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Using genetics for social science

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Social science genetics is concerned with understanding whether, how and why genetic differences between human beings are linked to differences in behaviours and socioeconomic outcomes. Our review discusses the goals, methods, challenges and implications of this research endeavour. We survey how the recent developments in genetics are beginning to provide social scientists with a powerful new toolbox they can use to better understand environmental effects, and we illustrate this with several substantive examples. Furthermore, we examine how medical research can benefit from genetic insights into social-scientific outcomes and vice versa. Finally, we discuss the ethical challenges of this work and clarify several common misunderstandings and misinterpretations of genetic research on individual differences.

According to the dictionary definition, social science focuses on understanding "the institutions and functioning of human society and […] the interpersonal relationships of individuals as members of society."[1] The phrase 'social science genetics' might, therefore, appear oxymoronic, as genetics traditionally focuses on phenomena (such as the translation of DNA sequence differences into proteins) that are squarely outside the typical purview of the social sciences. As an economist and a psychologist who both study human behaviour and social phenomena, such as people's risky behaviours, we would consider the actions and interactions among subatomic particles as obviously irrelevant to our work—what do quarks have to do with understanding, for example, who starts a new business? What, then, makes DNA any different?

The difference is that decades of twin research—and more recent research using genome-wide measures of DNA—have shown that nearly every aspect of human individual differences is partly heritable[2,3]. That is, differences between people in their personality, educational attainment, income, risk tolerance, well-being, occupational choice, financial decision-making, political ideology, sexual behaviour, physical and psychiatric health, longevity and number of children are all affected in some way by differences in their inherited DNA sequence variation[3–6]. Genetic differences between people, therefore, have incontrovertible relevance for all branches of the social sciences that are concerned with or affected by individual differences in behaviour and outcomes.

Research to identify specific genes associated with human individual differences has made tremendous progress in the past decade[5]. Much of this work has focused on health outcomes, but these developments have begun to influence the social sciences as well[7]. Attempts to link genetics to social and behavioural outcomes are often met with greater scepticism and concerns about potential consequences than medical applications of genetic research (Box 1)[8]. These concerns have to be taken seriously, because they are based on a long, troublesome history of abusing genetic research to justify discrimination and atrocities, including forced sterilization and even genocide. Continued vigilance about the misappropriation of genetics is necessary (Box 2).

We believe that modern social science genetics can and should play a central role in combatting this misappropriation by showcasing the myriad ways in which genetic and environmental factors are entangled with each other and interact. Furthermore, integrating molecular genetics into the social sciences can deliver richer, more precise answers to old questions in psychology, sociology, economics and related fields. Ultimately, the greatest impact from integrating genetics into the social sciences will probably not come from simply applying new tools to old questions, but from changing how people think about the world around them, allowing them to ask new questions and to pursue new answers that would not have been feasible before. For example, the realization that success in life is partly the result of a genetic lottery raises new questions not only about underlying mechanisms, but also about fairness and what a desirable distribution of wealth in a society should look like. In this sense, genetics is akin to other new tools that have made inroads into the social sciences in the past few decades (for example, experiments, game theory or neuroscience), all of which have contributed to a more realistic understanding of human behaviour and the functioning of societies.

In this review, we will describe the main tools of statistical genetics, discuss some of the underlying assumptions and implications of these tools, and illustrate their current use in the social sciences with concrete examples. We restrict our discourse here to genetics but note that there is also a growing literature that uses other types of biological data (for example, the metabolome, the epigenome, hormones, neurotransmitters) to address social-scientific research questions.

The toolbox of statistical genetics

The ambition to bring the insights and tools of genetics into the social sciences is not new. For decades, behavioural genetics (a psychology-focused subfield of the larger field of social science genetics) has been estimating the heritability of psychological traits, such as personality, intelligence and psychopathology[3]. The conclusion of this line of research was simple: everything is heritable[2], even ostensibly 'environmental' variables such as life stress, divorce or harsh parenting. The ubiquitous heritability of individual differences can pose a serious threat to inferences about the impact of specific environments, as these environments, particularly when they are provided by genetic relatives of the focal person, cannot be considered exogenous to the genotype of the person[9]. This critique continues to be important. Now, the combination of genetic data and family data (for example, genotyped samples of trios) offers exciting new possibilities to tackle this and many other challenges[10,11].

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Box 1 | Three common concerns about social science genetics

Do social scientists have the training to work with genetic data?

The word 'genetics' might conjure up scientific activities that most social scientists consider alien to their training. But the uses of genetic data that lend themselves most readily to social science research actually resemble the typical tools of social science, with a heavy reliance on statistical methods and natural experiments. Unfortunately, social scientists still often miss training on how they can utilize genetic data and methods. Curricula that fill these knowledge gaps are needed, and graduate programs at an increasing number of top research universities are moving in this direction.

Does genetic research imply bio-determinism?

The goal of the natural sciences is often to identify universal 'laws of nature' that are invariant across time and place. In contrast, nearly all of the causal regularities discovered by social scientists are (i) probabilistic rather than deterministic and (ii) exception-ridden rather than universal. The observation that human behaviour is influenced by genetic differences between people should not be misinterpreted as bio-determinism[92]. Although DNA variants do not change after conception, their potential influence on social and behavioural outcomes can vary across different environments.

Is genetic research a threat to social justice?

