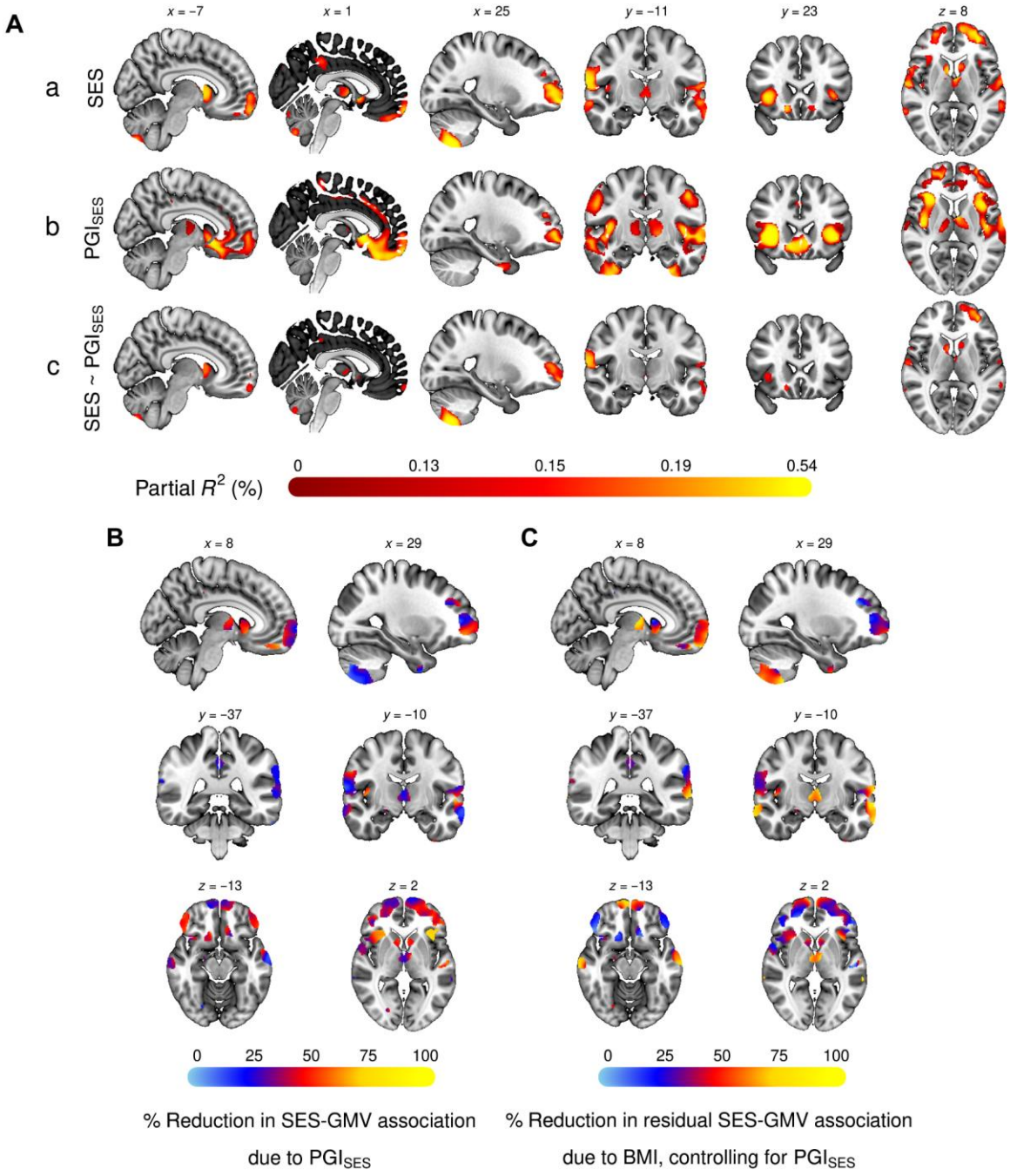

Fig 3. VBM of SES and its genetic and environmental components

A. Univariate VBM results, with `GMV as the dependent variable. Voxels significant at FWE rate of 5% level are plotted for: **a.** the two PCs measuring SES, **b.** The polygenic index for SES (PGI_{SES}), **c.** SES while controlling for PGI_{SES}. **B.** Percent reduction in the association between GMV and the two PC for SES due to controlling for PGI_{SES}. **C.** Percent reduction due to controlling for body mass index (BMI) in the residual association between GMV and the two PC for SES after controlling for PGI_{SES}. The figures plot only voxels which had significant SES-GMV association before PGI_{SES} and BMI were controlled for. MNI coordinates are indicated for **A.** and **B.** Measurement error in PGI_{SES} was adjusted for with genetic instrument variable regression for **B.** and **C.** The sample was restricted to individuals of European ancestry.

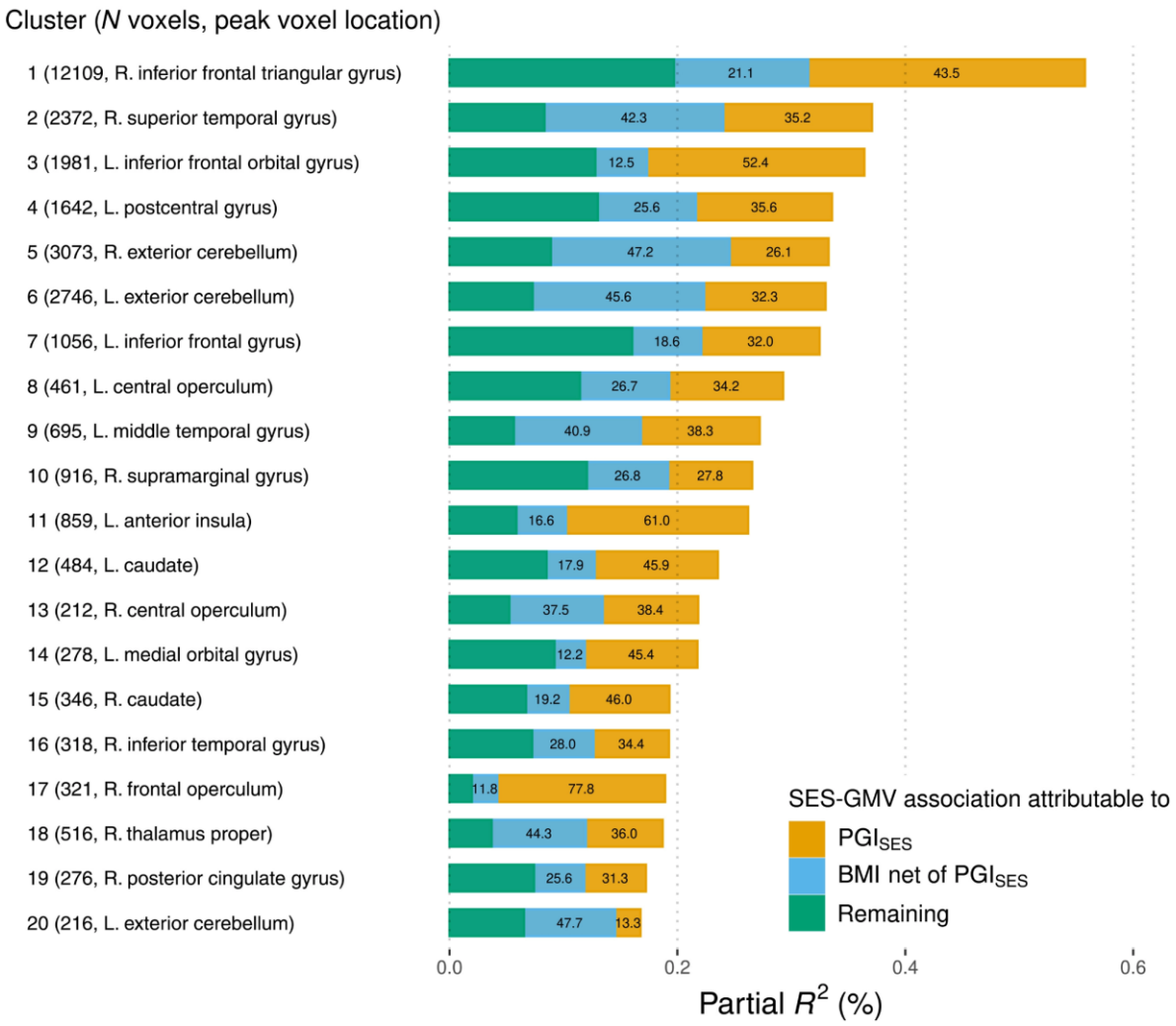

Fig. 4. Genetic and environmental components in the association between SES and GMV of voxel clusters

Associations in partial R^2 between the two PC for SES and GMV in voxel clusters attributable to PGI_{SES} and BMI. The numbers in the bars report the percent share in the SES-GMV association statistically attributable to PGI_{SES} or BMI partialled out of PGI_{SES}. The clusters were formed from the VBM results plotted in Fig. 3A.a. See Table S9 for more information about the clusters. Measurement error in PGI_{SES} was adjusted for with genetic instrument variable regression. The sample was restricted to individuals of European ancestry.

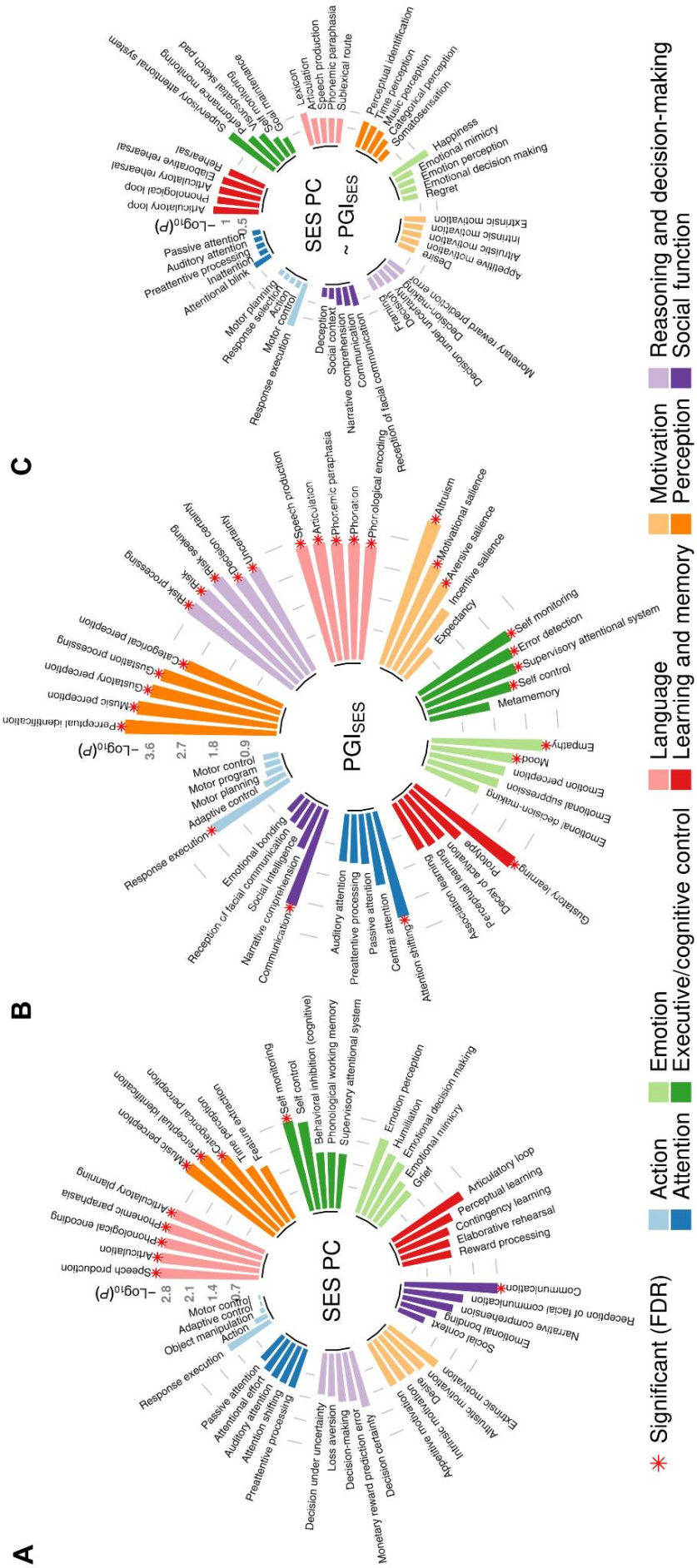

Fig. 5. Functional annotation of brain regions associated with SES

492 cognitive concepts, belonging to 10 categories, were taken from Cognitive Atlas and their predicted fMRI meta-analysis results were generated by NeuroQuery. For each concept, we computed the difference in mean χ^2 between voxels statistically significant at nominal 1% level and the rest of voxels. Then, a pseudo T score for the difference was computed and its p-value was obtained by 10,000 spatial permutations. This procedure was carried out for the voxel-based morphometry results respectively for **A.** two PCs of SES, **B.** the polygenic index for SES (PGI_{SES}), and **C.** SES controlling for PGI_{SES}. The p-values of the top five concepts from each category were plotted on log_{10} scale, where each category was ordered by the average of the top five concepts. The asterisk indicates the significance at the false discovery rate of 5% level. See Table S17 and Fig. S15 for the full results.

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Chapter 3

Large-scale genome-wide study of income highlights heterogeneous pleiotropy across the genome

Based on forthcoming work by H. Kweon, C.A.P. Burik, R. Ahlskog, C. Xia, W.D. Hill, A. Okbay, R. Karlsson Linnér, R. de Vlaming, T.A. DiPerte, A. Abdellaoui. J. Beauchamp, D.J. Benjamin, K.P. Harden, 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.

Online supplements are available at https://tinyurl.com/hermonphd.

1. Introduction

Differences in wealth and income are not only robust predictors of subjective well-being (Sacks et al., 2012; Stevenson and Wolfers, 2013), but low socioeconomic status (SES, *i.e.* the combination of education, occupation, and income) is also a major risk factor for mental and physical diseases as well as lower life expectancy (Wilkinson and Marmot, 2003; Chetty et al., 2016; Stringhini et al., 2017). Low SES is a proxy for material hardship that manifests itself in various forms (Nelson, 2011), all of which affect quality of life and have negative health implications.

Paying attention to these robust health-related consequences of SES is particularly important and timely now as the income and wealth gap between the richest and the poorest 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.

It has long been recognized that parental SES is a major determinant of a child's expected trajectory in terms of cognitive and non-cognitive skill development, behaviors (Heckman and Mosso, 2014), educational attainment (Haveman and Smeeding, 2006), career prospects, and adult income (Acemoglu, 2002). In other words, differences in SES are partially transmitted across generations. At the same time, education, income, personality, cognitive abilities, and occupational choices are all heritable to some extent as parents pass on both their environments and their genes to their offspring (Polderman et al., 2015; Knopik et al., 2017).

In efforts to shed light on the genetic factors linked to SES, there have been a series of genome-wide association studies (GWAS) on components of SES, which include educational attainment (EA) and household income (Rietveld et al., 2013; Okbay et al., 2016; Hill et al., 2016; Lee et al., 2018; Hill et al., 2019; Demange et al., 2021). Numerous loci have robustly been shown to associate with EA and household income among individuals of European ancestries and the predictive accuracy of a resulting polygenic index has now exceeded incremental R^2 = 10% for EA. In follow-up studies, these results have proven to be useful in scrutinizing both physical and mental health with various research designs (Barcellos et al., 2018; Sanderson et al., 2019; Wendt et al., 2021; Marees et al., 2021).

Contributing to this strand of research efforts, here we present a GWAS meta-analysis of income based on approximately 756,000 individuals of European ancestry from 31 cohorts. With the aim to measure individual earning potential, we

used four measures of income: individual, occupational, household, and parental income. We then conducted a multivariate GWAS to combine these different measures and identified 206 approximately independent loci at a genome-wide significance.

In light of the substantial genetic correlation of income with EA (r_g = 0.90 ~ 0.94) (Hill et al., 2019, 2016; Kweon et al., 2020), we performed extensive comparisons of income and EA in their genetic architecture. The loci associated with income are estimated to be completely nested in the loci with EA while having the perfect genetic correlation within the shared loci. To further explore this finding, we then estimated the genetic mediation model of
income with EA as a mediator. This approach allowed us to classify single-nucleotide polymorphisms (SNP) into two sets on the basis of the sign concordance between direct and indirect paths from SNPs to income. The sign discordance here implies that genetic associations of EA may not be well-translated into genetic associations of income. In a series of analyses, we show that concordant and discordant SNPs have marked differences in the way that they contribute to the genetic architecture of various phenotypes, in particular behavioral and psychiatric traits.

2. Results

2.1. Multivariate GWAS of income

At each cohort level, sex-stratified association analyses were carried out on each of available income measures in samples restricted to individuals of European ancestry who completed education or who were above the age of 30. The natural log transformation was applied to the income measures. We centrally applied standardized quality control procedures to each of the cohort-level results. For each sex and for each income measure, we performed a sample-size-weighted meta-analysis with METAL (Willer et al., 2010). We then meta-analyzed the male and female results of each income measure by using the meta-analysis version of MTAG (Turley et al., 2018), which helps account for the unadjusted relatedness between the male and female samples. Finally, we performed a meta-analysis of each income measure result by using MTAG under the perfect genetic correlation assumption. This approach allows for a meta-analysis of results from different measures that may have different heritability or measurement error while accounting for the sample overlap. Since MTAG already applies a bias-correction with the intercept of linkage disequilibrium (LD) score regression (LDSC) (B. K. Bulik-Sullivan et al., 2015),

Table 1. Summary of GWAS of four income measures

Measure	*N*	% Female	# SNP	Mean χ^2	# Loci	SNP h^2 (*s.e.*)
Individual	72,601	0.54	5,986,804	1.06	0	0.04 (0.01)
Occupational	443,064	0.57	11,500,419	1.36	70	0.07 (0.00)
Household	497,413	0.55	11,500,222	1.31	50	0.06 (0.00)
Parental	128,724	0.50	6,144,179	1.08	1	0.05 (0.01)

Some individuals contributed multiple times to different income measures. The SNP heritability (h^2) was estimated with LD score regression. # Loci reports the number of lead SNPs. One lead SNP is overlapping in occupational and household income.

we did not apply further bias adjustments for cryptic relatedness and population stratification.

Across the four GWAS of each income measure, we identified a total of 120 approximately independent SNPs (lead SNP hereafter, pairwise $r^2 < 0.1$) that reached genome-wide significance at $P < 5 \times 10^{-8}$ (**Table 1**). Occupational and household income attained the most genetic associations (70 and 50 loci, respectively) as well as the highest SNP-based heritability estimated by LDSC (h^2 = 0.07 (*s.e.* = 0.00) and 0.06 (*s.e.* = 0.00), respectively). The pairwise genetic correlation (r_g) estimates of each income measure demonstrate substantial shared genetic variance among these measures with r_g at least 0.8 (**Fig. 1a**).