A major obstacle to admitting genetics into the social sciences is fear that their integration "runs along a knife edge, with cliffs of eugenic risk on either side."[8] This fear is well-founded, as genetic research has been used to justify numerous crimes against humanity[104]. But, as the political philosopher John Rawls summarized,[105] "The natural distribution is neither just nor unjust…. These are simply natural facts. What is just and unjust is the way that institutions deal with these facts." We would expand this idea: which genetic variants are present in which people, and what they do within a person's cellular machinery, are natural facts. How these genetic variants are associated, in a particular time and a particular place, with outcomes such as education or wealth are social facts. How these natural and social facts should be used—by governments, schools, businesses, hospitals, etc.—is the appropriate locus of social justice concerns.

Box 2 | Genetics and scientific racism

Scientific racism invokes genetic differences to explain racial disparities in health, wealth, power and life opportunities as inevitable and insurmountable[106,107]. Peeling apart genetic inquiry from scientific racism requires attention to four important points:

Race and genetic ancestry are not the same thing.
Racial and ethnic categories are correlated with genetic ancestry, but race is not reducible to genetics[108]. The US Census categories for race and ethnicity do not have a neat 1:1 correspondence with genetic diversity. More importantly, what is considered a 'race' is socially defined and culturally specific[109].

Genetic research has a profound Eurocentric bias.
The vast majority of social science research is conducted with "the WEIRDest people in the world" (Western, educated, industrialized, rich, and democratic)[110], and social science genetics is no exception. Over 75% of participants in GWAS are from European populations, and the exclusion of non-European participants from genomic research has the potential to exacerbate health disparities[111].

Polygenic scores are not comparable or perfectly portable across ancestry groups.
If the environments of two groups are not identical, the same genetic endowment may give rise to drastically different outcomes. And, differences in ancestry can lead to differences in LD patterns and minor allele frequencies, such that GWAS results from one ancestry group are, at best, only partially portable to another. For example, a PGS that captures approximately 11% of the variation of educational attainment in white Americans captures only about 2% of the variation among African Americans[34]. Neither can average PGSs be meaningfully compared across populations[112].

Geneticists have a special responsibility to communicate their results responsibly.
Extremist groups pay close attention to developments in genetic research and can sometimes show a surprising level of technical sophistication[113]. Given the potential for rampant and pernicious misinformation, researchers have an ethical responsibility to communicate those results clearly to the general public[114].

Genome-wide association studies. Thanks to rapid technological progress, people can now be cheaply genotyped on arrays that measure specific DNA sequences that commonly vary between people. This advance has led to the emergence of large-scale biobanks[12] and consumer genetics companies[13], explosively increasing the sample sizes available for genetic research[5]. As sample sizes increased, human molecular genetics and social science genetics went through a painful—but, ultimately, highly productive—paradigm change. During the mid-2000s, many researchers embraced a 'candidate gene' approach, focusing on a small handful of genetic variants that were selected on the basis of a priori reasoning about their possible functional significance. However, as genotyping became cheaper and more people were genotyped, it became clear that most studies reporting associations between single genetic variants and behavioural phenotypes did not replicate[7,14]. Clearly, something was wrong.

But thanks to growing data availability, an alternative approach became feasible: genome-wide association studies (GWAS). A GWAS systematically scans the entire genome for possible associations with an outcome, examining millions of single nucleotide polymorphisms (SNPs), i.e., variations in individual DNA 'letters', or base pairs. GWASs are typically conducted in samples with similar ancestries, most commonly people of European descent (Box 2). Researchers run a separate regression of the outcome of interest on each SNP separately to deal with the fact that there are typically many more SNPs than individuals in a particular dataset, thereby ignoring any correlations between SNPs (i.e., linkage disequilibrium or LD[15]). This approach yields some association signal from all observed SNPs that are in LD with potentially causal genetic variants, which may or may not be observed directly in the available genetic data[16].

GWASs typically control for technical parameters, sex, age and, importantly, multiple principal components (PCs) of the genetic data, which are supposed to act as proxies for historical migration patterns and long-term ancestry (i.e., genetic population structure)[17]. This is intended to control for spurious genetic associations with outcomes that vary for non-genetic reasons in sub-populations that also vary in gene frequencies. Large-scale GWAS initiatives are often based on preregistered analysis plans; they rigorously control for multiple testing by imposing extremely stringent *P* value thresholds,

and they typically report replication results for novel findings based on evidence from different, independently collected samples in the same paper. All of the above dramatically decrease the risk of finding false positives in GWAS compared to earlier candidate gene studies.

The first GWASs of social scientific outcomes delivered humbling results, either coming up empty-handed or only finding a few genes, each of which accounted for mere fractions of a percent of variance[18]. This ostensible failure, however, was key to understanding why the candidate gene approach was flawed: social and behavioural outcomes, like fertility, education, personality and risk-taking, are massively polygenic[19]. That is, they are influenced by thousands upon thousands of genetic loci scattered throughout the genome, each with a tiny effect. In contrast, candidate gene studies were operating under the wrong assumption that a few genes with large effects are responsible for the heritability of most traits, and they were therefore conducted with sample sizes that were hopelessly underpowered[19].

Over the past 5 years, GWAS sample sizes have rapidly grown from tens of thousands to millions. As a result of this growing statistical power to detect tiny effects on highly polygenic traits, the GWAS approach has now yielded hundreds of replicable associations of specific genetic markers with social scientific outcomes[5,6]. The flood of discoveries had motivated big online repositories[20] and interactive atlases comparing the genetic architecture of thousands of traits[21,22]. Scientists are (finally) beginning to open the black box of heritability[23].

However, the threat of finding spurious genetic associations due to unobserved variable bias remains a serious challenge[24–26]. There is no guarantee that using samples with similar ancestry and adding genetic PCs as control variables will eliminate all forms of spurious genetic signal. For example, genetic PCs don't capture rare variants that are only weakly correlated with common SNPs, they seem to perform less well in small samples[24], and they can both under- and over-control for potential confounds that are associated with genetic variation among people[27].

New statistical methods are constantly being developed to tackle the challenge of spurious associations more rigorously, such as linear mixed models (which were previously used in the animal breeding literature)[28,29]. Yet even the most advanced methods rely on assumptions such as additivity that can be violated in practice. The gold standard to correct for confounds in genetic association studies is a research design that uses family data and exploits the random assortment of alleles during meiosis for the identification of causal genetic effects (for example, using dizygotic twins, siblings with the same biological parents, or trios of mother–father–child)[10,30]. The availability of such data keeps growing and will enable within-family GWAS and follow-up analyses for many heritable traits in the future. At the moment, however, the vast majority of GWAS are based on population samples or case–control cohorts that are not entirely immune to unobserved variable bias.

Genetic correlations. GWAS data makes it possible to calculate genetic correlations, including, surprisingly, between pairs of traits that have never been measured in the same sample. Specifically, the technique of bivariate LD-score regression uses the GWAS summary statistics from two traits to estimate co-heritability in a remarkably robust way[31,32]. As an illustration, Fig. 1 summarizes genetic correlations between educational attainment (EA) and a variety of other traits from LDHub, an online repository of genetic correlations[33]. EA-associated genes[34] are associated with traits across the lifespan, from birthweight (+), infant head circumference (+) and childhood IQ (+), to body mass index (BMI)-related traits (−), depressive symptoms (−), neuroticism (−), smoking (−) in adulthood, all the way to risk for lung cancer (−), Alzheimer's disease (−) and longevity (+) (as implied by parent's age at death). However, the

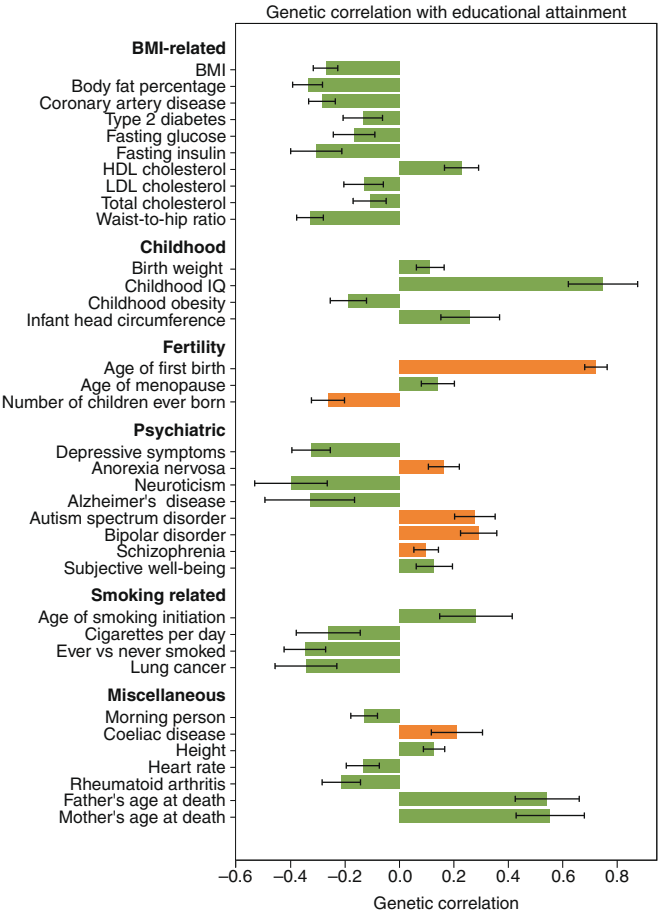

Fig. 1 | Genetic correlations of educational attainment with traits across the entire lifespan. Genetic correlations of EA[34] with 196 traits were computed using bivariate LD-score regression and GWAS summary statistics with varying sample sizes obtained from LDHub (http://ldsc.broadinstitute.org/ldhub/). The figure only shows a subset of all results for EA that are significant after Bonferroni correction ($P < 0.05/196 = 2.5 \times 10^{-4}$, two-sided tests). Error bars represent 95% confidence intervals. Green and orange represent positive and negative genetic relationships, respectively, between EA and health.

effects of EA-increasing genes are not universally positive: they are also linked to reduced reproductive success (fewer children born, most likely due to reproductive decisions rather than decreased fecundity) and an increased risk for several psychiatric disorders.

These findings underscore how tightly social-scientific outcomes, such as education, are linked with health. At the same time, it is important to remember that genetic correlations are not, by themselves, informative about causal mechanisms, nor do they necessarily imply direct, 'inside the skin' pleiotropic effects of genes on two traits[35]. They may also reflect indirect, possibly environmentally mediated pathways (for example, high childhood IQ → higher EA → less smoking → reduced risk for lung cancer).