The meta-analysis GWAS of these income measures was estimated to have an effective sample size of 668,288 based on the heritability of occupational wage. The meta-analysis led to a substantial increase in power, which allowed us to identify 206 lead SNPs (**Fig. 1b**). All of them had effect sizes (R^2) smaller than 0.025%. The median per-allele effect among these SNPs corresponds to an increase in income by 0.43% on the basis of the standard deviation estimate of log hourly occupational income from the UK Biobank (*s.d.* = 0.35).

As opposed to the substantial gender wage gap typically observed, we did not find compelling evidence for between-sex heterogeneity in the genetic associations of income (**Fig. S1**). While we did find that the between-sex genetic correlation is statistically different from one, the estimated r_g was still larger than 0.9, except for the parental income where the income of mother and father were used as phenotypes.

2.2. Polygenic overlap with educational attainment

Consistent with the previous reports (Hill et al., 2019, 2016; Kweon et al., 2020), we found a substantial genetic correlation between income and EA based on LDSC (r_g = 0.92; *s.e.* = 0.01). Among the input income measures, the genetic correlation with EA was highest for occupational income (r_g = 0.95; *s.e.* = 0.01) while lowest for individual and household income (r_g = 0.81 and 0.82; *s.e.* = 0.07 and 0.01 respectively). 165 out of 206 loci tagged by lead SNPs (each loci defined as SNPs in a 1000-kb window having LD $r^2 > 0.6$ with the lead SNP) for income were genome-wide significant for EA. Conversely, 151 out of 1,492 loci tagged by lead SNPs for EA were also genome-wide significant for income.

As further investigations, we quantified the number of variants associated with income and EA as well as their polygenic overlap on the basis of a bivariate mixture model by employing MiXeR (Frei et al., 2019). The estimated model suggests that all of the loci associated with income are entirely nested within the EA-associated loci, with approximately 83.2% of the EA loci estimated to have shared association with income (**Fig. 2a**). While the estimated global genetic correlation is 0.91 (*s.e.* = 0.01), the correlation within the shared loci was estimated to amount to unity precisely (*s.e.* = 0.002).

Such patterns of the polygenic overlap between income and EA provide important implications. First, the genetic associations of income appear to be mainly driven by the fact that income is a downstream outcome of EA, given the encompassed income-associated loci, whose associations were perfectly aligned with the genetic associations of EA. Second, some of the genetic associations of EA are not well-translated into genetic associations of income, which drives down the global genetic correlation.

2.3. Genetic mediation model of income via educational attainment

To fully explore these implications, we considered a genetic mediation model of income with EA as a mediator (**Fig. 2b**). In this model, the genetic association of income for SNP *j* (β_j^{INC}) consists of *1)* the indirect mediated path that captures the genetic association of EA (β_j^{EA}) scaled down by the correlation between income and EA (α) and *2)* the direct path that contains the genetic association independent of EA (δ_j). Then, in the absence of δ_j, β_j^{INC} will be proportionate to β_j^{EA}, which may explain the perfect genetic correlation within the shared loci. If δ_j takes a concordant sign to β_j^{EA}, β_j^{INC} will capture additional association in the same direction of β_j^{EA} given that α is expected to be positive. On the other hand, β_j^{INC} will be suppressed with a discordant value of δ_j and the genetic association for EA may not be

transferred to the genetic association for income. Therefore, this mediation model offers consistent explanations for the MiXeR results above and their implications. Henceforth, we refer to the SNPs as discordant or concordant based on the sign concordance of β_j^{EA} and δ_j estimates. We estimated the model with Genomic SEM framework (Grotzinger et al., 2019), which involved estimating α and δ_j (see Section 4.2.3 for details).

We identified one lead SNP (rs34177108) for the GWAS of direct income (δ_j), which had a discordant sign with its estimate of β_j^{EA}. Direct income tended to have stronger associations with the discordant SNPs, with mean χ^2 = 1.21 for discordant SNPs while 1.00 for concordant SNPs. This result suggests that direct income is likely to have suppressing rather than enhancing effects on the genetic associations of EA. The Miami plots separately presenting the discordant and concordant SNPs demonstrate the larger association strength with income for the concordant SNPs than for the discordant SNPs, while the associations with the concordant SNPs are not particularly stronger for EA compared to the discordant ones (**Fig. 2c**). Out of 1,492 lead SNPs for EA, 927 were discordant SNPs, only 17 of which achieved genome-wide significance for income by themselves or SNPs in LD. On the contrary, 565 of the EA lead SNPs had a concordant sign with direct income, 134 of which attained genome-wide significance for income.

2.4. Income-related heterogeneity in the genetic architecture of educational attainment

Seeking to understand why the discordant SNPs may have strong associations with EA that do not translate well into associations with income, we then investigated whether these discordant genetic associations of EA have different genetic implications for other traits in comparison to the concordant ones. Specifically, by leveraging GNOVA tool(Lu et al., 2017), we estimated genetic correlations of EA stratified for the discordant and concordant SNPs (denoted as r_g^d and r_g^c, respectively) with a wide set of phenotypes. If the classification of the discordant and concordant SNPs were to be merely an outcome of chance or the difference in the statistical power between the GWAS of income and EA, we would expect to observe no interpretable and significant difference between the two sets of SNPs.

The discordant and concordant SNPs showed different patterns of genetic correlation of EA with various types of traits (**Fig. 3**). Overall, the concordant SNPs had stronger or weaker genetic correlations in the direction typically expected for EA as an indicator of SES. The Townsend deprivation index(Hill et al., 2016), a neighborhood-based SES index, essentially had a perfect genetic correlation with

EA for the concordant SNPs, while non-significant correlation with the discordant SNPs (r_g^d = 0.17 (*s.e.* = 0.10), r_g^c = -1.14 (*s.e.* = 0.06), P_{diff_fdr} < 0.001). Subjective well-being did not have a particularly strong global genetic correlation with EA, which was due to the negative correlation of discordant SNPs (r_g^d = -0.19 (*s.e.* = 0.05), r_g^c = 0.44 (*s.e.* = 0.06), P_{diff_fdr} < 0.001). Parental life span had a much stronger positive genetic correlation based on the concordant SNPs (r_g^d = 0.24 (*s.e.* = 0.03), r_g^c = 0.70 (*s.e.* = 0.04), P_{diff_fdr} < 0.001). EA was also genetically correlated with cognitive skills much more strongly for the concordant SNPs (r_g^d = 0.48 (*s.e.* = 0.03), r_g^c = 0.90 (*s.e.* = 0.02), P_{diff_fdr} < 0.001), while more weakly with non-cognitive skills—the residual genetic variation in EA after conditioning on cognitive skills (r_g^d = 0.84 (*s.e.* = 0.01), r_g^c = 0.53 (*s.e.* = 0.04), P_{diff_fdr} < 0.001). Nonetheless, the discordant SNPs still attained a sizable positive genetic correlation with cognitive skills, and so do the concordant SNPs with noncognitive skills.

The difference was also found for health-related traits and risk behaviors. Concordant SNPs tended to have a stronger genetic correlation with the avoidance of risky smoking behaviors, albeit a relatively small difference. Alcohol consumption was positively correlated with EA for the concordant SNPs while negatively for discordant SNPs (r_g^d = -0.16 (*s.e.* = 0.04), r_g^c = 0.29 (*s.e.* = 0.05), P_{diff_fdr} < 0.001). Height had a positive and stronger genetic correlation with EA only based on the concordant SNPs (r_g^d = 0.01 (*s.e.* = 0.03), r_g^c = 0.28 (*s.e.* = 0.04), P_{diff_fdr} < 0.001), suggesting that the positive genetic covariance between height and EA is entirely driven by the concordant SNPs. While BMI showed no difference in genetic correlations with concordant and discordant SNPs, waist-to-hip ratio captured more negative correlation with the concordant SNPs (r_g^d = -0.22 (*s.e.* = 0.03), r_g^c = -0.43 (*s.e.* = 0.04), P_{diff_fdr} < 0.001). For other physical disease traits, we did not find meaningful differences between concordant and discordant SNPs.

Psychiatric traits were found to have pronounced contrasts between the discordant and concordant genetic associations of EA. In particular, increased EA has been reported to have a genetic correlation with increased risk of schizophrenia (Okbay et al., 2016; Lam et al., 2019), as also the case here (r_g = 0.05, *s.e.* = 0.02). The stratified results here suggest that this positive correlation was driven by the discordant genetic associations of EA (r_g^d = 0.21 (*s.e.* = 0.03), r_g^c = -0.18 (*s.e.* = 0.05), P_{diff_fdr} < 0.001). We also found similar results for bipolar disorder, autism spectrum, and cross disorder. Furthermore, internalizing disorders (major depressive disorder and anxiety disorder) as well as neuroticism, a related personality trait, all showed a substantially stronger negative correlation for the concordant SNPs while zero correlation for the discordant SNPs (r_g^d = 0.03 (*s.e.* = 0.04), r_g^c = -0.52 (*s.e.* = 0.04), P_{diff_fdr} < 0.001 for major depressive disorder, for example). These results also suggest that

the negative genetic covariance of EA with these traits are entirely due to the concordant SNPs. Albeit to a smaller extent, stress-related disorder showed similar patterns.

2.5. Polygenic validation

We conducted a validation analysis based on polygenic prediction with individuals of European ancestry in the Swedish Twin Registry (STR), which was not included in our meta-analysis. We chose the STR as the main prediction cohort for its accurate income data collected from administrative data sources, which include individual, occupational, and household income. In addition, we also exploited the UKB siblings (UKB-sib) as a prediction cohort, for which occupational and household income measures are available. In both cohorts, we randomly selected only one individual from each family.

We constructed a polygenic index (PGI), using LDpred2 (Privé et al., 2020) with the meta-analysis results of income excluding the prediction cohort, as well as a PGI based on the EA GWAS results in the same way. We measured the prediction accuracy on the basis of the incremental R^2 from adding the PGI to a regression of the phenotype on the baseline covariates. Because income distributions contain substantial demographic variation, we pre-residualized the log of income for demographic covariates. Then, as baseline covariates for income, we only included top 20 genetic principal components and genotype batch indicators.

In the STR (**Fig. 4a**, upper panel), the income PGI predicted ΔR^2 = 1.3% (95% CI: 1.0-1.6) for individual income, 3.7% (95% CI: 3.1-4.2) for occupational income, and 1.0% (95% CI: 0.6-1.4) for household income. The EA PGI had predictive accuracy results in a similar range for individual and household income, except for occupational income, for which the accuracy was ΔR^2 = 4.7% (95% CI: 4.0-5.4). In the UKB-sib (**Fig. 4a**, lower panel), the predictive accuracy of the income PGI was ΔR^2 = 4.7% (95% CI: 4.3-5.2) for occupational income and 3.9% (95% CI: 3.5-4.3) for household income. The EA PGI achieved a better predictive accuracy for occupational income (ΔR^2 = 6.9%, 95% CI: 6.3-7.4), while only slightly higher for household income (ΔR^2 = 4.4%, 95% CI: 3.9-4.8).

2.6. Stratified polygenic analyses

To see how the discordant and concordant SNPs contribute to polygenic prediction, we split the PGI into the discordant and concordant parts and tested their predictive power by including them separately in the regressions. Here the discordant and

concordant SNPs were classified again after re-estimating the mediation model with the EA summary statistics excluding the prediction cohort.

The results suggest that the higher accuracy of the EA PGI for predicting income compared to the income PGI was mainly due to the lack of genetic signals from the discordant SNPs for income, rather than due to the sample size difference. These results were consistent for both the cohorts. In the UKB-sib as an example, the concordant PGI of income predicted both occupational and household income (ΔR^2 = 4.2% (95% CI: 3.7-4.6) and 3.6% (95% CI: 3.2-3.9), respectively) just as well as did the concordant PGI of EA (ΔR^2 = 4.3% (95% CI: 3.9-4.8) and 3.4% (95% CI: 3.0-3.7), respectively) (**Fig. 4**). The discordant PGI of EA still predicted a sizable variation in occupational income (ΔR^2 = 4.4%, 95% CI: 3.9-4.8) presumably because this PGI can still predict EA, which in turn can help predict income. The discordant PGI of income predicted only 1.7% (95% CI: 1.4-2.0) for occupational income.

Exploiting sibling differences, we also conducted within-family polygenic prediction analyses, which can reduce confounds due to indirect genetic effects such as genetic nurture and population stratification (Kong et al., 2018; Morris et al., 2020; Trejo and Domingue, 2018). This was implemented by regressing the phenotype on the PGI while accounting for family-specific intercepts. In every case, the coefficient estimates from the within-family model were attenuated compared to the model without family-specific intercepts in similar magnitudes with the previous reports (**Fig. S4**). The attenuation was overall similar for the concordant and discordant parts of the PGI. This result was also consistent with the lack of genome-wide heterogeneity in attenuation reported in a recent study of within-sibling GWAS (Howe et al., 2022).

2.7. Stratified neurobiological analysis

We then investigated whether the concordant and discordant genetic associations of EA reflect different biological implications. Because the genetic associations of EA have been reported to have dominantly stronger expressions in the central nervous system (Lee et al., 2018), we focused on brain-related traits and functions and carried out stratified genetic correlation analysis with brain imaging phenotypes.

We estimated stratified genetic correlations of EA with an extensive set of brain imaging phenotypes in multiple modals. Specifically, we used 124 structural cortical phenotypes (62 regions from Desikan-Killiany-Tourville atlas) (Klein and Tourville, 2012; Smith et al., 2021), 191 functional network traits from resting-state functional imaging (75 node amplitudes and 116 connectivities) (Zhao et al., 2022),

and 215 white matter traits derived from diffusion tensor imaging (110 tract-averaged values and 105 tract-specific principal components for fractional anisotropy) (Zhao et al., 2021).

EA was genetically correlated with a number of structural and functional brain features in moderate magnitudes. These correlations were often driven dominantly by either the concordant or discordant set of SNPs, while their estimated differences were only nominally significant at 1% level. In particular, the concordant SNPs generally had stronger positive genetic correlation between EA and cortical surface areas, with the largest correlation in the right caudal anterior cingulate cortex (r_g^c = 0.39, *s.e.* = 0.07). The correlations were overall smaller for cortical thickness and no marked differences were found. With functional network amplitudes, EA tended to have weak negative genetic correlations largely due to discordant SNPs, except for functional regions involving the cerebellum and central executive, attention, and default mode networks. Among the functional network connectivities, the most divergent results were observed in a connectivity involving central executive, salience, and default mode networks (r_g^d = -0.13 (*s.e.* = 0.06), r_g^c = 0.30 (*s.e.* = 0.11), P_{diff} = 0.005), where only the concordant SNPs had positive correlation. On the contrary, in two connectivities involving motor and cerebellar regions, we found negative correlation only with the concordant SNPs.

Similar divergent patterns were also found for white matter tract traits. Overall, these results demonstrate that heterogenous implications of genetic associations of EA are reflected in structural and functional brain features.

3. Discussion

Our multivariate approach for meta-analysis that combined multiple income measures allowed us to identify 206 approximately independent loci, which is a marked improvement over the previous study on household income that found 30 loci (Hill et al., 2019). As can be seen from its higher genetic correlation with EA, our GWAS result better reflects the genetic associations of individual earning capacity than the GWAS of household income, which is a family-level proxy of individual income.

Studying income offers a unique opportunity to understand the genetic architecture of EA or socioeconomic factors in general since income is a downstream outcome of EA in one's life course. Taking direct advantage of this fact, we established the genetic mediation model of income with EA as a mediator, which allowed us to classify the genetic association of EA into those well-transferred to income and those not, based on the sign concordance. Our well-powered GWAS of

income was crucial in this regard, which helped determine the sign of estimates in higher confidence.

We also report that income and EA have not only a substantial genetic correlation, but also extensive polygenic overlap, within which income and EA share perfect associations. This result implies that the primary contribution of the GWAS of income will not be the identification of genetic variants associated with income. Rather, our GWAS results of income will be more valuable for understanding the genetic architecture of EA. Our results here highlight a subset of the genetic associations of EA that are more consistent with the typically observed SES gradients with behavioral and health phenotypes. For instance, the stratified genetic correlation results imply that the genetic associations for educational success will also correlate with higher income only if they are correlated with better mental health. Moreover, such concordant genetic associations of EA are shown to drive the entire negative genetic covariance between EA and internalizing disorders (i.e., anxiety disorder and major depressive disorder). The previous GWAS of EA have been used in various areas of research. Researchers could use our results to develop a more effective research design that recognizes the heterogeneity across the genetic associations of EA reported here.

4. Supplementary methods and materials

4.1. GWAS, Quality control, and Meta-analysis

We pre-registered our analysis plan for the main income GWAS meta-analysis on August 30 2018 (https://osf.io/rg8sh/). In total, we recruited 31 cohorts, which have one of the following income measures available: individual, occupational household, and parental income. Some of these cohorts contributed to multiple income measures.

4.1.1. Phenotype definition and construction

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 labor market, and personal choices about labor supply (e.g. due to personal preferences, decisions about division of labor among household members). In this paper, we aimed to study the genetic factor for such individual earning potential. For this purpose, it was ideal to use individual

income measures. However, individual income information was typically not collected in most of the genotyped samples. To circumvent such empirical challenges, we used four measures of income (individual, occupational, household, and parental income) and conducted a multivariate GWAS to combine these different measures.

4.1.1.1. General definition

For all income measures considered, we defined the main phenotype as the natural log of income before-tax. It is important to use the log transformation here because this allows us to correct for the typical skewness of the income distribution, which will return a better linear fit, as well as to model the percentage change in income, which is unit-free. Ideally, the phenotype included all "earned" financial compensation (salaries, income from self-employment, profits from running one's own business, bonuses, vacation benefits) but excluded non-earned monetary transfers such as rental income, capital gains, dividends, and transfers from the government, family, or former spouses.

Many cohorts opted to use categorical responses to measure individual or household income. In these cases, we converted 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 converted the top category by taking the logarithm of 4/3 times the lower bound of that category and the bottom category by taking the logarithm of 3/4 times the upper bound of that category.

When multiple observations of the income measure per individual were available (i.e. longitudinal data), we first regressed the income measure on all control variables including time-specific intercepts. Then, the mean of the residuals for each person were taken as the phenotype.

Some of the older cohorts had a large share of retired individuals who may have been receiving pension. For these individuals, we used their last observed wage. If their last wage was not available, we derived occupational wage from their last occupation. In either case, they were treated as if they were observed while they had their last job. For instance, if a 65-year-old retired individual was surveyed in 2009 and her past wage or occupational wage for the job that she had in 2006 was available, her age and year of observation was 62 and 2006, respectively, in the control variables.