Moving beyond atlases of pairwise genetic correlations, multivariate approaches further capitalize on genetic similarities among traits by jointly analysing GWAS summary statistics from several traits simultaneously. Multitrait analysis of GWAS (MTAG) and genomic structural equation modelling (genomic SEM) are two recently developed methods that are quickly gaining popularity[36,37]. A multivariate analyses can boost the power to detect genes associated with a trait by 'borrowing' relevant information from other genetically related traits (for example, neuroticism as a proxy for

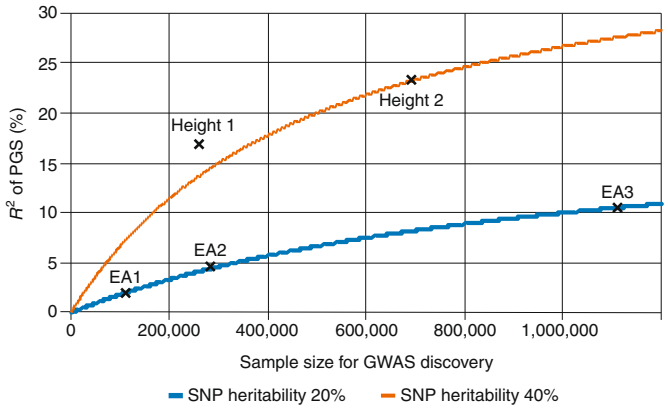

Fig. 2 | The influence of GWAS sample size on the accuracy of polygenic scores for two genetically complex traits with assumed SNP heritability of 20% and 40%. The two solid lines show theoretical expectations, assuming 200,000 causal genetic markers for both traits. De Vlaming et al.[43] estimate the SNP heritability of height and years of schooling with 43.3% (s.e.m. = 1.8%) and 16.4% (s.e.m. = 1.7%), respectively. In practice, the accuracy of polygenic scores depends on many technical parameters, such as the number of SNPs in the score and which prediction sample is used. The empirical results for years of schooling in this figure are for PGS based on all HapMap 3 SNPs, using the Swedish Twin Registry as a prediction sample for EA1 and the Health and Retirement Study (HRS) as a prediction sample for EA2 and EA3. The empirical results for height are based on the HRS prediction sample with SNP thresholds of $P < 5 \times 10^{-5}$ for Height1 and $P < 0.001$ for Height2 (ref. [47]). All statistical tests referred to here were two-sided.

depressive symptoms and vice versa)[38]. Other work is using multivariate GWAS to identify specific genes and biological pathways that confer general vulnerability to psychiatric disorders versus genes that operate uniquely on a specific symptom or syndrome[37]. Overall, the shift toward multivariate GWAS parallels an earlier development in twin studies, which shifted from estimating the heritability of single traits in isolation to estimating the extent to which the same (unobserved) genes influenced a variety of human phenotypes[39].

Polygenic scores. Answering biological questions that might, on their face, appear irrelevant to social scientists (how many polymorphisms in the genome affect human phenotypes?) can turn out to be crucial for developing tools that will, in fact, be broadly useful for social science[40]. Specifically, as it has become clear that the effects of individual variants are tiny, methods of aggregating the effects of many variants into a single composite, a polygenic score (PGS), have proliferated. In polygenic scoring, researchers take results from a GWAS of a specific trait and apply them in a new sample, weighting each person's genetic variants by the effect size from the GWAS and summing across the variants. The resulting PGS is therefore an index that summarizes current estimates of additive genetic influences towards a particular phenotype[41,42].

Because PGSs aggregate over many genetic markers, they capture a much larger share of the variance of the trait of interest than any one variant on its own. The accuracy of PGS primarily depends on the heritability of the trait (+), the GWAS sample size (+), the polygenicity of the trait (–) and whether the genetic architecture of the trait varies across different environments (–)[41]. So far, theoretical projections of the accuracy of PGS have been borne out by the data pretty well. Figure 2 illustrates this by comparing the theoretically expected[43] predictive accuracy of a PGS in a hold-out sample (assuming 200,000 independent causal SNPs) with results from studies of increasing sample size for educational attainment (EA1 (ref. [44]), EA2 (ref. [45]), EA3 (ref. [34])) and body height (Height1 (ref. [46]), Height2 (ref. [47])). As GWAS sample sizes increased, the number of genome-wide significant loci increased from three in EA1 to 1,271 in EA3.

The R^2 of the EA3 PGS mirrors the effect size seen for traditional social science variables, such as the relationship between family income and educational attainment. As a result, such PGSs are beginning to be useful for follow-up studies with much smaller sample sizes, including experimental studies, policy and intervention studies, and longitudinal datasets with deep phenotypes[48–51]. A researcher who has a PGS that captures 5% of the variance of the phenotype she is interested in needs only about 260 individuals if she wants to have 90% statistical power at $\alpha = 0.05$ (two-sided test) to find an association of the phenotype with that PGS.

At the same time, it is important to remember that even the best currently available PGS for behavioural outcomes cannot make accurate predictions for the outcome of any specific individual. Figure 3 illustrates this by plotting the EA3 PGS against actual years of schooling in a US sample of individuals with European ancestries. The relationship between the two variables is positive and statistically highly significant ($P = 2.2 \times 10^{-16}$, two-sided test). The PGS accounts for about 11% of the variance in the years of schooling after residualizing this variable for sex, birth year and the first ten genetic PCs. Yet we also see that, for almost any single value of the PGS, almost every level of actual education is observed. Even for PGS values that are 2 s.d. above or below the sample mean, we observe everything from high school drop-outs to people with PhDs.

It is also important to remember that PGS are not a 'clean' way to separate biological from non-biological factors that contribute to differences in phenotypes. GWAS results are not entirely immune to unobserved (e.g., environmental) confounds, such as parenting or neighbourhood characteristics, and genetic influences are often conditional on and/or mediated by environmental channels[52]. Thus, PGSs may exhibit different predictive accuracy even among members of the same ancestry group that vary from each other in sex or socioeconomic status[53].

Nevertheless, PGS have a variety of useful and exciting applications in the social sciences, including the possibilities of adding them as control variables to boost statistical power in experiments[44], reduce unobserved heterogeneity[54], investigate gene–environment interactions[49], study environmental factors mediating the effect of genes on the outcome of interest[55] and tease apart environmental and genetic channels of intergenerational transmission[10,11]. One particularly useful aspect is that once genetic data has been collected in a sample, it is (in principle) possible to construct PGS in that sample for all traits for which GWAS have ever been conducted[6], opening up the possibility of controlling for and investigating relationships that would have been practically impossible otherwise (for example, is a genetic predisposition for Alzheimer's disease associated with brain anatomy in infancy or with the tendency to purchase more complete health insurance?).

Although PGS are often frustrating for biologists who are interested in specific genomic mechanisms, our perhaps-controversial position is that PGS can hold the most utility for social scientists, precisely because they aggregate across lower-level mechanisms and refocus inquiry back onto the behaviour of the whole human organism in her or his environment[48]. The feasibility of integrating PGSs is aided by the fact that GWAS summary statistics are often freely available in the public domain[21]. Additionally, publicly available datasets that include genetic information have begun to release PGS for several traits to researchers who do not have access to the raw genetic data or lack the expertise to construct the scores themselves[56].

Integrating genetic data and family-based study designs. Although molecular genetic data is often perceived as supplanting twin or family designs as the workhorses of social science genetics, the combination of measured genotypes and samples with family

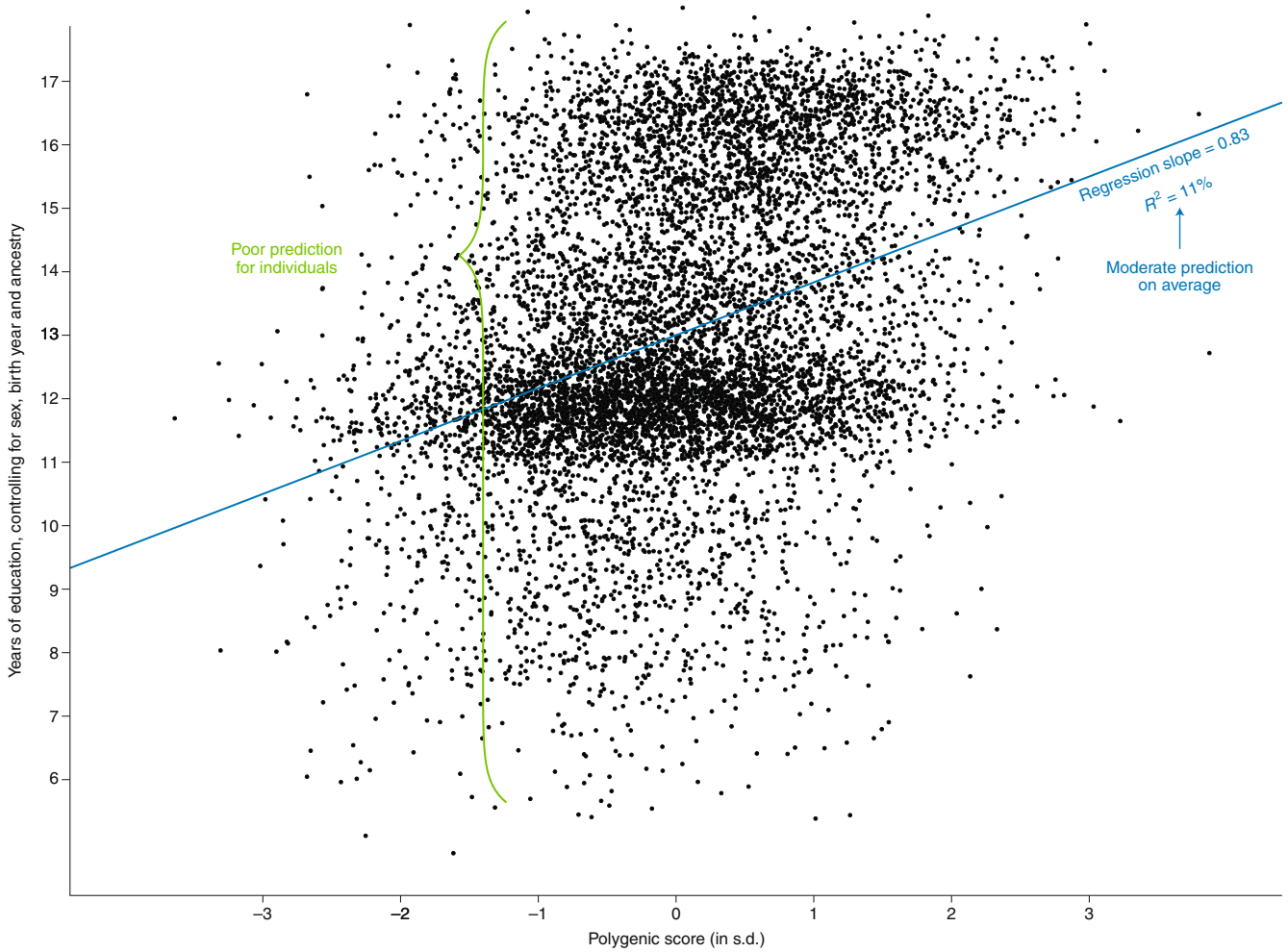

Fig. 3 | The relationship between a polygenic score for educational attainment and actual years of schooling in the Health and Retirement Study. The EA PGS was constructed using GWAS estimates from a sample of $N = 1{,}123{,}243$ individuals[34]. The prediction sample was restricted to individuals of European ancestries ($N = 8{,}638$, Health and Retirement Study). EA was measured in typical years of schooling required to obtain the highest academic degree of an individual. EA was residualized for birth year, sex and the first ten principal components from the genetic data, and then regressed on the polygenic score.