Individuals who are unemployed or economically inactive at the time of survey were treated like pensioners if they had an income in the past. In other words, their last observed income or occupation was used.

4.1.1.2. Individual income

In ideal scenarios, official registry data (e.g. from tax records) are preferred to obtain high-accuracy measures of individual income. However, the linkage between genetic data and registry data was normally not feasible due to privacy concerns. Therefore, we mainly relied on self-reports of income, despite likely measurement error.

4.1.1.3. Household income

We considered household income as an alternative measure of individual income. 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 the spouse. Nonetheless, household income can still serve as a reliable proxy of individual income.

4.1.1.4. Occupational income

When detailed occupation information was available with standardized coding, we derived (log) occupational income based on the national statistics data. Occupation encompasses income potential and typically also reflects educational attainment, personal interests, social prestige and labor market opportunities. In comparison to individual income, occupational income only captures between-occupation variation in individual income. However, occupational income is less likely to suffer large measurement error because it is easier to recall occupation than income, while occupation-specific income is obtained from the national statistics. Occupational income measures were mainly used for relatively larger cohorts. Due to different data availability across different countries in which those cohorts are based, slightly different approaches were used for different cohorts, which are summarized below.

UK Biobank and ALSPAC mothers

The UK Biobank recorded the occupation of participants with the UK's standardized occupational classification (SOC) 2000 version, which is coded in 4-digit numbers representing a hierarchical structure. Similarly, ALSPAC also

provided occupational information in the same coding for the mother participants, while their income was not surveyed. For these British cohorts, we applied the approach that we developed in Kweon et al. (2020). This approach was originally developed to impute income based on occupation and demographic information, rather than to derive occupational wage. The income imputed this way can be interpreted as expected income per occupation adjusted for demographics, which therefore is not essentially different from occupational income.

The details of the approach are available in the appendix of Kweon et al. (2020). Here we only provide the overall summary. From the Annual Survey of Hours and Earnings, we obtained the tax-registry-based estimates of sex-specific mean and median hourly wages for each occupational group defined by 4-digit level SOC. Using the Labour Force Survey (LFS), a large representative survey data of the UK population, we fit a regression model of log hourly wages using mean and median wages for each occupation along with demographic variables and interaction terms. The log occupational wages were then derived as the predicted outcomes from this regression. In the appendix of Kweon et al. (2020), it was shown that occupational wages constructed from this method yielded an out-of-sample R^2 = 0.50 with self-reported log hourly wages in British Household Panel Survey, another independent representative survey of the UK.

Lifelines and Netherlands Twin Registry

A similar approach was taken for two Dutch cohorts: Lifelines and Netherlands Twin Registry (NTR). We mirrored the approach for the British cohorts as closely as possible. Here we used data from the Dutch Labour Force Survey, 'Enquête Beroepsbevolking' (EBB). The EBB is a national representative survey of the Dutch labor force, conducted by Statistics Netherlands (CBS). We used a merged dataset containing 479,893 individuals in yearly waves from 2012 to 2017, where we excluded multiple observations per individual by taking the latest observation. The EBB used a Dutch version of standardized occupation codes, BRC, developed by CBS based on the International Standardized Classification of Occupation (ISCO) 08 standard.

As the EBB was the only national representative survey containing standardized occupation codes, we fit a regression model and calculated the mean and median hourly wages per occupation group in the same sample. We standardized hourly wages to the year 2012 using the consumer price index calculated by CBS. We then calculated the mean and median wage for each 4-digit occupation code separately for each sex. If there are less than 10 people per occupation code, we calculated the mean and median using a pooled sample of both

sexes. If there are less than 10 people per occupation code in the pooled sample, we used the 3-digit occupation code instead. If the 3 digit occupation code still did not yield a sufficient sample size, we used the 2-digit occupation code. The same model specification as the UK model was used for the wage prediction model.

Given the estimated model, we constructed the log hourly wages per occupation in the 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 the 2017 (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, which is similar to that for the UK case above.

4.1.1.5. Estonian Genome Center

For the Estonian Genome Center (EGCUT), we employed a simpler algorithm. We used the mean log wage of each occupation code, estimated for men and women separately, using the 2011 population census data from Statistics Estonia. EGCUT used 3-digit occupation codes based on the ISCO-88 standard while Statistics Estonia used occupation codes based on the ISCO-08 standard. 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. When multiple ISCO-08 codes corresponded to a single ISCO-88 code, we took the average of the estimated means of the ISCO-08 codes.

We tested the accuracy of the occupational wage estimates by examining their correlation with the self-reported log wages in the Structure of Earnings Survey (N=369,247 individuals aged 25 to 64). This resulted in R^2 = 0.44, which is similar to the results of the Ducth and British cases.

4.1.1.6. HUNT

For the Norwegian cohort HUNT, we used a similar approach to that for EGCUT. Here, we used sex-specific mean wage statistics from 2015 to 2019 from the Statistics Norway (https://www.ssb.no/en/statbank/table/11418/). Similarly to the case of EGCUT, HUNT used 3-digit occupation codes based on the ISCO-88 standard while Statistics Norway used occupation codes based on the ISCO-08. The two are matched together in the same way as was done for EGCUT.

4.1.2. Parental income (iPSYCH)

While the income information of the participants of iPSYCH was available, they were too young that their current income was unlikely to reflect their life-time earnings potential. Therefore, we opted to use the income of their parents instead, which was collected from the Danish registry data. Specifically, we used the average earnings of the age 30~55 for each parent. This approach can be thought of as using the offspring genotype as a proxy for the genotype of the parent. Alternatively, parental income can be considered as a proxy of the participant's own income.

4.1.3. Genotyping and imputation

Supplementary Table S3 reports cohort-level information on the genotyping platform, quality-control filters for the genotype data and subjects prior to imputation, subject-level exclusion criteria, and the reference panel and software used for imputation. As the reference panel for imputation, either the 1000 Genomes Project (The 1000 Genomes Project Consortium, 2012) or Haplotype Reference Consortium (HRC) (McCarthy et al., 2016) was used except for a few cohorts that additionally used cohort-specific reference data.

4.1.4. Association analyses

Each cohort estimated the following linear regression model for each SNP.

$$y_i = \beta_0 + \beta_1 SNP_i{}^j + Z_i{}'\gamma + \varepsilon_i$$

y_i is the log-transformed income phenotype for individual i, $SNP_i{}^j$ the count of effect-coded allele of the SNP j, Z_i the vector that contains control variables with corresponding coefficients γ, and ε_i the error component. Each cohort was asked to control for any sources of variation in income that do not reflect individual earning potential according to their data availability. This includes hours worked (with square and cubic terms), year of survey, indicators for employment status (retired, unemployed), self-employment, pension benefit, and etc (see Supplementary Table S4). Importantly, each cohort was asked to include at least top 15 genetic principal components (PC) to account for population stratification, as well as cohort-specific technical covariates related to genotyping (genotyping batches and platforms). For household income, the number of adult members was also controlled for if possible.

This model was estimated for male and female samples separately in light of the possible between-sex heterogeneity. Generally, the linear mixed model approach was preferred, which additionally models the error component with random genetic effects in order to account for the family structure and cryptic relatedness. The cohorts were advised to use BOLT-LMM (Loh et al., 2015) for

implementation. For smaller family-based cohorts, for which BOLT-LMM's approximation approach was not expected to work well, fastGWA (Jiang et al., 2019) was used instead. Otherwise, the association analysis was performed without the random effect component.

4.1.5. 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 (Lee et al., 2018; Okbay et al., 2016; Karlsson Linnér et al., 2019). As the reference panel, we used HRC v.1.1 (McCarthy et al., 2016). All issues raised during the QC protocol were resolved through iterations with cohort analysts, before the meta-analyses.

The details of the QC protocols as well as the QC of the HRC reference panel is described in the supplementary materials of Karlsson Linnér et al. (2019). Here we only provide the overall summary. The main steps include removing SNPs with missing or incorrect numerical values (a *p*-value outside of [0,1], for instance); a minor allele frequency (MAF) below 0.1% or a minor-allele count (MAC) below 200; a low imputation accuracy (0.6 for MACH, 0.7 for IMPUTE, 0.8 for PLINK); the effect-coded allele or the other allele with values different from "A," "C," "G," or "T."; a Hardy-Weinberg Equilibrium *p*-value lower than 10^{-3} ($N < 1000$), 10^{-4} ($1000 \leq N < 2000$), or 10^{-5} ($2000 \leq N < 10000$) ; and an allele frequency different from the allele frequency in the reference panel by more than 0.2. We also removed duplicate SNPs or SNPs absent in the reference panel.

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.

4.1.6. Meta-analysis

In order to obtain a single GWAS output that combines multiple GWAS results on different income measures collected from multiple cohorts, we performed the meta-analysis in several steps, as follows.

1. For each income measure and for each sex, we meta-analyzed the cohort-level GWAS results with METAL using sample-size weighting, which resulted in 8 sets of GWAS summary statistics given the four income measures.

2. For each income measure, we meta-analyzed the male and female results by using the meta-analysis version of MTAG, which assumes the perfect genetic correlation and equal heritability among the input traits. This version of MTAG can be interpreted as a generalized inverse-variance-weighted meta-analysis. In addition to the variance of the estimates, MTAG exploits additional information from the intercepts of LD score regressions to compute the weights and standard errors. This approach helped account for the unadjusted relatedness between the male and female samples. Prior to running MTAG, we dropped the SNPs with $N = N_{male} + N_{female}$ smaller than 50% of the maximum N to make sure that there were no SNPs with an excessively smaller sample size.
3. To combine the four GWAS results with different income measures, we again leveraged MTAG with the perfect genetic correlation assumption while allowing for different heritability among the input traits. This approach allowed us to meta-analyze results from different measures that may have different heritability or measurement error as well as to account for the sample overlap, which was important given that some individuals were included in multiple GWAS results with different income measures.

As opposed to the meta-analysis with METAL, MTAG, a multivariate analysis tool, can only output the common set of SNPs among the input GWAS summary statistics. This led to a considerably low number of SNPs (4,885,528) after Step 3 due to the individual income and parental income GWAS results, which did not have any biobank-scale cohort and therefore had a smaller coverage over the genome.

To circumvent this issue, we repeated Step 3 without 1) individual income, 2) parental income, and 3) both individual and parental income. We first verified that all of the four sets of meta-analyzed results, including the one with all the measures, had pairwise genetic correlation estimates larger than 0.99 and their heritability estimates were almost identical from LDSC. For each available SNP, we took the result that gave the largest Z statistic among the four results. As a result, we obtained 4,885,528 SNPs from the MTAG result with the all four measures and 6,599,628 SNPs from the MTAG result which only includes occupational and household income. We dropped 2,353,649 SNPs whose effective sample size (see below) fell below 70% of the maximum effective sample size (=692,936). In total, 9,131,507 SNPs were included in the final output.

We computed the effective sample size exploiting the fact that the standardized beta estimates can be approximated as $Z/\sqrt{N}$ for large N. Using the

MTAG-produced standardized estimates β_{std}, we computed the effective sample size per SNP as follows:

$$N_{eff} = (\frac{Z}{\beta_{std}})^2$$

In the downstream analyses, we used these per-SNP effective sample sizes since typical GWAS softwares re-compute the standardized estimates from the MAF, *N*, and *Z* statistic based on the same approximation. To evaluate the overall sample size, we took the average of these per-SNP effective sample sizes using the SNPs with 0.1 < MAF < 0.4 since these SNPs tend to be less noisy. As a result, we estimated that the overall sample size of our meta-analyzed income GWAS is 668,288.

Since MTAG already applies a bias-correction with the intercept of LD score regression, we did not apply further bias adjustments. Also, to measure the effect sizes, we used the (partial) coefficient of determination (R^2), which is the square of the standardized beta estimates.

We applied the clumping approach to identify approximately independent loci, which we refer to as lead SNPs. We identified 206 lead SNPs, using a chromosome-wide window (10,000 mb), requiring lead SNPs to be at least genome-wide significant and have LD (r^2) below 0.1 with each other, and including SNPs with *p*-value < 1×10^{-4} in each clump. Only one lead SNP had a MAF smaller than 1% and 8 lead SNPs had a MAF between 1% and 5%. The remaining 197 lead SNPs had a MAF > 5%.

4.2. Genetic mediation model of income via educational attainment

4.2.1. Comparison to educational attainment GWAS

We carried out a comparison of GWAS of educational attainment (EA, measured as years of education) and income in several approaches by examining 1) overlap in the identified genetic loci, 2) genetic correlation with LDSC, and 3) polygenic overlap with MiXeR (Frei et al., 2019).

Here, we used a version of EA summary statistics that is slightly different from those publicly available. The latest EA GWAS study (Okbay et al., 2022) revised the coding of the years of schooling in the UKB, which better reflects the educational qualification of the participants. We conducted a GWAS of EA in the UKB based on the new coding. Then, by using MTAG with the meta-analysis option, we meta-analyzed the UKB result with the pervious version of EA summary statistics (Lee et al., 2018) that did not include the UKB. This increased the mean χ^2 from 2.53 to 2.94. We found 1,492 lead SNPs, applying the clumping algorithm with the same parameters.

4.2.1.1. Comparison of GWAS estimates

As a starting point, we first examined the extent of overlap in the genetic loci found to be significantly associated with income or EA. We used the lead SNPs selected from the aforementioned clumping algorithm both for EA and income. When examining the overlap, we also included the SNPs in high LD with the lead SNPs ($r^2 > 0.6$, within a window of 1,000 base pairs) and determined that there is overlap if SNPs in LD are statistically significant for both traits even when the lead SNP itself is not statistically significant for the other trait.

4.2.1.2. LDSC and MiXeR

Using LDSC (B. Bulik-Sullivan et al., 2015), we estimated that the genetic correlation between income and EA is 0.92 (*s.e.* = 0.01). This result was consistent with the previous reports, which ranged from 0.90 to 0.94 (Hill et al., 2019, 2016; Kweon et al., 2020). Though providing a useful summary of the shared genetic basis, the global genetic correlation only estimates the average correlation of genetic associations and does not capture mixtures of effect directions. To gain further insights, we used MiXeR tool to estimate the degree of polygenic overlap between income and EA. MiXeR exploits a bivariate causal mixture model to estimate: 1) the count of causal variants specific to each trait, 2) the proportion of the shared causal variants, and 3) the genetic correlation within the shared loci as well as the sign concordance.

4.2.2. Genetic mediation model

To fully explore the heterogeneity in the genetic architecture of income and EA, we set up a genetic mediation model of income with EA as an mediator. This model recognizes the fact that income is a downstream outcome of EA in one's lifetime. Under this model, the genetic association of income for SNP j ($\beta_j{}^{INC}$) can be written as $\beta_j{}^{INC} = \alpha \times \beta_j{}^{EA} + \delta_j$, where each component is defined as:

- indirect mediated path that captures the genetic association of EA ($\beta_j{}^{EA}$) scaled by the correlation between income and EA (α)
- direct path representing the genetic association independent of EA (δ_j).

This mediation model offers consistent explanations for the MiXeR results above and their implications. In the absence of δ_j, $\beta_j{}^{INC}$ will be proportionate to $\beta_j{}^{EA}$, which may explain the perfect genetic correlation within the shared loci. If δ_j takes a concordant sign to $\beta_j{}^{EA}$, $\beta_j{}^{INC}$will capture additional association in the same

direction of β_j^{EA} given that α is expected to be positive. On the other hand, β_j^{INC} will be suppressed with a discordant value of δ_j and the genetic association for EA may not be well-transferred to the genetic association for income.

We estimated this model by using Genomic SEM, which essentially involves estimating the genetic association of the direct income (δ_j) and the correlation between EA to income (α). Instead of the default European reference panel from phase 3 of the 1000 Genomes Project (The 1000 Genomes Project Consortium, 2012) provided by Genomic SEM as the default, we used the HRC European reference panel to increase the SNP coverage. Genomic SEM uses a reference panel to align SNPs and obtain MAF estimates, which in turn are used to compute the per-allele effect sizes standardized with respect to the phenotype.

4.2.3. Concordant and discordant sets

As described above, the translation of the genetic association of EA into the genetic association of income hinges on the sign concordance of δ_j and β_j^{EA}. We therefore classified the SNPs as concordant or discordant on the basis of the sign concordance of $\hat{\delta}_j$ and $\hat{\beta}_j^{EA}$ estimates. Instead of using the output of Genomic SEM, we applied the following procedures to reflect statistical uncertainty in estimating α and determining the sign concordance. This was important because the sign of $\hat{\delta}_j$ was directly dependent on the magnitude of estimated α for given point estimates of $\hat{\beta}_j^{INC}$ and $\hat{\beta}_j^{EA}$.

To achieve this goal, we exploited the same block jackknife approach as Genomic SEM. α can analytically be estimated as the genetic covariance between income and EA, *Cov(INC, EA)*, divided by the heritability of EA, $h^2(EA)$, after partialling out the effect of a given SNP on income and EA. We ignored the latter individual SNP effect since the individual SNP effect has a very negligible effect, and hence we simply estimated α as:

$$\hat{\alpha} = \frac{Cov(INC, EA)}{h^2(EA)}$$

In each block jackknife iteration, we estimated the genetic covariance between income and EA, the heritability of EA, and, in turn, α. Then, for each SNP, we estimated $\hat{\delta}_j = \hat{\beta}_j^{INC} - \hat{\alpha}\,\hat{\beta}_j^{EA}$ and determined the sign concordance of $\hat{\delta}_j$ and $\hat{\beta}_j^{EA}$ estimates. With 200 blocks of jackknife, we obtained 200 sign concordance results for each SNP and determined the sign concordance of each SNP based on the majority vote.

As a result, we classified 3,531,029 SNPs as concordant and 4,475,214 SNPs as discordant. 90% of SNPs had 90% agreement in the 200 jacknife-produced

outcomes. Hence, for the majority of SNPs, the sign concordance was not extremely sensitive to the statistical uncertainty in the estimation of α.

Next, since the classification procedure above was only possible for the SNPs commonly included in the income and EA summary statistics, we added SNPs in high LD ($r^2 > 0.6$, 1,000 bp window) to increase the number of SNPs available in each set. We used the HRC reference panel and added previously non-included SNP in one of the concordant or discordant sets only if they were not tagged by both discordant and concordant SNPs. When tagging additional SNPs, we only used discordant or concordant SNPs that had at least 80% agreement in the jackknife procedure. In total, we yielded 3,533,256 SNPs in the concordant set and 4,478,461 in the discordant set for the SNPs covered in the EA GWAS.