structure provides the most compelling study designs[52]. Two types of family relationships are particularly noteworthy. First, dizygotic (DZ) twins or siblings can be used to estimate the within-family association between genetic variants (or PGS) and an outcome. This analysis takes advantage of the fact that a parent has two copies of each genetic locus (called alleles), and these alleles are randomly assigned to offspring during the process of making eggs or sperm. Which version of the parental genotype someone inherits, versus which version a sibling inherited, is the outcome of a true natural lottery. Because genotypes are assigned randomly with respect to all other variables, an association between sibling differences in PGS and sibling differences in phenotype is powerful evidence that the PGS is tapping genetic variants with a causal influence on the phenotype. This is a good starting point for investigating relevant causal mechanisms that might involve malleable environmental pathways.

Second, if genetic data for trios of mother, father and offspring are available, one can decompose the parental genotypes into two parts: the alleles transmitted to the offspring and the non-transmitted alleles. The non-transmitted alleles of the parent, then, are analogous to the genotype of an adoptive parent: if they are correlated with the phenotype of the offspring (an 'indirect genetic effect' or 'genetic nurture'), this association cannot be due to genetic transmission from parent-to-child and must be mediated via environmental channels, such as parenting style or socioeconomic advantage[10]. This 'virtual parent' design is conceptually similar to the logic of adoption studies or children-of-twins studies, in that it peels apart genetic and environmental pathways for intergenerational transmission[10,11]. At the same time, conditional on the genotypes of the parents, the directly transmitted alleles of the child are the outcome of a natural lottery that can be used for causal analyses, similar to the logic of within-sibling comparisons. Recent methodological work is considering the extent to which genetic nurture biases SNP-based heritability estimates and estimates from sibling fixed-effects models[57].

Third, the combination of family-based study designs and genetic data offers new, powerful approaches for causal inference using Mendelian randomization (MR)[58,59] and related approaches[54,60–62]. For example, results from large-scale GWAS on within-family differences would be immune to potential confounds from subtle differences in ancestry or unobserved environmental factors that correlate with family genotypes, thereby ruling out an important source of bias in MR-like analyses[63].

Substantive applications

We now turn to some examples of what we have already learnt from applying the social science genetics toolbox in five substantive areas: (i) intergenerational transmission of human capital, (ii) social mobility over the lifespan, (iii) genetic associations with

demographic variables (fertility, mortality and migration), (iv) gene × environment interactions and (v) the interconnections between social processes and disease processes. These research areas are of broad interest to scientists working in many different fields and focus on aspects of human functioning that resist bio-reductionism and yet are illuminated with biological data.

Intergenerational transmission of human capital. Human capital is transmitted from generation to generation[64], and understanding how 'nature' and 'nurture' shape children's resemblance to their parents can inform efforts to reduce inequalities that tend to persist over time. For example, studies of trios from several countries found that a PGS of the EA-associated alleles that parents did not transmit to their offspring are nevertheless associated with offspring EA, thereby providing new evidence for the importance of environmental mechanisms and parenting[10,11,65,66]. Such study designs can be extended to identify specific environmental variables and processes that mediate the effects of untransmitted parental genotypes on their children[55], thereby providing scientists with a promising new strategy for understanding the mechanisms that lead to inequalities in wealth and health.

Intragenerational social mobility. The combination of measured genotypes and family structure has also been used to examine intragenerational social mobility. In these studies, a PGS of education-associated genetic variants is used as a type of tracer dye: just as tracking the progress of ingested barium allows a radiologist to gain a higher-resolution picture of the digestive tract's twists and turns, tracking individuals with a high or low PGS allows social scientists to gain a higher-resolution picture of the life-course twists and turns that ultimately produce high or low social attainments in adulthood. The developmental pathways toward greater social mobility are already evident early in childhood: the EA PGS is also associated with earlier achievement of developmental milestones and faster reading development[51]. Looking across the lifespan, people born with a higher number of EA variants show greater upward mobility, relative to their family-of-origin, in occupational status, income and educational attainment, even compared to their siblings[67]. The EA PGS is also associated with wealth at retirement, with a 1 s.d. increase in PGS estimated to be worth $137,000 in 2010 dollars. This wealth association persists even controlling for education and labour income, and it operates in part through better financial decision-making[68].

Evidence that children's genotypes are associated with their educations, occupations and financial success in adulthood should not be interpreted to mean that children are genetically determined to be rich or poor (Box 1). And, following Holland's distinction between the 'effects of causes' versus the 'causes of effects'[69], reverse inferences that people are poor because of their genetics are entirely unwarranted. In fact, evidence from five longitudinal studies across three continents showed that children from rich families with low PGS scores still have more socioeconomic success as adults than children from poor families with high PGS scores[67].

Genetics and demography: fertility, mortality, migration. Over generations, fertility, mortality and migration shape the size and genetic distribution of a population. At the same time, genetic differences within a population are associated with all three of these key demographic variables. Twin studies have long established that time to reproductive maturity, reproductive behaviour and completed fertility are all heritable[70], and more recently, large-scale GWASs have found multiple specific loci associated with fertility-relevant traits and behaviours[71–73]. Genetic research on fertility has been used to illuminate the mechanisms underlying the association between parental age and offspring risk for mental disease, as genetic risk for schizophrenia has been associated with both early and late age at first birth[74,75]. Earlier work using children-of-twins similarly suggested that part of the elevated burden of mental health problems in children of adolescent mothers was due to transmission of genetic liabilities affecting both fertility behaviours and psychopathology[76].

One active and politically sensitive area of research is the relationship between education and fertility. Genetic variants associated with education are also associated with a lower number of children born, resulting in declines in the average EA PGS in the 20th century[77,78]. A variety of twin and family studies have probed whether education operates causally to delay childbearing and sexual behaviour, above and beyond shared genetic influences, with mixed results[79,80]. Interestingly, two variables that are heritable and have robust epidemiological associations with fertility behaviour—marital history[81] and religiousness[82]—have received almost no attention in molecular genetic research and represent an untapped opportunity for integrating genetics into classic questions in the social sciences.

At the other end of the lifespan, some genetic loci have also been discovered for mortality risk, as imputed by the lifespan of one's parents[83]. Finally, migration, either to another country or within a country, has turned out to be linked to genetic differences in intriguing, and sometimes troubling, ways. People with a higher PGS for EA were found to be more likely to immigrate to other countries from New Zealand or to leave former coal-mining areas in the UK, perhaps to seek better educational and occupational opportunities elsewhere[51,84]. In contrast, people who stayed behind in economically depressed coal mining regions in the UK tend to have lower EA PGS and also carry more genetic risk factors for obesity, smoking and coronary artery disease[84]. In fact, genetic differences across geographical regions in the UK are so systematic that one can conduct a GWAS on neighbourhood characteristics (for example, the Townsend index, a measure derived from registry data that reflects regional variation in over-crowding, unemployment and lack of home and car ownership) using standard adjustments against population stratification such as genetic PCs or linear mixed models and still find many genome-wide significant loci[85].

Again, this does not mean that social outcomes like neighbourhood poverty are inevitable or determined by biology (Box 1). Rather, any social process that unequally concentrates educational and economic opportunity in some places, but not others, will induce geographical variation in genotypes, because people choose (or lack the capability to choose) their place of residence on the basis of their own genetically influenced preferences, abilities and characteristics. This coupling between genetics and geography complicates efforts to draw causal inferences about how the characteristics of places shape inequalities in health and other life outcomes[86].

Gene × environment and gene × intervention interactions. Earlier iterations of gene × environment (G × E) interaction work, either using candidate genes or latent components of genetic variance estimated in a twin model, have been criticized for being vulnerable to bias and false positives[14,87,88]. Recent work to examine gene × intervention (G × I) interactions is a promising reinvigoration of the more general G × E topic, as such work examines robust measures of genotype (for example, PGSs estimated from large-scale GWAS rather than candidate genes) and interventions that can be reasonably assumed to be exogenous (for example, policy shocks).

A G × I analysis can test whether intervention effects are larger or smaller for people who are genetically more likely to develop the outcome that is targeted by the intervention, thus addressing three key questions about the intervention: (i) does it serve a high-need population segment, (ii) will it shrink existing inequalities or amplify them and (iii) can its delivery be personalized? For example, an intervention could be particularly impactful for people at high genetic risk, therefore shrinking inequalities by serving a high-need segment of the population. Alternatively, the

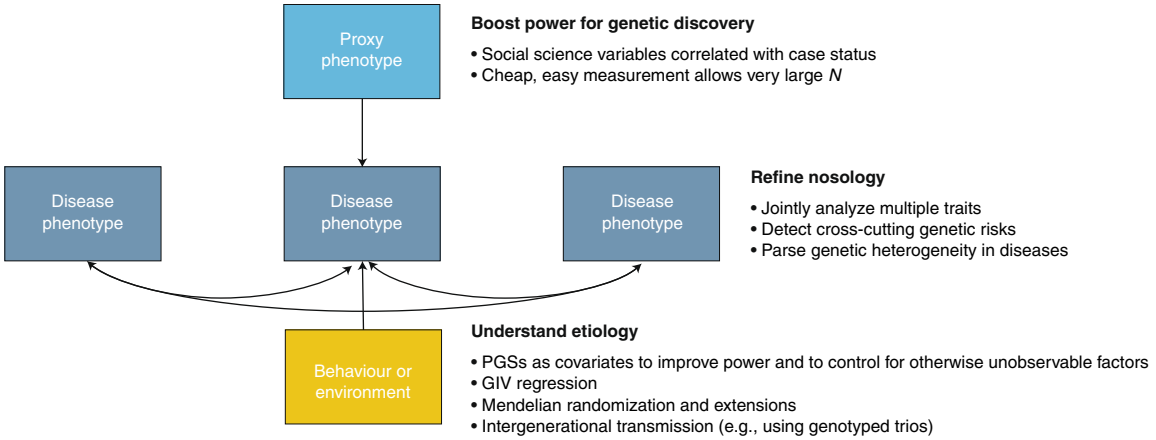

Fig. 4 | How medical science can benefit from social science genetics. The figure displays relationships between genetic epidemiology and social science genetics. GIV, genetic instrumental variable.

intervention could operate equivalently across levels of genetic risk, suggesting few potential gains from targeting the intervention to specific people on the basis of genetic characteristics (although including genetic information might improve the estimate of the intervention main effect, by accounting for residual heterogeneity[44]). Or the intervention could deliver the most benefit to those who are already at lower risk, a 'Matthew effect' that improves the average level of functioning in a population but also exacerbates inequalities[89]. This result would point to the need to develop new interventions for high-risk segments of the population[90].