4.3. Stratified analyses of educational attainment GWAS

4.3.1. Stratified genetic correlation

We conducted stratified genetic correlation analyses to investigate the potential heterogeneity between concordant and discordant genetic associations of EA. To estimate stratified genetic correlations, we used GNOVA tool that allows for partitioning genetic correlations by SNP annotation. We estimated genetic correlations of EA stratified for the discordant and concordant SNPs (denoted as $r_g{}^d$ and $r_g{}^c$, respectively) with a wide set of phenotypes, including socioeconomic, behavioral, and physical and mental health traits. If the classification of the discordant and concordant SNPs were to be merely an outcome of chance or the difference in the statistical power between the GWAS of income and EA, we would expect to observe no interpretable and significant difference between the two sets of SNPs.

We only used HapMap3 SNPs (The International HapMap 3 Consortium, 2010) and estimated LD scores with the European reference panel from phase 3 of the 1000 Genomes Project (downloaded from https://alkesgroup.broadinstitute.org/LDSCORE/). The annotation files indicating concordant or discordant for each SNP were created and provided to GNOVA as inputs. The standard errors were computed from the covariance matrix constructed from 200 block-jackknifes. By retrieving the block-jackknife output, we also computed the standard error for the estimated difference in $r_g{}^d$ and $r_g{}^c$ as:

$$\sqrt{\widehat{Var}(\hat{r}_G{}^c) + \widehat{Var}(\hat{r}_G{}^d) - 2\widehat{Cov}(\hat{r}_G{}^c, \hat{r}_G{}^d)}$$

4.3.2. Stratified heritability

We also applied stratified LDSC (Finucane et al., 2015) to estimate SNP heritability of traits stratified for the concordant and discordant sets. Originally, stratified LDSC is used to examine whether heritability of a trait is enriched for certain sets of SNPs reflecting different biological functions by comparing the proportion of heritability with the expected proportion of heritability (the proportion of SNPs). Here we used stratified LDSC to see whether concordant or discordant SNPs contribute disproportionately to SNP heritability of various phenotypes. Specifically, we tested the difference in enrichment by examining the difference in per-SNP heritability between concordant and discordant sets. We computed the standard error for the difference by using the jackknife-based covariance matrix of the regression coefficients. We used the same set of phenotypes analyzed in the GNOVA analysis.

4.4. Polygenic score analyses

4.4.1. Baseline polygenic prediction

We conducted a validation analysis based on polygenic prediction with individuals of European ancestry in the Swedish Twin Registry (STR), which was not included in our meta-analysis. We chose the STR as the main prediction cohort for its accurate income data collected from administrative data sources, which include individual, occupational, and household income. In addition, we also exploited the UKB siblings as a prediction cohort, for which occupational and household income measures are available.

We constructed polygenic indexes (PGI), using the meta-analysis results of income excluding the prediction cohort, as well as a PGI based on the EA GWAS summary statistics in the same way for comparison. PGIs were created only with HapMap3 SNPs (The International HapMap 3 Consortium, 2010) as these SNPs are known to have good imputation quality and provide good coverage in the European ancestry population. We used the reference panel from the HRC. The details of QC for this panel can be found in the Supplementary Information of Okbay et al. (2022).

We derived PGIs based on a Bayesian approach implemented in the software LDpred2 (Privé et al., 2020). LDpred2 is an extension of LDpred (Vilhjálmsson et al., 2015), which adjusts for LD and computes individual SNP weights by using posterior means of LD-independent effect-size distributions. LDpred2 improves LDpred approach by 1) using a LD window based on genetic distances, which can better accommodate long LD regions and 2) allowing for Bayesian updating of p

(the proportion of causal SNPs) and h^2 (SNP heritability) parameters (called LDpred2-auto). As priors, we set 0.2 for p and LDSC h^2 estimates for h^2 parameters. While the authors of LDpred2 recommend running LDpred2 genome-wide, we ran Ldpred2 per chromosome for its computation efficiency given that prediction results are barely different for a well-powered GWAS.

Since the STR sample was genotyped with three different platforms, which gave too few common HapMap3 SNPs after quality-control filters, we applied LDpred2 for the SNPs available in each batch and created PGIs for each batch. We then included indicators for these different batches in the prediction analyses.

In order to create PGIs for the UKB siblings, we re-conducted the GWAS of income and EA excluding the sibling sample as well as their close relatives (up to the third degree of relatedness). We then performed the meta analyses again.

For both the STR and the UKB siblings, we randomly chose one sibling from each family to avoid complications due to having relatives in the sample. We measured the prediction accuracy on the basis of the incremental R^2, which is the difference between the R^2 from a regression of the phenotype on the PGI and the baseline covariates and the R^2 from a regression on the baseline covariates only. We constructed confidence intervals for the incremental R^2 by bootstrapping the sample 1,000 times.

Because income typically contains substantial demographic variation, we pre-residualized the log of income for demographic covariates. Then, as baseline covariates, we only included top 20 genetic PCs and genotype batch indicators. Because STR's income data was available for multiple years, we residualized the log of income for age, age^2, age^3, sex, and interactions between sex and the age terms within each year and obtained the mean of residuals for each individual. For the UKB siblings, which only had cross-sectional data, we residualized the log of income for age, age^2, age^3, sex, dummies for survey year, and interactions between sex and the rest. For EA measure (years of education), we applied the same procedure for consistency while using dummies of birth year in place of the age terms.

4.4.2. Stratified polygenic prediction

To see whether the discordant and concordant SNPs contribute differently to polygenic prediction, we split the PGI into the discordant and concordant parts and tested their predictive power by including them separately in the regressions. Here the discordant and concordant SNPs were classified again after re-estimating the mediation model with the EA summary statistics excluding the prediction sample.

Note that it is possible that some concordant and discordant SNPs are in the same LD region. While in principle, the LD between each of the included SNPs should be accounted for by LDpred2 procedure, there may still be remaining correlation between the concordant and discordant parts of the PGI due to the SNPs in the same LD region or due to assortative mating. Nonetheless, as long as the concordant and discordant PGIs are together included in the regression, each PGI will only capture its unique contribution. Therefore, the results are likely to be more conservative than when all the SNPs in the same LD region were perfectly classified as concordant or discordant.

4.4.3. Within-family polygenic prediction

Genetic associations of SES traits are known to particularly suffer confounds due to indirect genetic effects such as genetic nurture and population stratification (Kong et al., 2018; Morris et al., 2020; Trejo and Domingue, 2018). To reduce such confounds, we exploited the sibling differences to estimate the associations between the PGI and the phenotypes in the STR and UKB siblings. This was implemented by regressing the phenotype on the PGI while accounting for family-specific intercepts. Including family-specific intercepts (also called family fixed effects) accounts for between-family variation in the variables, which allows the model to reflect relationships due to within-family variation. We standardized both the phenotype and the PGI so that they have zero mean and unit variance. The standard errors were clustered by family. As opposed to the baseline prediction analyses, here all available individuals for each family were included while we dropped individuals that did not have any siblings.

Our quantity of interest here was the relative degree of attenuation measured as: $1 - \hat{\beta}_{WF} \,/\, \hat{\beta}$, where $\hat{\beta}$ is the coefficient estimate of the regression without family-specific intercepts and $\hat{\beta}_{WF}$ the coefficient estimate with family-specific intercepts.

4.4.4. Stratified polygenic prediction of behavioral traits

Our results from the stratified genetic correlation analyses found marked differences between the concordant and discordant SNPs in their genetic correlation of EA with behavioral and psychiatric traits. We validated these results in independent samples by examining whether a stratified PGI captures additional variation in the phenotype with a similar set of traits. We used a sample of unrelated adolescents of European ancestry in the US from the Adolescent Brain Cognitive Development (ABCD) study. This sample was not included both in the income and EA GWAS meta-analysis.

We used a wide set of traits that measure cognitive abilities, personality, and mental health. Due to the longitudinal design of the ABCD study, multiple observations were available for each trait (up to four). Therefore, prior to running the main analyses, we regressed the phenotype on demographic covariates (sex, age in months, age^2, and interactions between sex and two age terms) within each wave and obtained the mean of the residuals across the waves for each individiual. Then, in the main analyses we only controlled for indicators for genotyping batches and 20 genetic PCs. The sample size varied from 4,149 to 4,577.

For each trait, we estimated three sets of regression as follows:

$$y_i = \alpha_1 + \beta_1 PGI_i + Z_i'\gamma_1 + \varepsilon_{1i}$$
$$y_i = \alpha_2 + \beta_2{}^c PGI_i{}^c + \beta_2{}^d PGI_i{}^d + Z_i'\gamma_2 + \varepsilon_{2i}$$
$$y_i = \alpha_3 + \beta_3 PGI_i + \delta PGI_i{}^c + Z_i'\gamma_3 + \varepsilon_{3i}$$

where y_i is the phenotype, PGI_i the EA PGI constructed with all the available SNPs, $PGI_i{}^c$ the EA PGI with the concordant SNPs, and $PGI_i{}^d$ the EA PGI with discordant SNPs. Z_i is a vector of the covariates. The first regression represents the standard polygenic prediction model, whereas in the second regression, we separately included the concordant and discordant parts of the PGI.

Here one could test the equality of the coefficients $\beta_2{}^c$ and $\beta_2{}^d$ to test the difference between the concordant and discordant PGIs. However, these coefficients reflect not only the genetic correlation between EA and the given trait, but also the stratified heritability and the number of effective variants in the concordant and discordant SNP sets. In other words, the scales of the two coefficients are not directly comparable. Therefore, this test does not give the same interpretation as testing the difference in the stratified genetic correlations as done in Section 4.3.1.

For this reason, we instead estimated the third regression, where we included the concordant PGI in addition to the original PGI. Testing whether δ is different from zero allows us to examine whether the stratification of the concordant and discordant parts in the EA PGI leads to capturing additional information in the phenotype without concerning the scales of the PGIs. The concordant sign of δ with β_1 implies that the concordant PGI has more importance than the discordant PGI, whereas the discordant sign δ with β_1 implies less importance of the concordant PGI. Note that including the discordant PGI instead in the third regression only flips the sign of δ and the interpretation changes accordingly.

4.4.4.1. Results

Overall, the estimated association patterns of EA PGI with behavioral traits in ABCD cohorts were consistent with the results from the stratified genetic

correlation analysis (**Fig. S5**). At the 5% nominal significance level, the stratification of concordant and discordant SNPs was estimated to capture additional variation (evaluated by δ) in behavioral traits related to attention problems, internalizing behaviors, lack of perseverance, sensation seeking, and oppositional defiant behavior. Among the cognitive measures, only a dimensional change card sort test was statistically significant at 5% level. After correcting the multiple comparison, only sluggish cognitive tempo was significant at the false discovery rate (FDR) of 5% ($P_\delta < 0.001$). For all of these traits with nominal statistical significance, the concordant PGI contributed more than did the discordant PGI. While not statistically significant, the discordant PGI contributed more only for crystallized cognitive measures (picture vocabulary test, oral reading recognition test, and composite crystallized intelligence score).

The concordant part of EA PGI was particularly important for the association between EA PGI and internalizing behaviors. This was well aligned with the stratified genetic correlation between EA and internalizing-behavior traits (major depressive disorder, anxiety disorder, neuroticism), which was almost entirely driven by the concordant SNPs (Fig. 3). Albeit to a lesser extent, this pattern of associations was also similar for traits related to externalizing behavior, while nominal statistical significance was attained only for oppositional defiant problems (P_δ=0.02). The associations with attention-related traits, such as sluggish cognitive tempo and attention problem score, as well as a subset of impulsive behaviors (negative urgency and sensation seeking) were also shown to be driven mainly by the concordant PGI.

In sum, these results suggest that the heterogeneous correlations of genetic associations of EA with behavioral traits shown in the stratified genetic correlation analysis can generally be replicated in an independent sample by using stratified parts of EA PGI.

4.4.5. Phenome-wide association study

In order to see whether the concordant and discordant genetic associations of EA have different implications for medical outcomes, we applied the same analysis of Section 4.4.4 on the disease diagnoses from the electronic health records of the UKB siblings of European ancestry. We derived case-control status according to the phecode scheme by mapping the UKB's ICD-9/10 records to phecodes (https://phewascatalog.org/phecodes, version 1.2) (Wei et al., 2017; Wu et al., 2019). These ICD-9/10 records were collected from hospitalization, cancer, and death registries (as of May 2021). We only analyzed diseases whose sex-specific sample

prevalence was at least 1% for both men and women, which included 165 diseases covering 15 categories.

Given the binary outcomes, we estimated logistic regressions instead, while the model specifications were the same as Section 4.4.4. Because within-family correlation invalidates the model specification for logistic regression with sibling data, we estimated a logistic regression with family-specific random-effect intercepts to account for within-family correlation. As covariates, we used year of birth, its square term, and their interactions with sex, genotype batch dummies, and 20 genetic PCs.

4.4.5.1. Results

We found that EA PGI were associated with 106 out of 165 disease phenotypes at the FDR of 5%, covering a wide range of disease categories (**Fig. S6**). A lower value of EA PGI was associated with higher incidents of these diseases, in particular, essential hypertension, obesity, tobacco use disorder, and gastroesophageal reflux disease (GERD). 64 and 73 diseases were associated independently with concordant and discordant EA PGIs, respectively, at the FDR of 5%. 16 of these associations were suggested to reflect the difference between the concordant and discordant SNPs (as measured by δ; see Section 4.4.4) at the nominal significance level of 5%. However, none of these remained significant after the multiple comparison correction based on the FDR. The concordant PGI had a larger association with these diseases than the discordant PGI, except for only "abdominal pain", "cholecystitis without cholelithiasis", and "other disorders of bladder".

While the different contribution by discordant and concordant SNPs was found in a number of disease categories, the most differences were found in mental disorders, which included anxiety disorder, depression, altered mental status, and tobacco use disorder. The concordant PGI was found to have more importance for these disorders, albeit only with nominal significance, which was consistent with the results from the ABCD study as well as the stratified genetic correlation analysis.

The concordant SNPs were also disproportionately more important for the association between EA PGI and some of the respiratory conditions, such as pulmonary collapse, pleurisy, shortness of breath, and asthma. On the contrary, the protective association of a higher value of EA PGI against abdominal pain was suggested to be almost entirely due to the discordant SNPs.

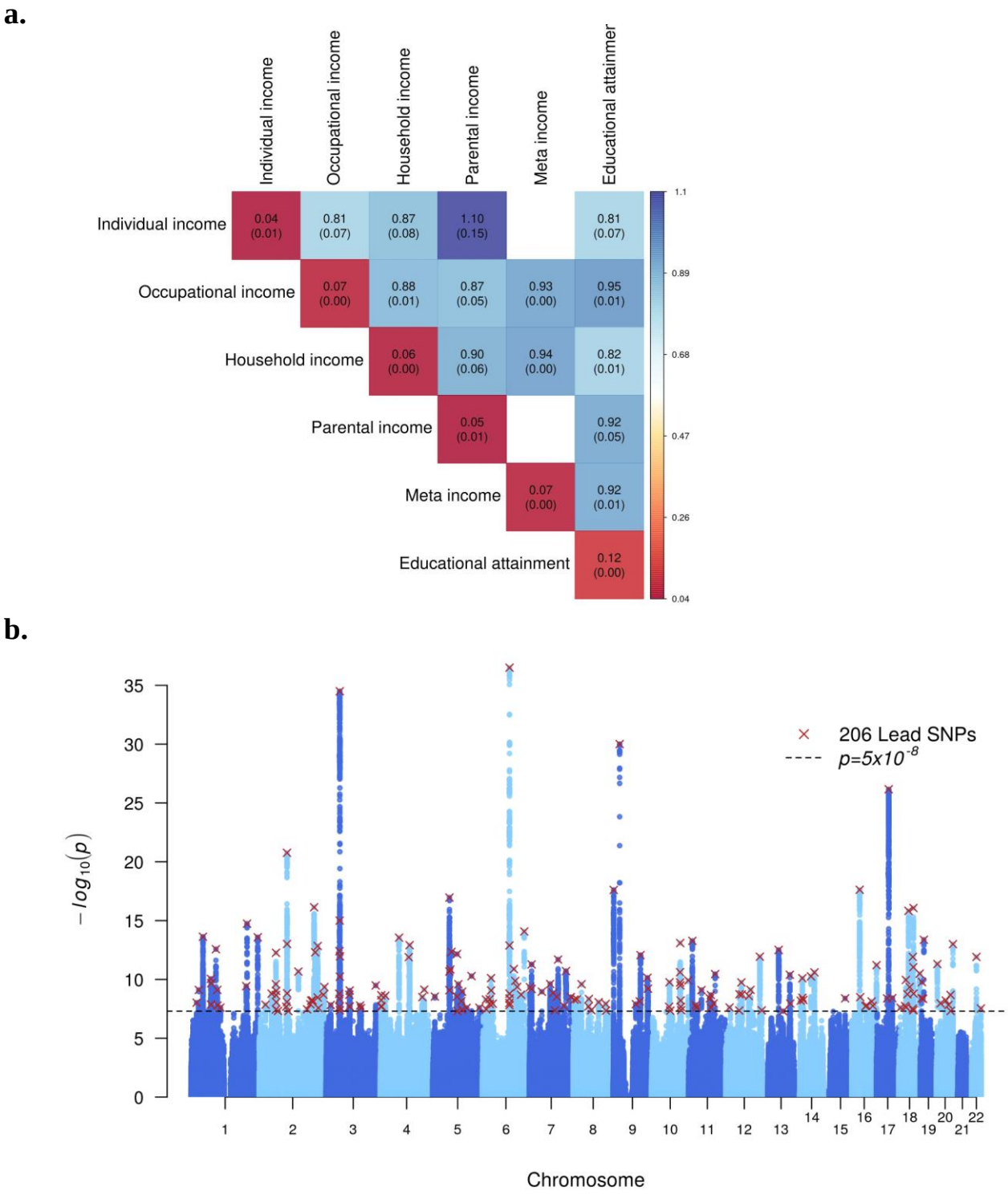

Fig. 1. Multivariate genome-wide association study of income

a. LD score regression (LDSC) estimates of pairwise genetic correlations between the four input income measures, the meta-analyzed income, and educational attainment. The diagonal elements report SNP heritabilities from LDSC. The standard errors are reported in the parentheses. Some of the results were not reported due to out-of-bound estimates.

b. Manhattan plot presenting the result of MTAG meta-analysis of four income measures. *P* values are plotted on -log_{10} scale. The red crosses indicate the 206 lead SNPs found from clumping ($r^2 < 0.1$, chromosome-wide window).

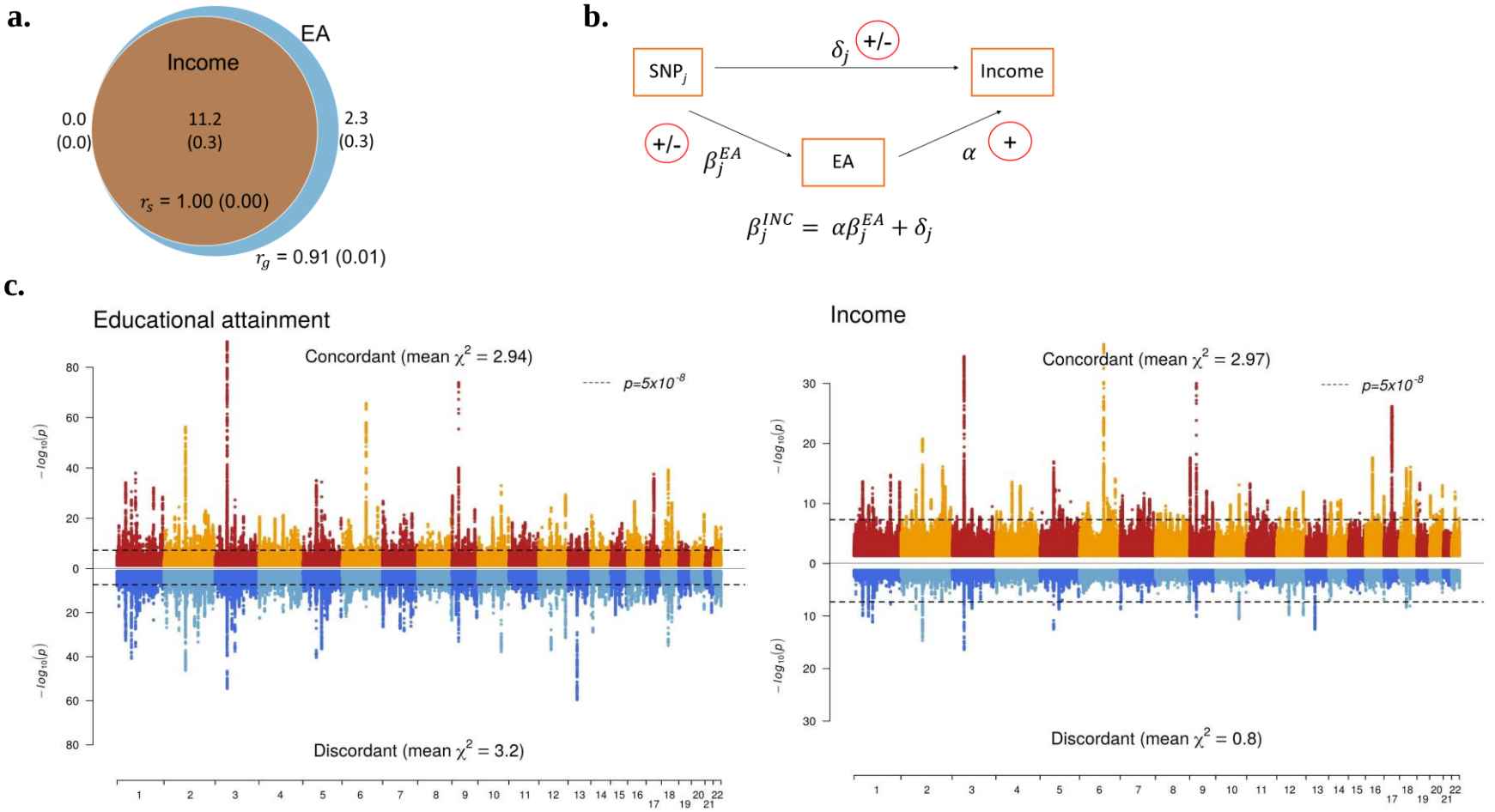

Fig. 2. Comparison of income GWAS with EA GWAS

a. The Venn diagram presents MiXeR results on income and EA. The estimated numbers of unique and shared causal variants are reported in thousands and by the areas of the circles. r_g the global genetic correlation while r_s is the correlation within the shared variants. The standard errors are reported in the parentheses. **b.** The genetic mediation model of income via EA describes the genetic association of income for SNP *j* (β_j^{INC}) as the sum of *1)* the indirect mediation path that captures the genetic association of EA (β_j^{EA}) scaled down by the correlation between income and EA (α) and *2)* the direct path from SNP to income that contains the genetic association independent of EA (δ_j). **c.** Miami plots for GWAS of EA and income separately presenting *P* values of the concordant and discordant SNPs plotted on -log_{10} scale. The concordant and discordant SNPs were classified based on the sign concordance of $\hat{\beta}_j^{EA}$ and $\hat{\delta}_j$ estimates.

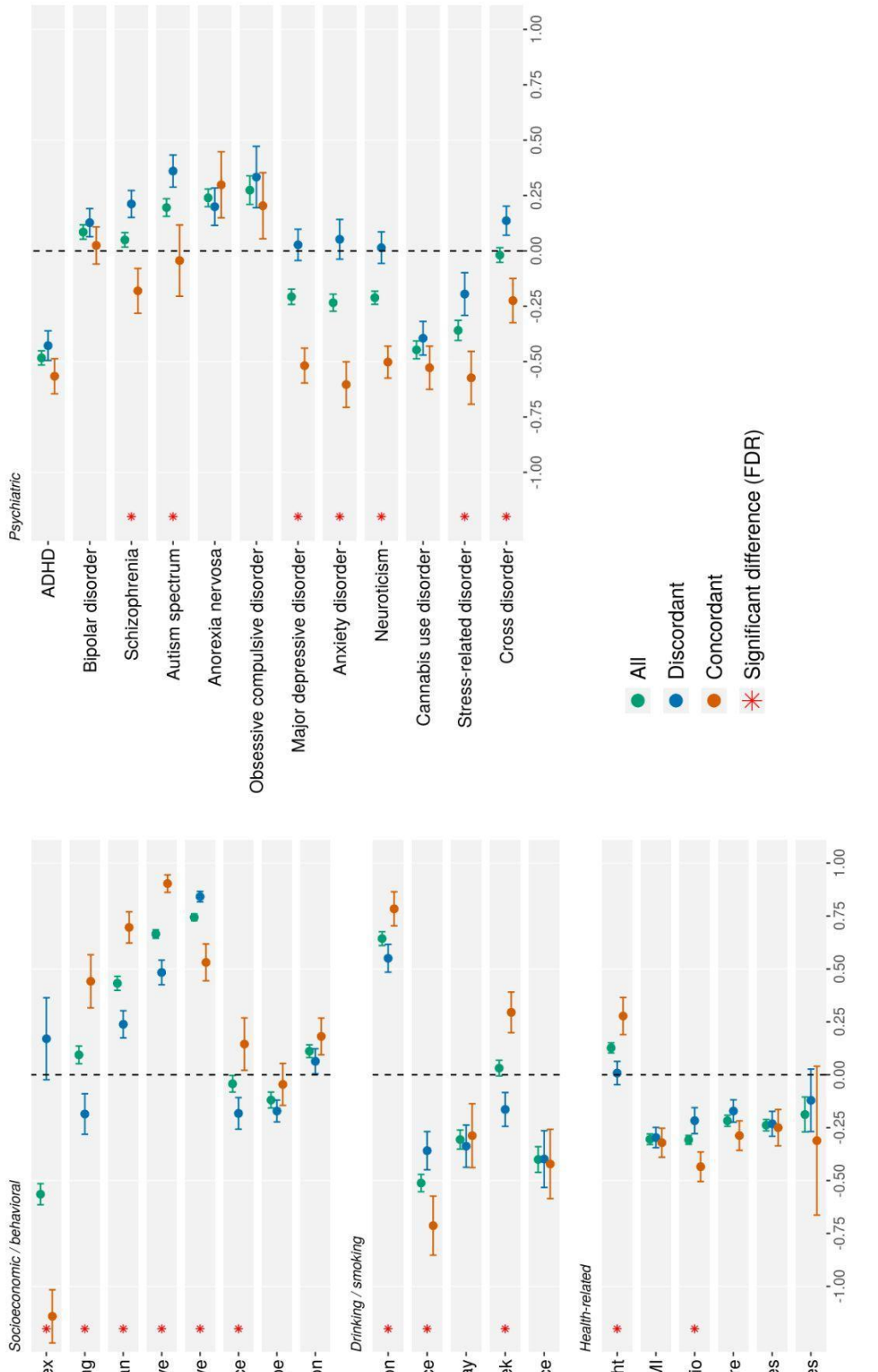

Fig. 3. Stratified genetic correlations of educational attainment (EA)

The figure reports estimated genetic correlations of EA stratified for concordant and discordant SNPs as well as global estimates based on all the SNPs. The results were estimated by GNOVA. The asterisks indicate the significant difference between the concordant and discordant estimates at the false discovery rate of 5%. The *P* value for the difference was computed with the covariance matrix obtained from block-wise jackknife.

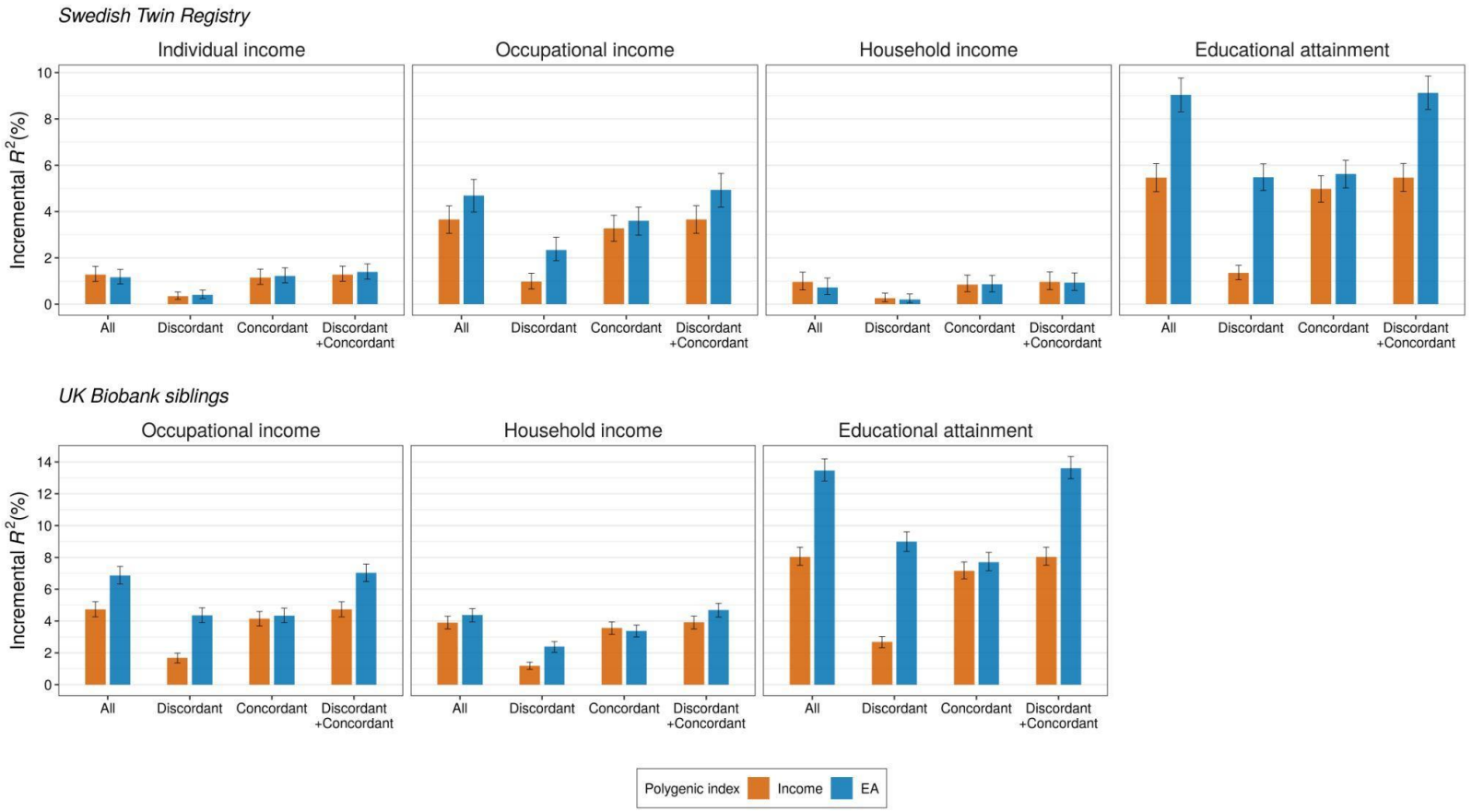

Fig. 4. Stratified polygenic prediction in Swedish Twin Registry (STR) and the UK Biobank (UKB) siblings

The figure reports polygenic prediction results in the STR and the UKB siblings with polygenic indexes (PGI) for income and EA splitted into concordant and discordant parts. "All" refers to the results based on the original PGI and "Discordant + Concordant" refers to the results where the discordant and concordant PGIs were included in the model together. The PGIs were constructed from either income or EA GWAS results. Prior to fitting the regressions, each phenotype was resualized of demographic covariates (see Supplementary Note section 5) within each wave and the mean of the residuals was obtained across the waves for each individual (only a single wave for the UKB siblings). Incremental R^2 is the difference between the R^2 from regressing the residualized outcome on the PGI and the controls (20 genetic PCs and genotyping batch indicators) and the R^2 from a regression only on the controls. Only individuals of European ancestry were included and one sibling from each family was randomly chosen: N = 24,946 (individual), 19,245 (occupational), 15,655 (household), 33,743 (EA) for the STR and 15,556 (occupational), 18,303 (household), and 18,797 (EA) for the UKB siblings. The error bars indicate 95% confidence intervals obtained by bootstrapping the sample 1,000 times.

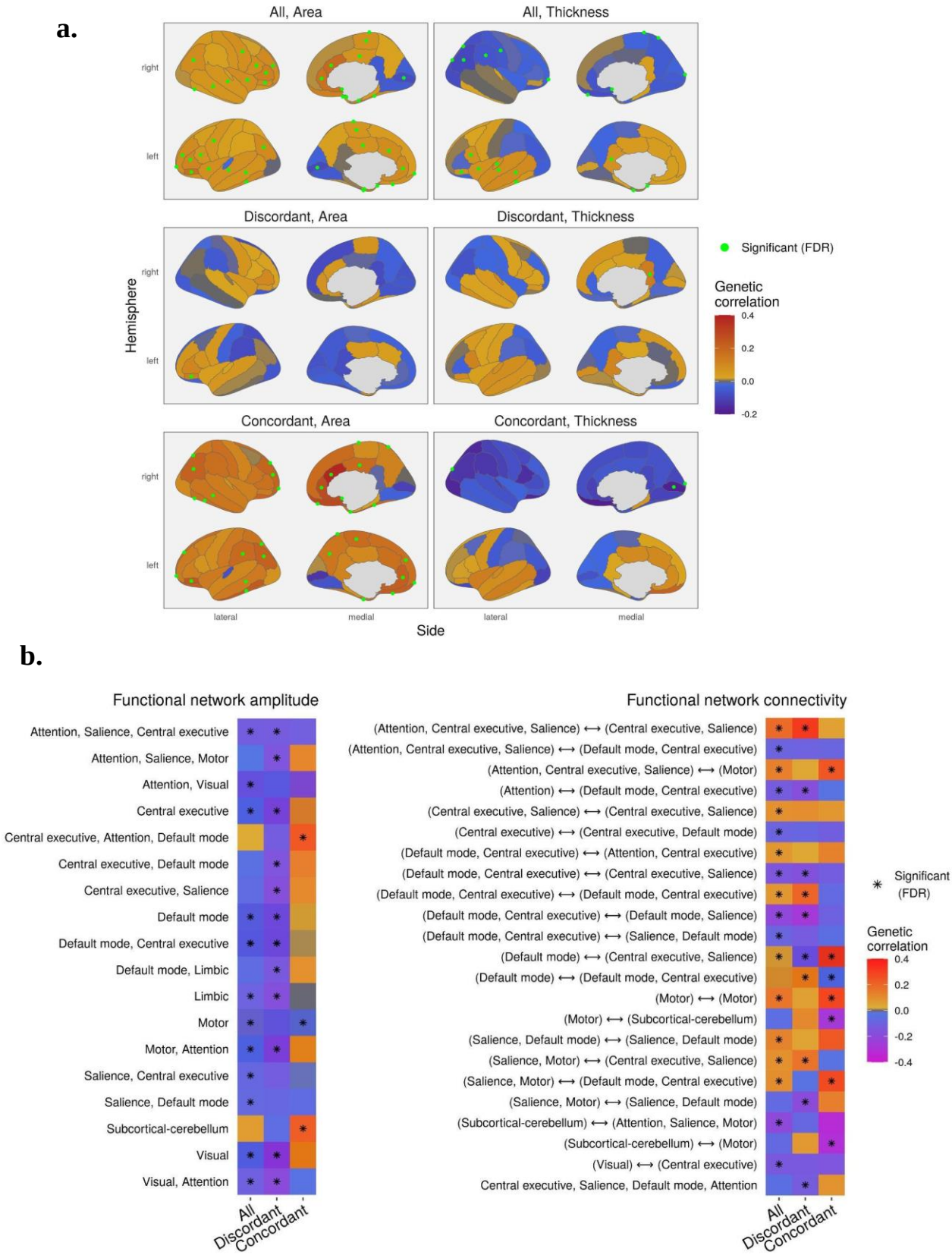

Fig. 5. Stratified neurobiological annotation of EA GWAS

a. surface area and cortical thickness (62 regions from Desikan-Killiany-Tourville atlas) and **b.** functional network traits from resting-state functional imaging (75 node amplitudes and 116 connectivities). The results were estimated by GNOVA. The statistical significance of genetic correlation at the FDR of 5% are indicated by the green dots (a.) and the asterisks (b.). For functional network traits (b.), only the results with at least one significant result were presented.

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Chapter 4

Genetic data in the German Socio-Economic Panel innovation sample

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1. Introduction

Almost all human traits are partly heritable, including health outcomes, personality, and behavioral tendencies (Goldberger, 1979; Ssgac, 2018). All properties that make us unique as individuals are to some degree affected by random genetic variation within and between families. Moreover, genetic and environmental causes of individual differences are interrelated. For example, environmental conditions can affect how genetic differences between individuals translate into differences in socio-economic and health outcomes (Barcellos et al., 2018; Kong et al., 2018; Young et al., 2019). Also, genetic differences among people manifest in trait differences partly via environmental channels, for example via genetically influenced personal interests that lead to a self-selection into specific environments and reinforcement mechanisms consisting, for instance, of behaviors of parents, teachers, peers, or colleagues.(Jencks, 1980; Kweon et al., 2020) Importantly, the fact that genetic differences are linked to differences in behavior and health does not imply simplistic biological determinism and puts no upper bound on the relevance of the environment or the possibilities for intervention (Goldberger, 1979; Ssgac, 2018).