One of the recent studies of G × E showed that a policy reform in the UK that increased compulsory schooling by one year improved obesity-related health outcomes and lung function in mid-adulthood. The reform had particularly positive effects for individuals who carried more genetic risk factors for a high BMI, effectively reducing health disparities by counteracting genetic risks[49]. Beyond understanding the impact of that specific policy reform, this study is also valuable as a novel empirical illustration of an old idea: genetic differences between people do not necessarily restrict the possibilities for intervention[91].

Part of the reason that genetic associations might be dependent on environmental factors, for example, political regime, policy interventions, economic conditions or school environment, is that genetic differences might be expressed via modifiable, context-dependent environmental channels[92,93]. For example, genetic predispositions toward height and psychomotor speed could lead to self-selection into a sports club; the training and reinforcement received by coaches, parents and peers, then, could amplify these initial differences to produce associations between genetic variants and basketball 'talent'.[94] In a different macro-environmental context, where these training and reinforcement experiences are not available (i.e., in a different 'cafeteria of experience'[95]), genetic associations would be disrupted.

Tracing these sorts of gene–environment interplays, in which people with different genotypes are systematically more likely to elicit different environmental responses, to select different peer groups, to engage in different training experiences and, more generally, to carve different environmental niches for themselves, has long been a topic of interest in the twin and family literature[96–98], and we anticipate that research with PGSs will offer new opportunities for testing hypotheses in this area.

However, we also note some methodological challenges in estimating G × E and G × I interactions. First, PGS are typically constructed from large-scale GWAS results that estimate the average effects of SNPs across samples and environments, missing or attenuating potential environment-specific genetic effects. Second, PGS tend to capture only part of the relevant genetic influences on a trait[54]. For both of these reasons, G × E and G × I will be biased towards zero and provide only a lower bound estimate of the true effects. Third, because GWAS results are typically not immune to population structure, genetic nurture or other unobserved environmental confounds (see above), PGS may capture some of the environmental causes of an outcome. And fourth, since genes and environments are often correlated, G × E and G × I may be endogenous terms in a regression equation. All of the above makes the interpretation of G × E and G × I interactions more difficult unless GWAS results from within-family analyses are used and combined with reasonably exogenous variations in E or I.

Implications of 'disease' genetics for social processes (and vice versa). GWAS is perhaps most commonly conceptualized as a tool for understanding the biology of psychiatric and physical diseases, and advocates for investing in GWAS often emphasize the relevance of results for drug development[5,99]. But genetic discoveries for 'diseases' turn out to be relevant for a much broader array of social phenomena in 'healthy' or non-clinical populations. For example, genetic risks for physical health conditions, like coronary artery disease, are associated with long-term wealth, education and self-rated health in hold-out samples[100]. Similarly, the schizophrenia PGS is associated with the escalation of illicit drug use in typically developing university students[101].

Conversely, genetic discoveries for 'healthy' phenotypes can be useful for understanding medical and psychiatric diseases. GWAS results for EA were used to parse the genetic heterogeneity of schizophrenia into disease subtypes with different genetic architectures and biological underpinnings, which might benefit from different treatments[50]. As another example, the first robust genetic associations with major depressive disorder (MDD) among individuals of European descent were found using self-reports of subjective well-being and neuroticism as proxy-phenotypes[36,102]. Recent multivariate work has investigated the joint genetic architecture of a 'well-being spectrum' encompassing depression, neuroticism, life satisfaction and positive affect[38]. The genetics of subjective well-being have also been leveraged to understand its relationship to cardiometabolic health and body size[103]. These results demonstrate that there is no clear boundary between social science genetics and medical genetics: investments in either area of research will enrich the other (Fig. 4).

Conclusion

The rapidly increasing availability of genetic data now allows scientists to unravel the genetic underpinnings of individual differ-

ences in social, behavioural and health outcomes. Although not without caveats, the current workhorses of statistical genetics (e.g., GWAS, LD score regression, polygenic scores) are useful for social scientists whose primary interests lie in understanding effects of environments, such as parenting, policies or interventions, that might lead to or entrench inequalities. Genetic effects influence most dimensions of individual differences that social scientists care about, and genetic differences between people are tightly interwoven with environmental differences that social scientists study. This is both a challenge as well as an opportunity for the social science: ignoring the relevance of genes would mean ignoring an important part of reality, which could lead to erroneous and misleading conclusions about environmental or behavioural effects. Thus, the social sciences are incomplete without genetics, and they can benefit from genetically informed study designs in their quest for accurate and comprehensive answers to the questions they are asking. The tools and data to do so keep emerging at a rapid pace. Now is the time to begin training social scientists to understand and use these new tools.

Clearly, the genetic revolution raises a host of new ethical, social and legal challenges that are important and urgent to address. Genetic data are possibly the most personal piece of information about an individual that exist, and the scope of potential uses and abuses is rapidly increasing, ranging from 'genetic entertainment' by learning about one's ancestry or creating 'customized' music playlists, to potential applications in insurance and labour markets, marketing campaigns, dating apps, criminal justice proceedings, the testing and selection of embryos during in vitro fertilization, to biohacking and engineered differences in human DNA. The genetic revolution will change our lives and our societies, whether or not we want it to. As social scientists, we have expertise in considering the ethical, cultural, political, economic, environmental and historical forces that shape human lives and societies. As a consequence, we can make valuable contributions to the unfolding conversation about the uses and abuses of human genomics. But to do so, we need to take genetics seriously.

Data availability

The genetic correlations reported in Fig. 1 are based on publicly available GWAS summary statistics on LDHub (http://ldsc.broadinstitute.org/ldhub/). The Health and Retirement Study data in Fig. 3 can be accessed via dbGaP and the University of Michigan.

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Competing interests

The authors declare no competing interests.

Additional information

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