The heritabilities of behavioral, psychological, and economic phenotypes (e.g. educational attainment, personality, risk attitudes) and health outcomes (e.g. cardiovascular disease, dementia) are typically between 30% and 70%, with an average heritability of 49% across all traits (Polderman et al., 2015)/ Thus, a substantial amount of variation in outcomes that epidemiologists and behavioral scientists study can be statistically linked to genetic differences among people. Ignoring genetics would imply that a substantial source of individual differences would remain unobserved, potentially leading to biased estimations that could prompt wrong and possibly counterproductive conclusions (Diprete et al., 2018).
Twin studies also suggest that environmental factors are important not only for social scientific outcomes, but also for a broad variety of diseases (Polderman et al., 2015). Thus, detailed information about living conditions, attitudes, and behavior could inform health-related research questions. However, most medical research datasets only contain basic information about these factors, limiting possibilities to fully understand their importance for health outcomes (Brulle and Pellow, 2006).

While genetically informed study designs are already common in medical research and have yielded numerous important insights into disease mechanisms (Davey Smith and Hemani, 2014; Visscher et al., 2017), the use of genetic data in the social sciences is still relatively rare (Harden and Koellinger, 2020). Nevertheless, integrating genetic data into social-scientific research (*e.g.*, economics, psychology, sociology, political science) opens up new possibilities to (i) control for genetic

confounders that are otherwise unobservable and that may lead to biased empirical results, (ii) increase the statistical power of empirical analyses by absorbing residual variance in multiple regression analyses, yielding smaller standard errors of the estimated parameters, (iii) study the interactions of genetic factors and environmental exposures, (iv) use random genetic differences among individuals to identify causal pathways, and (v) better understand how social (dis)advantages are transmitted across generations and how parents, peers, teachers, and policy makers can potentially alleviate or amplify such (dis)advantages (Benjamin et al., 2012; Harden and Koellinger, 2020). Thus, integrating genetic data into the social sciences offers researchers new tools to study questions they are interested in and to reach more robust inference on the basis of their empirical analyses.

The genetic underpinnings of behavior, socio-economic outcomes, and health are often overlapping. For example, educational attainment has substantial genetic correlations with smoking (-0.3), lung cancer (-0.4), obesity (-0.2), Alzheimer's disease (-0.3), and longevity (+0.6) (Harden and Koellinger, 2020; Lee et al., 2018), illustrating the complex relationships between components of genetic variation, human behavior, environmental conditions, and health outcomes.

These considerations motivated us to collect genetic data in the Innovation Sample of the German Socio-Economic Panel Study (SOEP-IS), with the goal of contributing additional value to an already existing and widely known interdisciplinary and longitudinal data set that is accessible and frequently used by the global scientific community.(Richter and Schupp, 2015) The addition of genetic data to this sample opens up many new research opportunities for both the medical and the social-science research community.

SOEP-IS was started in 2011 as an addition to the SOEP-Core sample, which provides representative annual data of private households in Germany since 1984 (Goebel et al., 2019). Similar to the SOEP-Core sample, SOEP-IS is a valuable data resource for researchers who want to explore long-time societal changes; relationships between early life events and later life outcomes; interdependencies between the individual and the family or household; mechanisms of intergenerational mobility and transmission; accumulation processes of resources; short- and long-term effects of institutional change and policy reforms; and migration dynamics (Goebel et al., 2019). Besides containing a set of basic questions that are identical to the SOEP-Core, the SOEP-IS longitudinal panel survey incorporates innovative content that is purely user-designed, including measurements that go beyond the scope of standardized questionnaire formats.

As a household study, the SOEP-IS typically contains data about all household members, including a large number of mother-father-child trios, parent-

offspring duos, childhood development, parenting practices, and family dynamics. Furthermore, due to the sampling method and longitudinal nature of the data, the available phenotypes in the SOEP-IS span all stages of life -- from the (pre-)natal stage, early childhood, adolescence, adulthood, all the way to retirement and the end of life (see **Figure 1**). We refer to the genotyped part of the SOEP-IS as the Gene-SOEP sample.

Already existing genotyped cohorts in Germany (e.g. BASE-II (Bertram et al., 2014), DHS (Pfaffenrath et al., 2009), HNRS (Mahabadi et al., 2011), KORA (Wichmann et al., 2005), SHIP (Völzke et al., 2011)) focus on specific health outcomes or are limited in scope to specific regions or age groups. Thus, as of now, Gene-SOEP is the only genotyped sample that is representative of the entire German population and that contains family data as well as a rich array of longitudinal information about health, personality, family dynamics, living conditions, attitudes, and socio-economic behaviors and outcomes. This makes the sample particularly valuable to study long-term developments and the intergenerational transmission of inequalities in health and well-being. Furthermore, the sample is ideally suited to study the impact of environmental conditions that are unique to Germany, such as specific public policies and changes therein or the potential consequences of German reunification. **Figure 2** shows the geographic distribution of genotyped households in the Gene-SOEP sample, illustrating the sample's coverage of all German states and metropolitan areas (e.g. Berlin, Hamburg, Munich, Ruhrgebiet).

To enable the collection of genetic data in the SOEP-IS, we established a research consortium of scientists from Germany (Max-Planck Institute for Human Development, German Institute of Economic Research), the Netherlands (Vrije Universiteit Amsterdam), Switzerland (University of Zurich, University of Basel), and the USA (University of Texas at Austin, Columbia University). The consortium was spearheaded by Philipp Koellinger (Vrije Universiteit Amsterdam) and Ralph Hertwig (Max-Planck Institute for Human Development). Koellinger's team in Amsterdam developed and guided the data collection procedures, processed the collected genetic data, and generated polygenic indices for public use.

2. Who is in the cohort?

The sampling and interviewing methods, as well as baseline characteristics of the sample, were previously described in detail (Goebel et al., 2019; Richter and Schupp, 2015). In short, SOEP-IS is based on a random sample of German households. Annual computer-assisted personal interviews are conducted face-to-face and information is collected on the household- and individual-levels (e.g. individual

and household incomes). The central survey instruments are a household questionnaire. It is being answered by the household head. In addition, there is an individual questionnaire that each household member age 17 and older is supposed to answer. The surveyed information usually covers the current situation (e.g., family composition or satisfaction with life), but in some contexts it includes the past (e.g., job changes and employment biographies) and the future (e.g., expected life satisfaction in 5 years, and chance of re-employment).

The main caretaker (usually the mother) is asked about their children who are younger than 17 years. If members of an originally sampled household leave the household, (e.g. because of a divorce or children forming their own household), both the original as well as the split household are interviewed. The comprehensive tracing rules, which cover all individuals who (even temporarily) lived in SOEP households, represents a comparative advantage of SOEP compared to other household panel surveys. They allow users to track various forms of household dynamics and their implications at the household and individual level. To maintain a reasonable sample size and to address panel attrition, refreshment samples of the residential population of Germany were integrated in 2012, 2013, 2014, and 2016.

The precondition for participation in the Gene-SOEP - as part of SOEP-IS 2019 - was that the person or child lives in a participating household. 6,576 people were originally invited to participate in SOEP-IS 2019, 1,074 of whom were children. Not everyone takes part every year and there are always people who move away, die, or do not want to take part in the survey anymore. Therefore, of the original sample, 4,283 persons who were at least 17 years old (i.e., persons of survey age) as well as 875 children and youths (<17 years of age) lived in a participating household in 2019. 2,598 individuals provided a valid genetic sample, including 215 children and teenagers. A requirement for an offspring of at most 17 years of age to participate in the collection of genetic data was that both guardians agreed. The valid genetic samples were sent from the survey company Kantar Public to the Human Genomics Facility (HuGe-F) at the Erasmus Medical Center in Rotterdam for analysis.

Compared with census data (www.destatis.de), the Gene-SOEP sample is very similar to the German population in terms of age ($Mean_{census}$ = 52 years vs. $Mean_{Gene\text{-}SOEP}$ = 55 years), sex (51% $Female_{census}$ vs. 54% $Female_{Gene\text{-}SOEP}$), and living region (20% East $Germany_{census}$ vs. 19% East $Germany_{Gene\text{-}SOEP}$). However, residents without German citizenship are under-represented in the Gene-SOEP sample (12% census vs. 4% Gene-SOEP).

Participants who agreed to donate DNA are very similar to the overall SOEP-IS sample in terms of socio-demographics, subjective health ratings, and life satisfaction (see **Table 1**).

Table 1 - Descriptive statistics of the Gene-SOEP adult sample (≥ 17 years old)

	Total		Interview		Consent		Genotyped		Polygenic Indices Created	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age	54	19	55	18	55	19	55	19	55	19
Sex (% female)	53	50	53	50	54	50	54	50	54	50
East Germany (% yes)	20	40	20	40	19	40	19	40	20	40
German (% yes)	95	22	96	20	96	19	96	19	98	16
Partnered (% yes)			41	49	40	49	40	49	41	49
School degree: low (% yes)			38	49	40	49	40	49	38	48
School degree: high (% yes)			31	46	29	45	29	45	30	46
Employment (% yes)			53	50	51	50	51	50	51	50
Mean Net Income (EUR)			1,959	1,304	1,922	1,300	1,915	1,258	1,924	1,263
Subjective Health (1-5)			3.33	0.97	3.34	0.96	3.34	0.96	3.33	0.96
Life Satisfaction (0-10)			7.54	1.69	7.57	1.68	7.59	1.66	7.58	1.66
Observations	5,502		4,283		2,496		2,372		2,063	

Parents were somewhat hesitant to enroll their offspring (<17 years of age) for the collection of genetic data. Compared to an overall consent rate of 58% (2,496 out of 4,282 valid interviews), only 26% of the eligible offspring participated in the collection of genetic data (228 out of 875). However, offspring for whom genetic data was collected closely resemble the overall sample of offspring in the sample in terms of age, sex, geographic location, and citizenship (see **Table 2**).

Table 2 - Descriptive statistics of children and adolescents (<17 years old) in the Gene-SOEP sample

	Total		Consent		Genotyped Sample		Polygenic Indices Created	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age	8	5	9	5	9	5	9	5
Sex (% female)	49	50	50	50	50	50	50	50
East Germany (% yes)	18	39	19	40	18	39	20	40
German (% yes)	96	20	96	18	96	19	99	8
Observations	1,074		228		215		173	

3. What has been measured?

Phenotypes

The SOEP-IS (Goebel et al., 2021a; Richter and Schupp, 2015) contains a set of core questions that are identical to about 44% of the questions asked in the SOEP-Core survey (Goebel et al., 2019), including variables such as age, gender, height, weight, education, employment status, income, life satisfaction, personality, living conditions, attitudes, preferences, and occupational classifications following the International Standard Classification of Occupations (ISCO). In addition, the SOEP-IS contains a broad range of short-term experiments and longer-term surveys that were not deemed to be suitable to the SOEP-Core survey (yet) because they pose a higher risk of refusal and panel attrition or because they deal with very specific research issues. Every year, researchers can propose new survey modules or experiments for inclusion in the SOEP-IS. The SOEP management team and the SOEP survey committee then select which modules will be included in the next survey wave (Richter and Schupp, 2015). The SOEP-IS innovation modules also act as a test bed for how respondents react and some particularly important and successful modules (e.g. risk attitudes) can later be integrated into the much larger SOEP-Core survey, which collects data from ~15,000 households comprising ~26,000 individuals per year, including ~3,000 children and youths.

Health outcomes in the SOEP-IS are primarily measured based on self-reports of doctor diagnoses for a range of diseases, subjective evaluations of health and well-being, doctor visits, and the need for care. Furthermore, dried blood samples were tested for SARS-CoV-2 antibodies and oral-nasal swabs for viral RNA in a part of the SOEP-IS sample between Oct 2020 and Feb 2021, providing

opportunities to study factors influencing infections with SARS-CoV-2 and long-term consequences (Hoebel et al., 2021).

Furthermore, the SOEP-IS allows users to add anonymized spatial information (e.g. federal states, spatial planning regions, counties, municipalities, and postal codes as well as GPS coordinates) and can be linked to administrative records from the German Pension Insurance and the Employer-Employee Study (Goebel et al., 2019; Weinhardt et al., 2017).

An overview of the SOEP-IS survey content and examples of modules is provided in **Box 1**. The complete questionnaire of the 2019 survey wave, the 2019 SOEP annual report, and a description of all SOEP-IS modules from 2011-2018 are available online (Goebel et al., 2021b, 2020; Kara et al., 2021). An online companion for the entire data collection is available (http://companion-is.soep.de/).

Box 1. Summary of SOEP-IS survey content by topics and examples of modules

1. *Demography and Population*
   Country of origin, birth history

2. *Work and Employment*
   Change of job, contractual working hours, employment status, evening and weekend work, financial compensation for overtime, industry sector and occupational classification, job search, leaving a job, maternity / parental leave, registered unemployed, self-employment reasons, side jobs, supervisory position, use of professional skills, vacation entitlement, work from home, work time regulations, workload

3. *Income, Taxes, and Social Security*
   Asset balance, benefits and bonuses from employer, financial support received, individual gross / net income, inheritances, pension plans, social security, wage tax classification, alimony, household income and expenses, investments, repayments of loans

4. *Family and Social Networks*
   Circle of friends, family changes, family network, marital / partnership status, attitude toward parental role, breastfeeding, childcare, language use, leisure and activities, parenting goals, parenting style, pregnancy, relationship to other parent or child

5. *Health and Care*
   Alcohol consumption, health insurance, illness (self-reports of doctor diagnoses for sleep disorder, thyroid disorder, diabetes, asthma, cardiac disease, cancer, apoplectic stroke, migraine, high blood pressure, depression, dementia, joint disorder, chronic back problems, burnout, hypercholesterolemia, or other illness), reduced ability to work, sickness notifications to employer, smoking, state of health, stress and exhaustion, visits to the doctor, satisfaction with availability of care, health of child, physical and mental health of mother, nutrition, physical activity

6. *Home, Amenities, and Contributions of Private Households*
   Childcare hours, leisure activities and costs, school attendance by child, change in residential situation, consumption, costs of housing, home ownership / rental, loans and mortgages, birth of children, number of books in the household, persons in household in need of care, pets, residential

area, size and condition of home

7. *Education and Qualification*
   Completed education and training, vocational training, educational aspirations for children, school enrollment of children

8. *Attitudes, Values, and Personality*
   Affective well-being, Big Five personality traits, depressive traits, goals in life, impulsivity and patience, income justice, life satisfaction, lottery question, optimism/pessimism, political tendency and orientation, reciprocity, religious affiliation, risk aversion in different domains, satisfaction with various aspects, social responsibility, trust and fairness, wage justice, well-being aspects, worries, temperament of child

9. *Time Use and Environmental Behavior*
   Time use for different activities, trip to work, use of transportation for different purposes

10. *Integration, Migration, Transnationalization*
    Applying for German citizenship, disadvantage / discrimination based on ethnic origins, integration indicators, language skills, native language, regional attachment, sense of home

11. *Innovative Modules*
    Anxiety and depression, assessment of contextualized emotions, risk attitudes, confusion, control strivings, dementia worry, determinants of ambiguity aversion, emotion regulation, expected financial market earnings, future life events, grit and entrepreneurship, happiness analyzer, impostor phenomenon, inattentional blindness, inequality attitudes, job preferences, job tasks, justice sensitivity, lottery play, multilingualism, narcissistic admiration and rivalry, ostracism, pension claims, perceived discrimination, physical attractivenes, self-control, self-evaluation and overconfidence in different life domains, sleep characteristics, smartphone usage, socio-economic effects of physical activity, status confidence and anxiety, subjective social status, work time preferences

Genetics

DNA was extracted from saliva samples that were collected using Isohelix IS SK-1S buccal swabs with Dri-Capsules. Genotyping was carried out using Illumina Infinium Global Screening Array-24 v3.0 BeadChips, yielding raw data for 2,598 individuals and 725,831 variants, of which 688,618 were autosomal.

Call rates were smaller than 95% in 484 genotyped individuals. Further analyses revealed that the low call rates for these individuals were largely driven by interviewer effects, possibly due to not following the sample collection protocol accurately, including an incorrect use of (or entirely missing) DriCapsules that slow down the decay of DNA, low saliva and DNA yield, or polluted samples (see SI sections 2 and 3).

Since we expect that the vast majority of analyses in the genotyped SOEP-IS data will rely on polygenic indices (PGIs) (Becker et al., 2021) rather than single genetic variant analyses, we implemented two different quality control (QC) pipelines, mild-QC and strict-QC, that are described in detail in the Supplementary

Information. The mild-QC pipeline yields a higher sample size and both QC protocols yield approximately equally predictive PGIs (see below and Supplementary Information section 7). Depending on the research question investigators will want to address, either the mild-QC or the strict-QC data can be used to maximize the statistical power of the analyses.

In short, both pipelines filtered out 14 individuals with sex mismatch. The strict-QC pipeline excluded 260 individuals whose genotype missingness rate was more than 20% within any chromosome and 59 individuals with excess heterozygosity/homozygosity. The mild-QC pipeline excluded only 36 individuals based on a per-chromosome missingness of more than 50% and 22 heterozygosity/homozygosity outliers. Using the mild-QC data, we identified 44 individuals of non-European ancestries, 25 of whom were available in the strict-QC sample. These individuals were also excluded from the mild- and strict-QC samples prior to imputation.

We used the Haplotype Reference Consortium reference panel (r1.1) for imputation (McCarthy et al., 2016). Imputation was completed for 2,497 individuals and 23,185,386 SNPs with imputation accuracy (R^2) greater than 0.1 in the mild-QC data, and 2,299 individuals and 22,201,548 SNPs with R^2>0.1 in the strict-QC data. Approximately 66% of the imputed SNPs are rare with minor allele frequencies (MAF) smaller than 0.01 and ~24% SNPs are common (MAF≥0.05; 5,463,110 in mild-QC, 5,463,110 in strict-QC). The average imputation accuracy in the mild-QC data is 0.664 and 0.695 in the strict-QC data. However, common SNPs (MAF≥0.05) are much more reliably imputed than rare SNPs, with an average imputation accuracy of 0.92 and 0.93 in the mild- and strict-QC data, respectively.

Using the imputed SNPs, we identified an additional 37 (2) individuals of non-European ancestries in the strict (mild) QC data on top of the 44 (25) individuals of non-European ancestries excluded prior to imputation, respectively. Thus, ~98% of the genotyped SOEP-IS sample is of European ancestries (see Supplementary Information section 4).

We constructed the first 20 principal components (PCs) of the genetic data for individuals with European ancestries based on ~160,000 approximately independent SNPs with imputation accuracy ≥70% and MAF≥0.01. We recommend using these genetic PCs in analyses as control variables for population stratification (Price et al., 2006).

Family relationship among genotyped participants

With the exemption of parent-offspring pairs, family relationships among the participants are only surveyed via their relationship to the household head. For the genotyped participants in the SOEP-IS across the available waves from 1998 to 2019, there are 877 reported relationships for the 602 household heads. The majority (515) of these relationships are with their spouse or partner, while 346 relationships are with their child (324 biological, 11 adopted or biological, and 11 stepchild). The remaining relationships of household heads are with grandchildren (5), parents (4), a parent-in-law (1), a niece/nephew (3), a son/daughter-in-law (1), and a half sibling (1).

By using the reported relationships to the household head as well as directly reported parent-child relationships, we inferred or found 609 parent-offspring, 142 full-sibling, and 17 second-degree relative pairs in the Gene-SOEP sample. In Table S1, we compared these reported relationships to genetically inferred relationships obtained from KING (Manichaikul et al., 2010). We found that 19% of the pairs have inconsistencies between the reported and genetically inferred relationships. The deviations were mainly due to low genotyping quality of some individuals. When considering only the individuals whose genotyping call rate was greater than 90% using directly genotyped SNPs, 92% of the pairs in the Gene-SOEP have consistent self-reported and genetic family relationships (see section 3 and 6 of the Supplementary Information for details). We found that most of the remaining inconsistencies are due to self-reported full-siblings who are likely to be only half siblings (13 out of 97 pairs). We also found 28 self-reported parent-child pairs that appear to be non-biological from 437 pairs in total.

Furthermore, restricting to the individuals with the genotype call rate greater than 90%, we identified 88 pairs whose family relationship information was not available in the survey data. These pairs consist of 7 parent-offspring, 19 full-siblings, 33 second-degree relatives, and 29 third or fourth degree relative pairs.

Overall, out of 2,497 individuals, we genetically identified 703 individuals with at least one first-degree relatives (parent-child or full sibling) and 728 individuals that have at least one relative with at least third-degree of relatedness (first cousins or great grandparent-child). 1,769 individuals do not have close relatives on the basis of the genetic data. Note that the related pairs reported here are not mutually exclusive and some individuals can be related to multiple people.

Polygenic indices

The effect sizes of individual single nucleotide polymorphisms (SNPs) on behavioral traits and complex diseases are usually tiny (R^2 < 0.05%). Polygenic indices (PGI) aggregate the effects of observed SNPs, weighting them by their estimated effect sizes from an independent genome-wide association study (GWAS) sample (Becker et al., 2021). The predictive accuracy of a PGI depends on the GWAS sample size (+), the heritability of the trait (+), the number of causal genetic variants that influence the trait (-), and the extent to which the genetic architecture of the trait is similar across various environments and datasets (+) (Daetwyler et al., 2008; de Vlaming et al., 2017). Thanks to rapidly growing GWAS sample sizes in the past few years, the accuracy of PGIs has increased greatly, especially for individuals of European ancestries (Harden and Koellinger, 2020; Mills and Rahal, 2019). PGIs are now beginning to capture a substantial part of the heritability of many traits, making them valuable for research in many scientific disciplines. For example, PGIs from the latest generation of GWAS analyses capture ~12% of the variation in years of schooling (Lee et al., 2018), ~10% of general cognitive ability (Lee et al., 2018), and up to 2% of various personality characteristics such as risk tolerance (Karlsson Linnér et al., 2019).

This makes these PGIs useful for follow-up analyses in samples that are much smaller than the original GWAS (Harden and Koellinger, 2020). For example, a sample of N = 1,000 yields >90% statistical power to detect an association between a PGI and an outcome of interest if the PGI captures at least 1% of the phenotypic variation (two-sided t-test with α=0.05). An association between an outcome and a PGI with R^2 = 10% can even be detected in a sample of only N = 110 individuals with 90% power.

We followed the methods used by Becker et al. (2021) to create a repository of single- and multi-trait polygenic indices for 66 social-scientific and health traits for individuals of European ancestries in the Gene-SOEP sample. We used the largest currently available GWAS samples to create these PGIs, including publicly available GWAS summary statistics as well as non-publicly available GWAS results from 23andMe. We extended the list of 36 single-trait and 35 multi-trait PGIs in Becker at al. 2021 by including single-trait PGIs for 19 medical outcomes with well-powered GWAS summary statistics. The single-trait PGIs were based on univariate GWAS summary statistics (**Table 3**), whereas the multi-trait PGI were based on multivariate MTAG analyses that exploit genetic correlations between several traits to improve predictive accuracy (SI Table 3) (Turley et al., 2018).

Some of the PGIs that we created have corresponding phenotypes in the Gene-SOEP sample (e.g. educational attainment, height, BMI, risk tolerance), while others capture genetic predispositions for phenotypes that are not observable or

incompletely measured (e.g. longevity, HDL cholesterol, blood pressure, and a variety of diseases including Alzheimer's, schizophrenia, stroke, atrial fibrillation and breast cancer). These PGIs are useful proxies for unobserved traits and outcomes. For example, they can be used as control variables in studies that focus on environmental processes such as socio-economic factors that influence health(Benjamin et al., 2012), to detect gene-environment interactions (e.g. heterogeneous responses to policy interventions) (Barcellos et al., 2018; Harden and Koellinger, 2020), or as exogenously given proxies that do not change over the lifecourse (e.g. to study genetic predisposition for health on labor market outcomes). Finally, the availability of genetic data and PGIs from parents and their children offers exciting, new ways to disentangle genetic and environmental channels of intergenerational transmission of health, behavior, and socio-economic outcomes (Koellinger and Harden, 2018; Kong et al., 2018).

Table 3 - Polygenic indices in the Gene-SOEP sample from single trait GWAS results

Phenotype	**# SNPs**	**GWAS *N***
Adventurousness(Becker et al., 2021; Karlsson Linnér et al., 2019)	1,147,160	557,923
Age First Birth(Barban et al., 2016; Becker et al., 2021)	996,620	169,901
Age First Menses (Women)(Becker et al., 2021; Day et al., 2015)	1,142,133	309,043
Alcohol Misuse(Becker et al., 2021; Sanchez-Roige et al., 2019)	1,145,324	120,684
Alzheimer's*(Linner and Koellinger, 2020)	1,115,709	455,258
Any Ischemic Stroke*(Linner and Koellinger, 2020)	850,822	446,696
Any Stroke*(Linner and Koellinger, 2020)	844,962	446,696
Atrial Fibrillation*(Linner and Koellinger, 2020)	850,822	1,030,836
Asthma(Becker et al., 2021)	1,159,334	418,164
Asthma/Eczema/Rhinitis(Becker et al., 2021; Ferreira et al., 2017)	1,137,288	513,889
Attention Deficit Hyperactivity Disorder (ADHD)(Becker et al., 2021; Demontis et al., 2019)	1,083,048	57,386
Body Mass Index (BMI)(Becker et al., 2021; Locke et al., 2015)	1,023,282	582,457
Breast Cancer*(Linner and Koellinger, 2020)	809,475	228,951
Cannabis Use(Becker et al., 2021; Pasman et al., 2018; Stringer et al., 2016)	1,087,000	156,756
Cardioembolic Stroke*(Linner and Koellinger, 2020)	844,996	446,696
Childhood Reading(Becker et al., 2021)	1,147,169	172,502
Chronic Kidney Disease*(Linner and Koellinger, 2020)	845,145	444,971
Cigarettes per Day(Becker et al., 2021; Liu et al., 2019)	1,150,910	250,057

Cognitive Performance(Becker et al., 2021; Trampush et al., 2017)	1,148,362	222,914
Depression*(Linner and Koellinger, 2020)	835,515	500,199
Depressive Symptoms(Becker et al., 2021; Wray et al., 2018)	1,138,362	619,272
Diastolic Blood Pressure* (Linner and Koellinger, 2020)	843,500	757,601
Drinks per Week(Becker et al., 2021; Liu et al., 2019)	1,150,775	723,487
Educational Attainment(Becker et al., 2021; Lee et al., 2018)	1,147,926	1,047,538
Ever Smoker(Becker et al., 2021; Liu et al., 2019)	1,143,561	1,129,163
Externalizing*(Linner and Koellinger, 2020)	1,020,283	1,492,085
Extraversion(Becker et al., 2021; Lo et al., 2017; van den Berg et al., 2016)	1,113,746	73,906
Hay Fever(Becker et al., 2021)	1,159,334	403,179
HDL Cholesterol*(Linner and Koellinger, 2020)	847,159	187,167
Height(Becker et al., 2021; Wood et al., 2014)	1,022,784	448,198
Highest Math(Becker et al., 2021; Lee et al., 2018)	1,147,159	430,439
Insomnia* (Linner and Koellinger, 2020)	824,863	386,533
Large Artery Stroke*(Linner and Koellinger, 2020)	1,159,551	446,696
Left Out of Social Activity(Becker et al., 2021)	1,147,159	507,803
Life Satisfaction: Family(Becker et al., 2021)	1,159,202	141,864
Life Satisfaction: Friends(Becker et al., 2021)	1,159,184	138,807
Longevity*(Linner and Koellinger, 2020)	832,850	640,189
Migraine(Becker et al., 2021; Pickrell et al., 2016)	1,146,834	421,013
Morning Person(Becker et al., 2021; Hu et al., 2016)	1,123,260	362,840
Narcissism(Becker et al., 2021)	1,147,153	452,535
Nearsightedness(Becker et al., 2021; Pickrell et al., 2016)	1,146,729	301,938
Neuroticism(Becker et al., 2021; Genetics of Personality Consortium et al., 2015; Lo et al., 2017)	1,029,577	389,237
Number Ever Born (Women)(Barban et al., 2016; Becker et al., 2021)	1,034,474	207,393
Openness(Becker et al., 2021; De Moor et al., 2012; Lo et al., 2017)	987,746	72,308
Physical Activity(Becker et al., 2021; Doherty et al., 2018)	1,108,549	140,190
Religious Attendance(Becker et al., 2021)	1,159,336	383,466
Risk Tolerance(Becker et al., 2021; Karlsson Linnér et al., 2019)	1,076,002	1,070,480
Schizophrenia*(Linner and Koellinger, 2020)	829,801	105,318
Self-Rated Health(Becker et al., 2021)	1,144,515	911,102

Self-Rated Math Ability(Becker et al., 2021; Lee et al., 2018)	1,147,159	564,692
Small Vessel Stroke*(Linner and Koellinger, 2020)	1,159,163	446,696
Subjective Well-Being(Becker et al., 2021; Okbay et al., 2016a)	906,574	502,976
Systolic Blood Pressure*(Linner and Koellinger, 2020)	842,552	745,820
Triglycerides*(Linner and Koellinger, 2020)	847,159	177,861
Type 2 Diabetes*(Linner and Koellinger, 2020)	851,227	231,426

Notes: "# SNPs" is the number of SNPs that were used to construct the PGI.
"*" indicates PGIs for medical outcomes that were not originally included in Becker et al. 2021.
All 55 PGIs are constructed only for individuals of European ancestry (N = 2,495).

4. Results - What has been found?

The SOEP sample is currently used by more than 9,000 registered users from 54 countries (Goebel et al., 2020). About 300-400 publications annually are based on SOEP data, including OECD reports on the international development of inequality. Roughly 25% of these publications are in journals listed in the (social) science citation index and more than 100 publications are based on SOEP-IS data. The SOEP is also an integral database for official government reports in Germany. Major research areas that include SOEP-based publications include life course development, inequality, mobility, psychological outcomes and attitudes, migration, transition to a unified Germany, and health. Thus, the SOEP data is widely used and provides an indispensable empirical foundation to describe longitudinal developments and relationships, and a better understanding of socioeconomic processes and behavior. It is a highly valuable resource to study relationships between behavior, socioeconomic status, and health (Goebel et al., 2019).

The genetic data that we collected in the SOEP-IS sample (Gene-SOEP) is a new addition to this valuable resource. We describe first findings using the genetic data below.

Predictive accuracy of polygenic indices for height, BMI, and educational attainment

Figure 3 shows the predictive accuracy of the PGIs for height and BMI in unrelated individuals from the Gene-SOEP sample, both for the mild and the strict version of the QC of the genetic data that we carried out. We measure the predictive accuracy of the PGIs as the difference in the explained variance (R^2) before and after adding the PGI to a baseline regression that controls for a second-degree polynomial in year of birth, sex and their interactions, genotype batch indicators, and the top 20 genetic PCs. Since height and BMI were surveyed multiple times across waves, we first

residualized height and BMI for age, age^2, sex and their interactions within each wave and took the mean for each individual; then, as covariates, we used only genotype batch indicators and the top 20 genetic PCs. We obtained 95% confidence intervals by bootstrapping the sample 2,000 times.

Using this approach, the PGIs explain 22~24% of the variance in height, 12~13% of the variance in BMI, and 9% of the variance in educational attainment. Furthermore, the predictive accuracy was very similar for different levels of QC, which implies that the low genotyping quality in a part of the sample does not substantially reduce the predictive accuracy of the PGIs. Thus, researchers may choose to use the mild-QC version of the data for analyses using PGIs to take advantage of its ~10% larger sample size and the corresponding gains in statistical power.

Genetic and environmental correlations with height and BMI

We demonstrate the advantages of combining a representative population sample with genetic data by analyzing birth year cohort trends in body height and BMI over time. Specifically, we split the Gene-SOEP sample into PGI values below and above the median for height and BMI and plotted the average residualized phenotypic values after adjusting for sex in both groups for adults >=20 years of age, binned into ten-year birth cohorts (Figures 4 and 5). Phenotypic values are residualized by regressing each observed phenotypic value on sex dummies using OLS. Each observation is assigned a residualized value which represents the remaining variation in the phenotype which cannot be predicted by sex. Residualized values are then averaged by individual across survey waves. The average residualized values for each bin are reported by the solid lines corresponding to the left axis.

In the non-residualized data, individuals with high PGI values for height are on average 5.2 cm taller than those with low PGI height values (95% CI: 3.4 - 7.1cm). Figure 4 shows that this difference in average height by genetic predisposition is robust across birth year cohorts, reflecting a stable influence of the height PGI. Interestingly, Figure 4 also demonstrates that younger birth cohorts are on average substantially taller than older birth cohorts. For example, individuals born in the 1923-1939 birth year cohort (~84 years old on average in the 2019 survey wave) are on average 6.6 cm shorter than those born in 1980-1999 birth year cohort (~31 years old on average in the 2019 survey wave). This gain in average height of younger birth cohorts cannot be explained by observed genetic changes in the population. As **Figure 4** shows through the dashed lines which correspond with the right *y*-axis, the average values of the (high and low) height PGI did not increase over time.

Instead, the younger birth cohorts exhibit a slightly smaller PGI value than the older birth cohorts, possibly due to sample selection and mortality effects among older participants (Domingue et al., 2017). In order to disentangle potential age effects from birth cohort effects, SI Table 5 presents estimates from height regressed on the standardized height PGI, birth cohort dummies, including five year age bin dummies. The results confirm a birth cohort effect on height that is separate from the genetic influences on height as well as aging effects. This implies that the substantial gains in average body height in the German population over time are partially due to improved environmental conditions, such as better nutrition and health care (Perkins et al., 2016; Silventoinen, 2003).

A similar analysis for BMI (**Figure 5**) shows that individuals with an above-median PGI have on average also higher BMI (1.6 points higher for the High-PGI group in the non-residualized results, 95% CI 1.04 - 2.17). Both the heritability and the predictive accuracy of the PGI are lower for BMI than for height (Becker et al., 2021; Polderman et al., 2015). Correspondingly, the average differences in BMI between the low and the high PGI group are not statistically significant for all birth year cohorts. Yet, similar to the analyses on height, we also observe birth cohort effects on BMI that cannot be explained by observed genetic variation in the BMI PGI. Individuals born in the youngest birth cohort (1980-1999, ~31 years old) have an average BMI that is 2.3 points lower than those in the oldest birth cohort (1923-1939, ~84 years old). The higher BMI in the older birth cohorts is not due to observed genetic changes in the population over time. In fact, the average PGI is slightly lower in the older birth cohorts than in the younger ones, again possibly due to sample selection and mortality effects among older participants (Domingue et al., 2017). SI Table 6 presents regression results from a robustness check that also included 5-year age bins as control variables, again confirming birth cohort effects that cannot be explained alone by aging or observed genetic variation. Thus, the higher BMI in the older birth-cohorts is likely to be caused by a combination of environmental effects such as differences in living conditions, socio-economic effects (Cardoso and Caninas, 2010), or nutrition (Meddens et al., 2020).

The broad set of PGIs we created are a valuable resource for research on inequalities in socio-economic and health outcomes. Previous research has demonstrated that the genetic architectures of socio-economic, behavioral and health outcomes are often substantially overlapping (Bulik-Sullivan et al., 2015; Harden and Koellinger, 2020; Okbay et al., 2016b). This implies that PGIs for socio-economic or behavioral traits can also be proxies for health outcomes.

This is demonstrated in **Figure 6**, which presents the effect size from regressions of self-rated health on 28 single-trait PGIs (out of 55 tested single-trait

PGIs overall) whose estimated standardized coefficients are greater than |±0.1| All regressions controlled for five year age bins, sex, and their interactions, and the first 20 genetic principal components. 18 PGIs are statistically distinguishable from zero after a Bonferonni correction for 55 tested hypotheses (marked with *).

We find positive associations between self-rated health and PGIs for self-rated health, age at first birth, educational attainment, subjective well-being, highest math class taken, religious attendance, longevity, cognitive performance, physical activity, self-rated math ability, and age at first menses. Furthermore, we find negative health correlations of the PGIs for externalizing, depression, ADHD, number of children ever born, insomnia, neuroticism, smoking, and being left out of social activities - all of which are PGIs for behavioral, social, or cognitive phenotypes. Moreover, the PGIs for BMI, high blood pressure, type 2 diabetes, large artery stroke, triglycerides and asthma all have the expected negative correlations with self-rated health.

5. Discussion - What are the main strengths and weaknesses?

Major strengths of the Gene-SOEP data include:

(i) the sample selection, which yields the only currently genotyped sample that is representative of the entire German population;
(ii) the longitudinal nature of the data with annual observations since 2011 (for a subset of individuals and phenotypes, annual observations even go back to 1998);
(iii) the rich questionnaire content, including self-reported health outcomes and detailed information on socio-economic status, living conditions, family dynamics, personality, preferences and attitudes is another major strength of the data;
(iv) the possibility to use detailed geo-coding, standardized occupation codes, and links to external databases such as the German Pension Insurance and the Employer-Employee Study;
(v) the broad set of state-of-the-art polygenic indices that we created, which lower the entry barriers for researchers to use genetically informed study designs;
(vi) the continuing annual collection of data that also allows researchers to integrate new survey modules, biomarkers, and experiments in the future by following the application procedures of the SOEP-IS management team (Richter and Schupp, 2015);
(vii) the household sampling procedure that collects data on all family members. The Gene-SOEP sample contains 501 parent-offspring pairs, 152 parent-offspring trios, 107 full-siblings, and 12 second degree relatives (including half-siblings) with matching self-reported and genetically-inferred relationships. This data structure

enables genetically informed studies on a wide range of research topics, including the intergenerational transmission of inequalities in health and well-being as well as studies that identify how environmental factors such as parenting style influence the developmental trajectory of children and youths;
(viii) the availability of epigenetic data, which will be added for a substantial part of the Gene-SOEP sample in the near future, further increasing research opportunities on the relationships between social environment and physical health;
(ix) the possibility to extend the collection of genetic data to all SOEP surveys, which would substantially increase the available sample size for genetically informed analyses.

Compared to other datasets that were included in the Polygenic Index (PGI) Repository of the SSGAC (Becker et al., 2021), the Gene-SOEP is the only German sample and it has the broadest coverage of social scientific outcomes, many of which have been repeatedly collected over time. Although the sample size of the Gene-SOEP is larger than several other studies included in the PGI Repository (e.g. Dunedin, E-Risk, Texas Twins), we still caution that researchers using the data should pay attention to statistical power in their analyses. In particular, the sample size may be too limited for analyses of single genetic variants or sub-parts of the sample (e.g. specific age groups or geographic areas). A further limitation is that a part of the sample (19%) did not pass the strict quality control thresholds of genetic data that are usually employed in genetic epidemiology (call rates > 95%). However, our mild-QC pipeline still enables the use of well-performing PGIs in 2,495 individuals (96% of the successfully genotyped sample).

Another possible limitation is that the currently available health outcomes are limited in detail and based on self-reports rather than detailed digital health records. Future expansions of the collected health data would further increase the utility of the SOEP samples for epidemiological research.

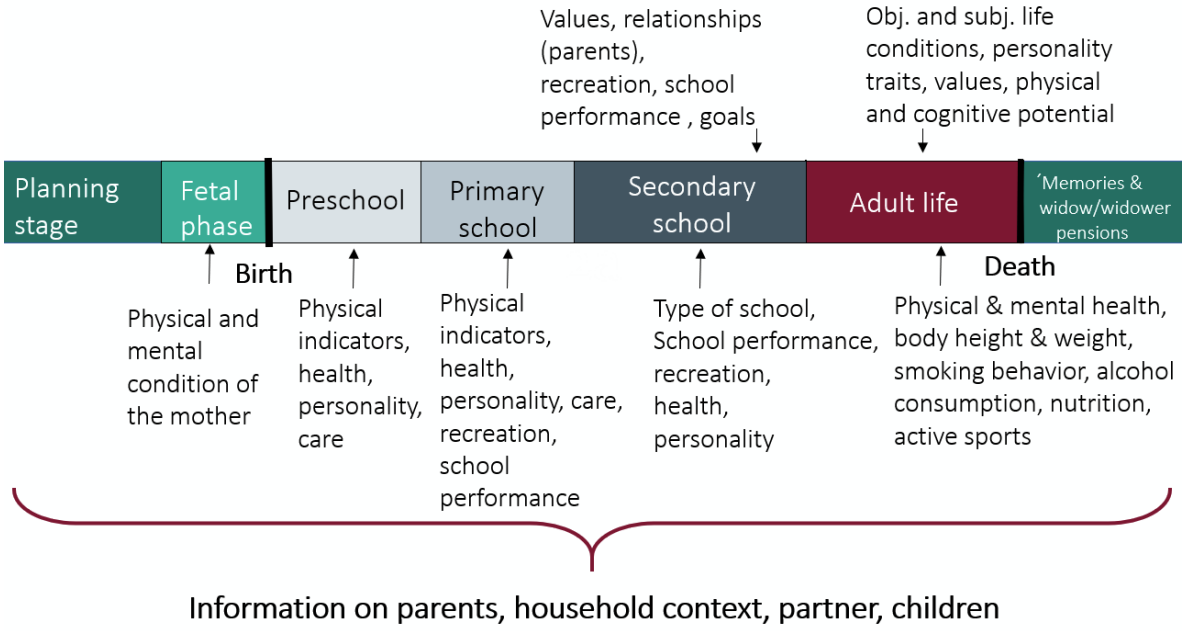

Figure 1. Life course perspective of the SOEP-IS sample

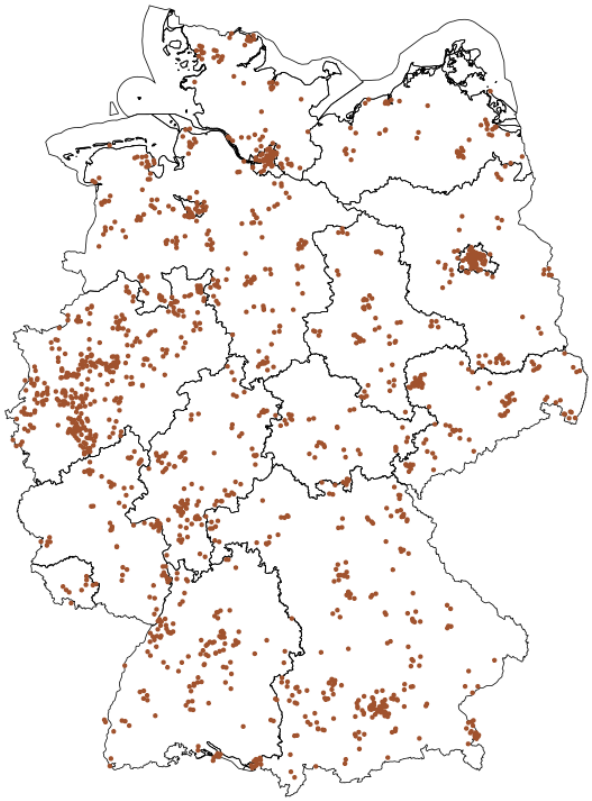

Figure 2. Geographic distribution of genotyped households in the Gene-SOEP sample

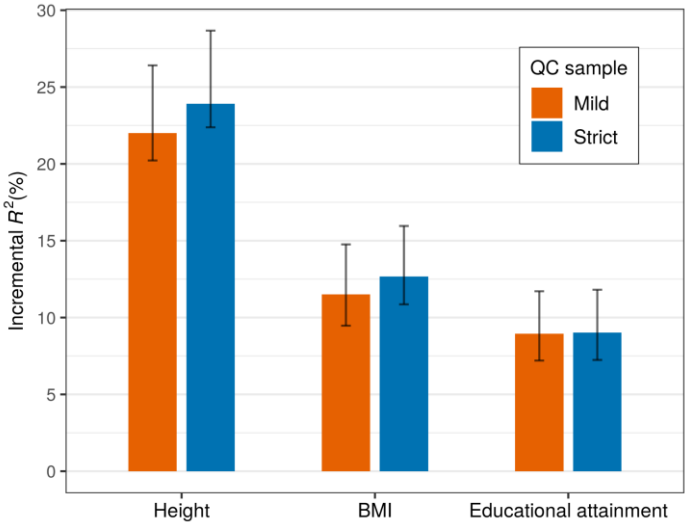

Figure 3. Polygenic prediction in the SOEP-IS sample

The bars report the prediction accuracy of polygenic indices among unrelated individuals of European ancestries measured as incremental R^2. The sample size of the strict (mild) QC sample is 1,904 (2,094), 1,897 (2,086), and 1,857 (2,036) for height, BMI, and educational attainment, respectively. The error bars indicate 95% bootstrapped confidence intervals with 2,000 replications.

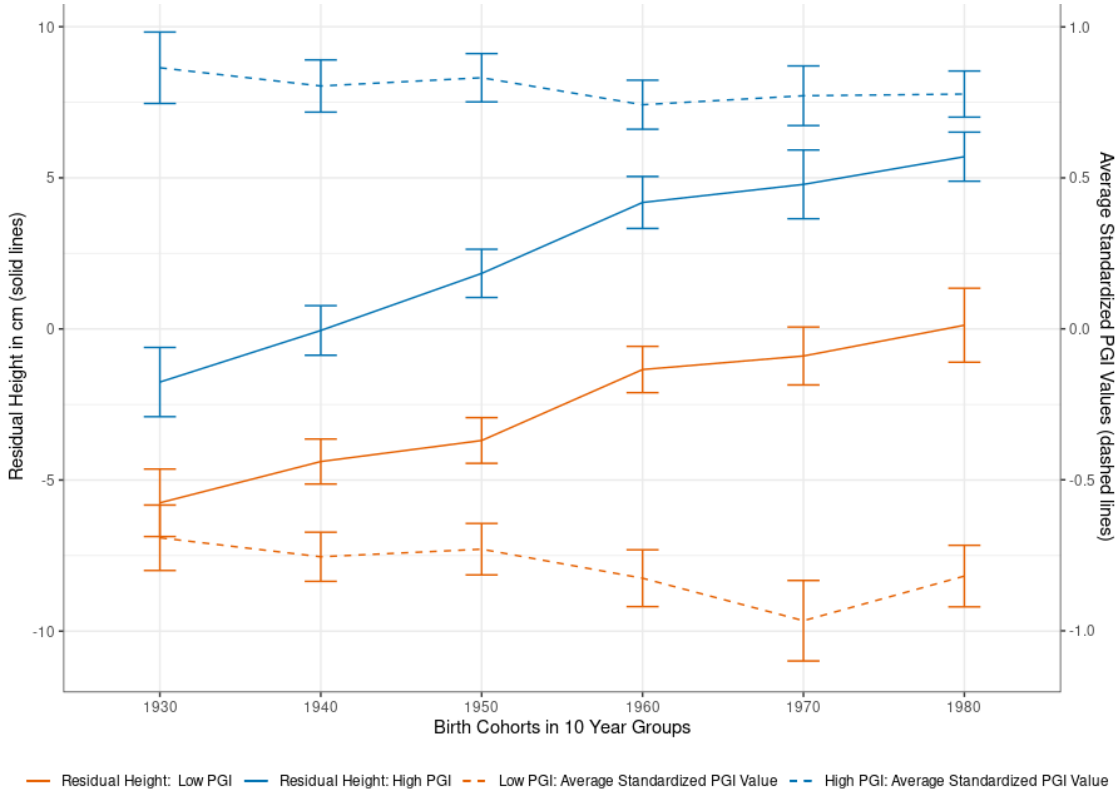

Figure 4. Body height by birth cohorts and PGI values

Using the single-trait polygenic index (PGI) for body height, we split the sample of adults (older than 20 years) into two parts at the median PGI value (High PGI N=1,085; Low PGI: N=1,079). Self-reported height is residualized on sex and survey year before being averaged across survey waves. Each individual is assigned to a decadal cohort. Individuals born before between 1923 and 1939 are all in the 1930s cohort, while individuals born after 1980 are all in the 1980 group. Individuals born between 1940-1949, 1950-1959, 1960-1969, and 1970-1979 are respectively labeled as 1940s, 1950s, 1960s, and 1970s. We plotted the average observed residual height for each decadal cohort by PGI bin, along with 95% confidence intervals.

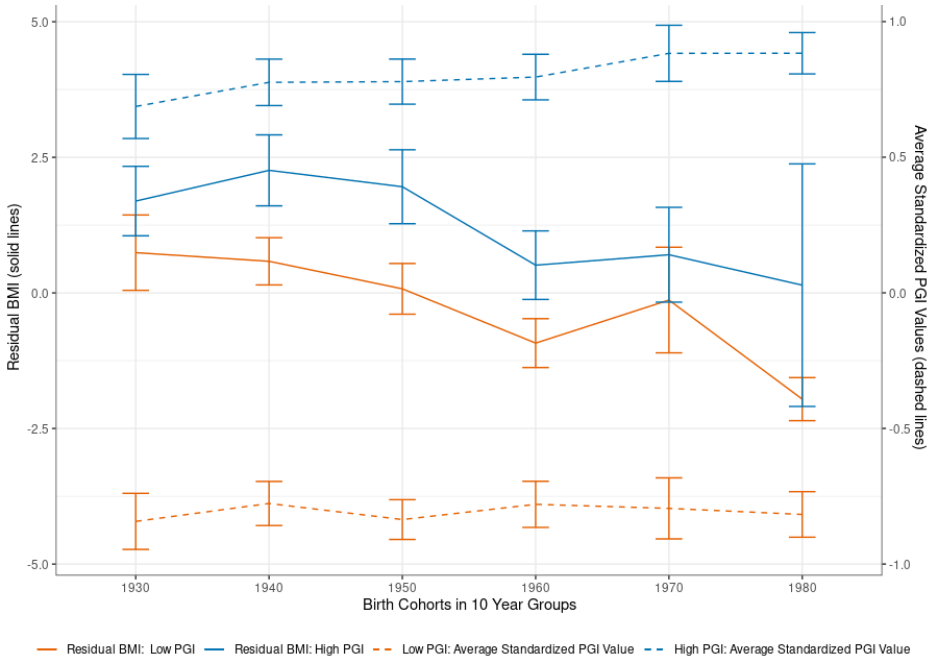

Figure 5. Body mass index (BMI) by birth cohort and PGI values

Using the single-trait polygenic index (PGI) for BMI, we split the sample of adults (older than 20 years) into two parts at the median PGI value (High PGI: *N*=683; Low PGI: *N*=775). Self-reported BMI is residualized for sex and survey year before being averaged across survey waves. Each individual is assigned to a decadal cohort. Individuals born before between 1923 and 1939 are all in the 1930s cohort, while individuals born after 1980 are all in the 1980 group. Individuals born between 1940-1949, 1950-1959, 1960-1969, and 1970-1979 are respectively labeled as 1940s, 1950s, 1960s, and 1970s. We plotted the average observed residual BMI for each decadal cohort by PGI bin, along with 95% confidence intervals.

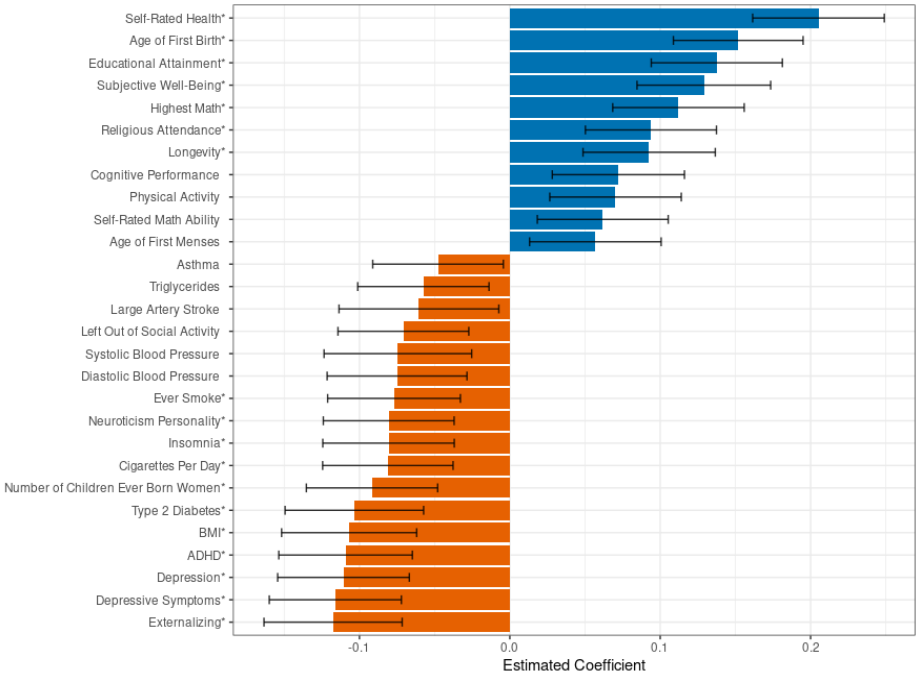

Figure 6. Associations between polygenic indices and self-rated health

Analyses in the Gene-SOEP sample, N = 2,060. Self-rated health is measured by a 5-point Likert scale where a 1 indicates poor health and a 5 indicates very good health. Each self-rated health observation is regressed on five year age-bin dummies, sex dummies, and the interaction of sex and age bin dummies with clustered standard errors by individual. We take the estimated residual from the previous regression, compute the average residual value for each individual, and regress each PGI along with 20 genetic principal components on these residuals where each individual has one observation. The estimated standardized betas from each PGI are reported in the figure. The figure represents 28 single-trait PGIs with an effect size of greater than |±0.1|, out of 55 single-trait PGIs overall. PGIs marked with an * are statistically distinguishable from zero after a Bonferonni correction. Error bars represent a 95% confidence interval around the estimated beta for each PGI..

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Conclusion

This thesis has presented four chapters that studied biological implications of socioeconomic inequality via genetic and neuroimaging data. **Chapter 1** demonstrated that siblings endowed with genetically better earning potential tend to be better-off throughout the lifetime in terms of educational achievements, income, and health. Therefore, the genetic differences do contribute to inequalities in socioeconomic outcomes and health. However, the genetic effects were also shown to work via environmental and behavioral pathways that can be intervened upon, with college education used as an example. **Chapter 2** highlighted another aspect of biological mechanisms by showing that brain anatomy and socioeconomic status are linked through regionally different degrees of genetic and environmental influences. These results emphasize a complex interplay of biological and social factors and that policy interventions should take both factors into account. **Chapter 3** investigated genetic factors for income and presented that genetic associations of income reflect a part of the genetic architecture of educational attainment via phenotypically mediated effects of educational attainment on income. In particular, genetic associations of educational achievement were shown to matter for higher income only if they are also associated with better mental health. Finally, **Chapter 4** introduced a new genetic data resource, which can potentially be used to study the genetic basis of socioeconomic inequality.

In sum, this thesis is a demonstration that biology matters for inequality both in terms of socioeconomic positions and health. While the biological aspects of inequality have been underlined throughout this thesis, the overall pieces of evidence, including those accumulated in the literature, are still premature to inform specific policies. This is partly because most of the findings are based on correlational studies, rather than causal effects of specific biological mechanisms. Also, due to the data availability, the findings are often limited to individuals of European genetic ancestry and cannot be directly generalized to other genetic population groups. Nonetheless, the studies in this thesis were presented as a step towards a better understanding of biological causes and consequences of socioeconomic inequality, which could ultimately inform policies.

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I first met Philipp, my first supervisor, while I was a research master student at Tinbergen Institute almost 6 years ago. At Tinbergen Institute, professors would come to advertise their research to recruit new PhD students. Philipp was also one of them and his session was titled "Genoeconomics". Thinking how strange to combine genetics and economics, I almost just went home. But, I decided to see what this was about at least. My life now would be very different if I had really gone home that day. I was completely fascinated by his talk and realized that "genoeconomics" actually suits my research interest in inequality of opportunity as I demonstrated in this thesis. It did not take me too long to make my mind up to do my PhD in this new field that I had never heard of by then. I still think what a great decision it was.

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